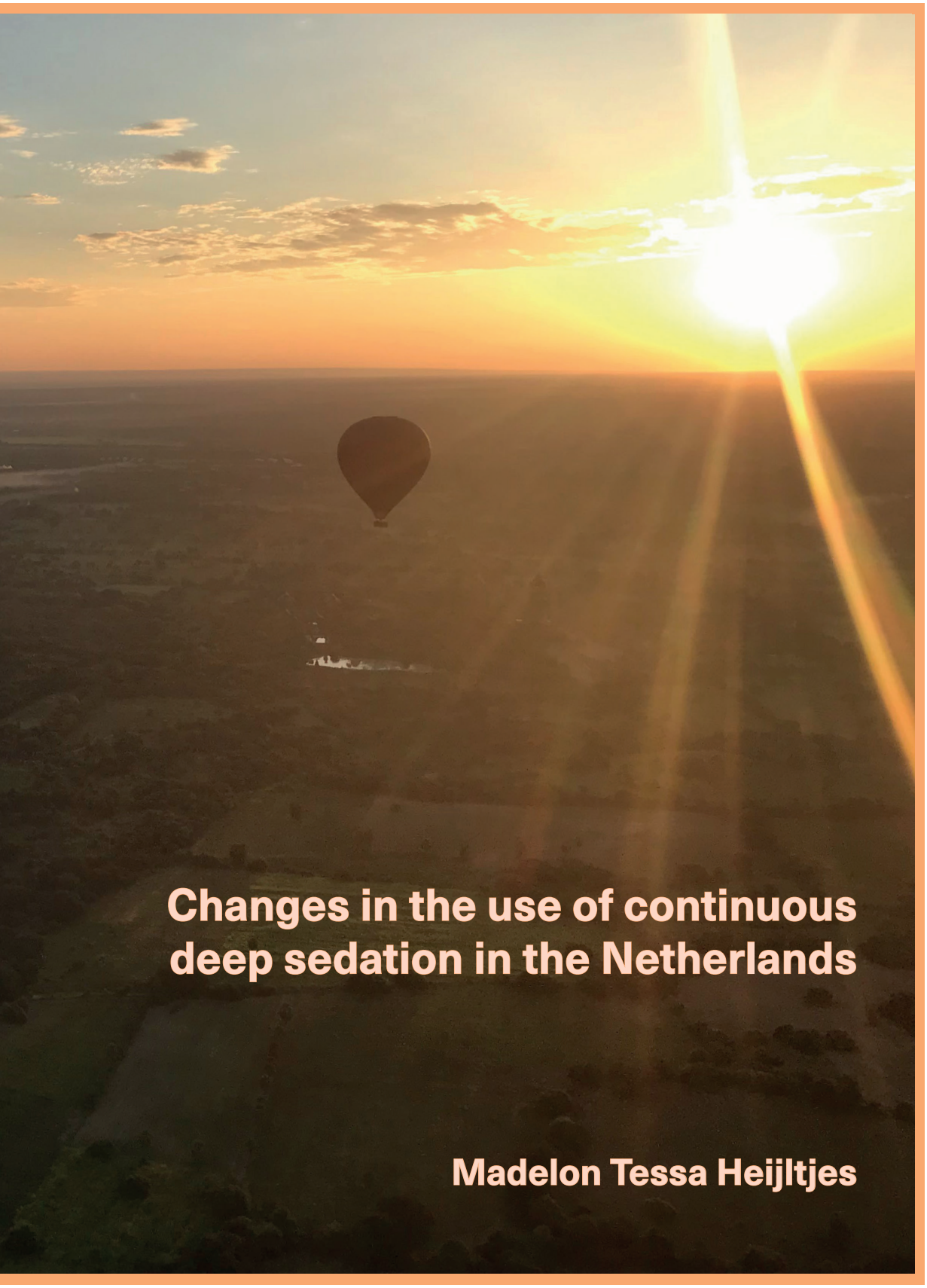

Changes in the use of continuous deep sedation in the Netherlands

Madelon Tessa Heijltjes

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Changes in the use of continuous deep sedation in the Netherlands

Veranderingen in de toepassing van continue diepe sedatie in Nederland

(met een samenvatting in het Nederlands)

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Chapter

1

General introduction

General introduction

At the end of life, patients may suffer from severe symptoms like pain, dyspnea, fatigue, and restlessness.[1,2] When these symptoms cannot be controlled by conventional treatment options, palliative sedation can relieve suffering. The most far reaching form of sedation is continuous deep sedation (CDS), which involves lowering the consciousness level of a dying patient deeply and continuously until the end of life. The acceptability of CDS has been highly debated in the past decades.[3,4] Its moral sensitivity stems from the fact that CDS may shorten a patient's life. Moreover, it may end someone's biographical life since patients lose the ability to communicate with their relatives.[4]

In the Netherlands, end-of-life practices have been studied approximately every 5 years from 1990 onwards. Stratified samples of deaths are drawn from the national death registry, and physicians who are involved in these deaths are invited to fill out a questionnaire.[5] The use of CDS is a topic of research in these repetitive nationwide questionnaire studies since 2005.[5,6] These studies showed that the use of CDS has increased from 8.2% to 18.3% of all deceased people between 2005 and 2015.[7] The latest report even shows a frequency of 23%.[8] This increase has raised questions about its background and about how this increase should be valued. The aim of this thesis is to provide insight in current practices of CDS, to explore how the use of CDS has changed in the Netherlands between 2005 and 2015, and to identify reasons for the increase of the use of CDS.

Terms and definitions of sedation

A variety of terms is used for the lowering of the level of consciousness of dying patients by the use of sedatives. Continuous sedation, deep sedation, end-of-life sedation, palliative sedation, terminal sedation and sedation until death are more or less commonly used terms in the literature.[9-14] For several years, terminal sedation was the term which was mostly used for the lowering of the level of consciousness of dying patients.[14,15] Experts opted to use the term palliative sedation therapy instead, as the word 'terminal' could be wrongly be associated with an act of terminating a patient's life.[16]

In 2002 Morita et al. found variety in the literature in the degree of sedation, its duration, medication used for sedation, target symptoms and patients, and proposed to define subcategories of palliative sedation therapy.[16] The many different forms of sedation make the discussion on the use of sedatives complex: the depth of sedation may vary from superficial to deep, and the duration may vary from intermittent to continuous sedation until the end of life. Table 1 shows the different types of sedation, covering different depth levels and different durations. The focus of this thesis will be on continuous deep sedation until the end of life (CDS). CDS is the most far reaching form of sedation, as sedatives are

provided with a continuous effect and the patient is deeply sedated until the end of life. Repetitive nationwide questionnaire studies showed a notable increase in the use of CDS in the Netherlands.[7] Little is known about how the use of CDS changed in the Netherlands over time and how this increase should be valued. Insight in the developments of CDS in the Netherlands is important, as for health care professionals, policy makers, and other stake holders involved it makes it possible to adjust to this evolving practice.

Table 1. Terms for sedation with varying depth and duration

		Duration of sedation	
		Intermittent	**Continuous**
Depth of sedation	**Superficial**	Intermittent sedation Terminal sedation End-of-life sedation Palliative sedation	Continuous sedation Terminal sedation End-of-life sedation Palliative sedation Sedation until death
	Deep	Intermittent sedation Terminal sedation End-of-life sedation Palliative sedation	Continuous deep sedation (CDS) Terminal sedation End-of-life sedation Palliative sedation Sedation until death

The regulation of CDS in the Netherlands

In the Netherlands, the use of CDS is considered as normal medical practice if certain conditions are met. In the past the relationship between the use of CDS and the death of the patient has been debated. In 2003, the Vencken case illustrated this lack of clarity in how to evaluate the use of CDS for terminally ill patients.[17] Vencken was an anesthesiologist in training who had administered sedatives to a 77-year old terminally ill patient during his weekend shift. The patient suffered from severe dyspnea, and shortly after the provision of sedatives by Vencken, the patient died. He was accused of ending the patient's life by the Public Prosecution Service and by the Dutch Health and Youth Care Inspectorate. After years of juridical proceedings, Vencken was acquitted of a criminal offence.

Physician assisted dying and euthanasia are regulated by the Termination of Life on Request and Assisted Suicide (Review Procedures) Act in the Netherlands since 2002.[18] Under this law, the practice of physician-assisted suicide and euthanasia by physicians is reviewed by a committee, which assesses in retrospect if all due care criteria were met.[18] It has been argued that CDS should also be reviewed by such an external committee.[19,20] It was argued that starting CDS and simultaneously withholding nutrition and hydration could result in the death of the patient, and that CDS therefore should be evaluated in the same way as euthanasia.[19] In 2005, the RDMA stated that, in contrast to physician-assisted

suicide and euthanasia, CDS should be considered as a normal medical practice, and that the Dutch Medical Treatment Contract Act (WGBO) applies to the use of CDS. By the introduction of the national guideline on palliative sedation in 2005 differences between CDS and life-ending practices like euthanasia could be outlined.

The RDMA guideline and conditions for sedation

For medical professionals, there was a need for a guideline with protocols that could be used in clinical practice.[21,22] To guide responsible practice, the RDMA in 2005 developed a national guideline in the Netherlands to clarify questions and misunderstandings about palliative sedation on a conceptual level and in actual practice. The guideline was updated in 2009, and more recently in 2022. The updated version of the guideline in 2022 emphasizes the cooperation of different health care professionals, comprises changes in medication schedules, and better clarifies intermittent and acute sedation.[23] The different studies in this thesis were carried out under the guideline of 2009.

The premise of the guideline is that the use of palliative sedation is, under certain circumstances, to be considered as normal medical practice. The guideline distinguishes different forms of sedation, and describes that continuous palliative sedation is administered in the final stage of life to patients who are dying and experiencing unbearable suffering. The RDMA guideline describes that the use of CDS differs in its aim from euthanasia because the aim of CDS is to relieve suffering and not to shorten a patient's life. Preconditions to start continuous sedation are that the patient suffers from one or more refractory symptoms, and that the patients' death is nearby, what means that the life-expectancy of the patient does not exceed more than two weeks. A symptom can be called refractory when there are no treatment options to relieve the suffering, or when treatment options do not work quickly enough. Core elements of the guideline are presented in table 2.[23]

Table 2. Core elements of the RDMA guideline on the use of Continuous sedation

1.	Continuous sedation is always administered in the final stage of life. The patients concerned are dying and experiencing unbearable suffering
2.	Continuous deep sedation differs from euthanasia in that its aim is not to shorten life
3.	Medical indications are present when one or more intractable or 'refractory' symptoms are causing the patient unbearable suffering. A symptom is considered to be refractory if none of the conventional modes of treatment is effective or fast acting enough, and/or if these modes of treatment are accompanied by unacceptable side-effects
4.	A precondition for the use of continuous sedation is the expectation that death will ensue in the reasonably near future – that is, within two weeks. Next to physical suffering, existential suffering can also play a role in determining if suffering is unbearable and refractory
5.	If indications are present and preconditions have been met, palliative sedation could be considered as a patient's right
6.	The general rule is that palliative sedation should not be initiated without the consent either of the patient himself or, if he is decisionally incompetent, his representative
7.	When a physician has doubts regarding his own expertise or has difficulty balancing the different considerations involved in deciding whether to start CDS, it is standard professional practice to consult the appropriate expert in good time
8.	Midazolam is the preferred drug of choice
9.	In principle, there is no artificial administration of fluids during the provision of continuous Sedation

Characteristics of patients receiving CDS

The use of CDS increased in the Netherlands between 2005 and 2015 from 8.2% to 18.3%. In 2005 most patients receiving CDS were under the care of a clinical specialist.[6] In the same year, most of the patients were younger than 80 years of age, while the majority of people who died were older than 80 years of age.[6] The majority of patients receiving CDS in 2005 were suffering from cancer or cardiovascular diseases.[6] It could be that the use of CDS increased more in patients with specific characteristics. Insight in these patient characteristics is important to better understand why the increase in CDS occurred over the years.

The use of CDS in the Netherlands in comparison to other countries

CDS is frequently used in many countries in different settings to relieve suffering of terminally ill patients.[24,25] Guidelines vary in their definition of the practice, indication for CDS, withholding artificial nutrition and hydration, medication, and timing of sedation.[26,27]

In the Netherlands repetitive nationwide questionnaire studies on the use of CDS make it possible to observe trends in the use of CDS. It is unknown if the increase in CDS also takes place in other countries. Insight in these practices could point towards explanations for the increase in CDS, e.g. in whether it is due to country-specific reasons, or to more generalizable factors.

Patients' symptoms for which CDS could be indicated

Symptoms that commonly require sedation are pain, dyspnea, terminal delirium, and restlessness.[28]

Swart et al. showed that the indication for CDS often originates from a combination of physical and nonphysical problems, resulting in a refractory state in which a patient suffers unbearably.[29]

The increase in CDS raises questions on the symptoms for which CDS is used. It could be that symptoms for which patients require CDS changed over time. A potential explanation for the increase is that CDS is increasingly used for patients without refractory symptoms.[6] Several studies report on symptoms in terminally ill patients.[30,31] Yet, studies about patients' symptoms in their last hours to days of life are limited.

Experiences and practices of health care professionals

Since the introduction of the national guideline on palliative sedation in 2005, the practice of CDS by physicians largely reflected the recommendations of the guideline.[32] It could be that, since the introduction of this guideline, health care professionals are more aware of CDS as an option to relieve severe suffering in terminally ill patients. It could also be that health care professionals better recognize refractory suffering in terminally ill patients, and therefore start sedation earlier.

Studies among nurses showed that they felt distressed when they felt that CDS was indicated, but the physician thought that palliative sedation was not an option yet.[33] Some studies show that health care professionals experience a pressure to start CDS.[12,32] It could be that this pressure increased and health care professionals are more inclined to start CDS. Little is known about the experiences and practices of health care professionals with the decision-making about and provision of CDS.

Expectations and experiences of patients and relatives

The most recent version of the guideline on palliative sedation states that patients or their surrogates, relatives, or health care professionals can initiate the conversation about the start of CDS. The guideline considers the use of CDS as a patient's right in case criteria to start are met.[23] Studies on the experiences of relatives with CDS showed that relatives generally look back positive on the use of CDS with their family member, but some relatives had discontent with information provision and communication.[34] Some studies showed that CDS was used without involving the patient and relatives in the decision-making.[34] It could be possible that CDS is increasingly used without involving the patient and relatives in the decision-making process.

Studies on the experiences of relatives with the use of CDS are often performed from the perspective of the health care professional. Literature on how relatives experience the suffering of their relatives and the decision to start CDS for these is limited. It is argued that CDS is used not only to relieve suffering of the dying patient, but also to provide comfort for the relatives involved. It could be possible that CDS is increasingly used for this indication.

Furthermore, an increasing number of patients would request for euthanasia in case of severe suffering. It could be possible that patients consider CDS as a suitable alternative option for euthanasia in case of severe suffering. Insight in the perspectives of patients and relatives is important to better understand current practices, and to better guide these patients and their relatives in the last phase of life.

Research questions addressed in this thesis

The previous paragraphs point to several knowledge gaps that lead to a number of research questions. The research questions of this thesis are:

1. What are the characteristics of the patients who received CDS, and did the characteristics of these patients change over the years?
2. Did the use of CDS change over the years on an international level?
3. What are symptoms that patients experience at the end of life for which CDS could be indicated?
4. What are the perspectives of health care professionals who use CDS for their patients and how did their perspectives change over the years?
5. What are patients' expectations about CDS and what are the experiences of relatives of patients who received CDS?

Outline of this thesis

This thesis is divided into 8 chapters. To answer the first research question, in **chapter two**, a nationwide questionnaire study in the Netherlands among physicians attending reported death is presented. This study aims to provide more insight into developments in the practice of continuous deep sedation until death in the Netherlands.

In **chapter three** a systematic literature review is presented, which was conducted to explore if there is an increase in the use of CSD between 2000 and 2020, and to provide insight into the indications to use CSD during this period.

In **chapter four** a retrospective descriptive analysis of data from registrations in the Care Program for the Dying provides is described, which gives insight in the evolvement of symptoms in patients who are in the last hours to days of life by analyzing to what extent symptom-related goals of care are achieved, and provides insight in differences in the occurrence of symptoms between different health care settings, according to the third research question of this thesis.

In **chapter five** an international questionnaire study is presented among physicians caring for terminally ill patients about their experiences and practices on CDS in eight resource-rich countries: Belgium, Germany, Italy, Japan, the Netherlands, Singapore, the United Kingdom, and the United States. Together with the systematic literature review of chapter three, this study provides insight in changes the use of CDS on an international level, and provides an answer to the second research question of this thesis.

In **chapter six** a qualitative interview study among Dutch health care providers experienced in providing CDS is reported, which explores potential causes of the rise in the use of CDS in the Netherlands. This study aims to provide an insight in the perspectives of health care professionals who use CDS for their patients and aim to describe how their perspectives changed over the years, according to research question four of this thesis.

In **chapter seven**, a qualitative interview study among Dutch patients and relatives is presented, which explores the expectations and experiences of patients and relatives with CDS. Patients expectations about CDS and the experiences of relatives of patients who received CDS are explored. This chapter provides an answer on research question five.

In **chapter eight** the general discussion is presented. This chapter summarizes the results of the different chapters, provides a reflection on the changed practices in the use of CDS and on the increase in use of CDS in the Netherlands. Strengths and limitations of this thesis are reported in this chapter, recommendations are made and this thesis ends with a final conclusion.

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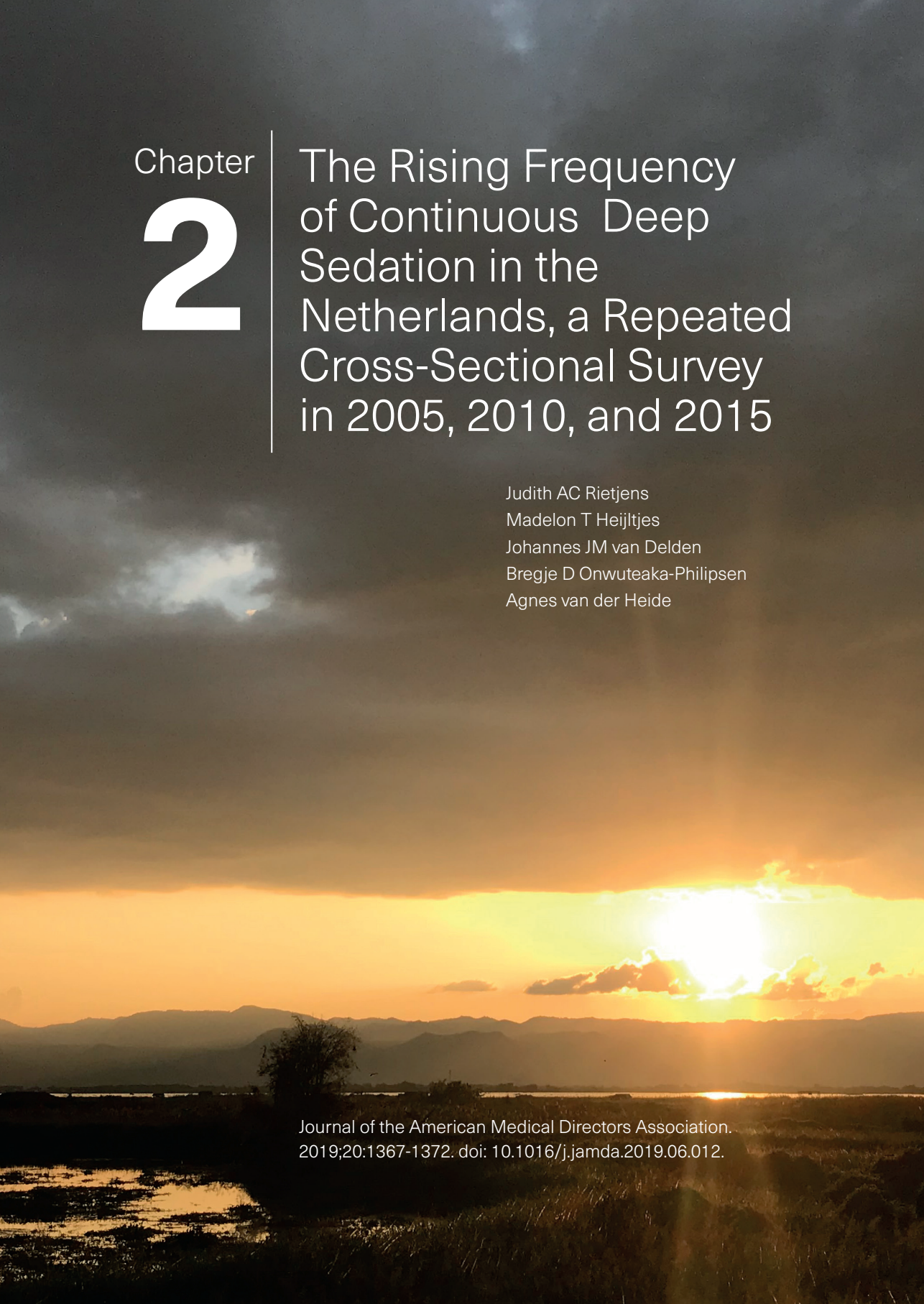

Chapter

2

The Rising Frequency of Continuous Deep Sedation in the Netherlands, a Repeated Cross-Sectional Survey in 2005, 2010, and 2015

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Abstract

Objectives
In the Netherlands, the use of continuous deep sedation at the end of life has sharply increased from 8.2% of all deaths in 2005 to 12.3% in 2010 to 18.3 % in 2015. We describe its clinical characteristics in 2015 and compare it with 2010 and 2005.

Design
Questionnaire study in random samples of death reported to a central death registry.

Setting and Participants
A nationwide study in the Netherlands among physicians attending reported deaths.

Methods
CDS characteristics (patient characteristics, drugs, duration, estimated shortening of life, palliative consultation) from the Netherlands in 2015 were compared with CDS characteristics of 2010 and 2005.

Results
The response rate was 78% (n=7277) in 2015, 74% (n=6263) in 2010 and 78% (n=6860) in 2005. The increased frequency of CDS was notable in all patient subgroups, but mainly occurred among deaths attended by general practitioners, particularly in patients older than 80 years and patients with cancer. In 2015, CDS was in 93% performed through administration of benzodiazepines. In 3%, the sedation lasted more than one week. 60% of physicians reported they had no intention to hasten death, 38% to have taken hastening of death into account, and 2% reported their intention was to hasten death. For one in five patients, an palliative care expert was consulted prior the start of sedation. These characteristics were comparable between 2015 and 2010.

Conclusions and Implications
The increase in CDS mainly occurred in deaths attended by general practitioners, especially in older patients and patients with cancer. As there are no major shifts in demographic and epidemiological patterns of dying, future studies should investigate possible explanations for the increase predominantly in societal developments, as increased attention to sedation in education and society, a broader interpretation of the concept of refractoriness, and an increased need to control the dying process.

Introduction

Patients nearing death may experience severe symptoms, such as pain, dyspnea and delirium.[1] When these symptoms are difficult to treat, sedating drugs can be used to decrease the patient's consciousness, as a treatment option of last resort. Sedatives can be used intermittent or continuously, and the depth of the sedation can vary from reduced consciousness to unconsciousness. These different practices are usually covered by the term palliative sedation.[2, 3]

Debates about the use of sedation in end-of-life care typically focus on the most far-reaching type of sedation: continuous deep sedation until death. In the past decades, several guidelines have been developed to support the proper use of palliative sedation, in the Netherlands and beyond. Core conditions of the Dutch guideline[4] are that palliative sedation is a last resort alternative for the alleviation of refractory symptoms only if palliative care is optimal, to be used for patients with a life expectancy of days, at most 1-2 weeks. The most common indications for palliative sedation include agitated delirium, dyspnea and pain.[5] There is less consensus on the appropriateness of sedation for severe non-physical symptoms such as refractory depression or anxiety.[5] The Dutch guideline recommends that benzodiazepines should be the first choice medication, via subcutaneous administration, that hydration should be offered to sedated patients only when its benefits outweigh the harms, and that the intention of the sedation should not be to shorten life.[6, 7] The guideline further argues that the medications should be administered by clinicians (usually a physician or a nurse), that the responsible physician should be present at the start of sedation and monitors the patient at least once a day.[7] Also, where a physician has doubts regarding his expertise, the guideline states that it is standard professional practice to timely consult an appropriate expert. Such consultation is mandatory when it is hard to judge whether the patient actually is in the final stages of life. In addition, the guideline recommends to consult an expert in the areas of psycho-social and spiritual problems in case of existential suffering.[7] By these recommendations, guidelines position *lege artis* palliative sedation within normal medical practice, and distinguish it from practices that intentionally shorten life, such as euthanasia. Questionnaire studies among physicians in 2005 and 2008, showed that the practice of continuous deep sedation in the Netherlands, largely reflected the recommendations of the national guidelines.[8, 9] In 81% of the cases, physicians were present at the start of sedation, 53% of the respondents indicated that they had used the national guideline on palliative sedation for their last patient receiving CDS, and 10% reported that they had used another guideline.[9] A qualitative study of Seymour et al. in 2015 showed that healthcare providers in the UK, the Netherlands and Belgium described different practices of sedation at the end of patients' lives. UK respondents reported a continuum of practice from

the provision of low doses of sedatives to control terminal restlessness to rarely encountered deep sedation.[10] In contrast, Belgian respondents predominantly described the use of deep sedation, emphasizing the importance of responding to the patient's request. Dutch respondents emphasized making a formal medical decision informed by the patient's wish and establishing that a severe refractory symptom was present.[10]

In 2015, as part of a larger study that evaluated the Dutch Euthanasia Act, we repeated a large scale nationwide study in the Netherlands that was also carried out in 2010 and 2005.[11] One of the main conclusions of this study was that the use of continuous deep sedation until death has sharply increased in the past 15 years: from 8.2% of all deceased patients in 2005, to 12.3% in 2010, up to 18.3% of all patients in 2015. As rendering patients unconscious until death is a far reaching intervention that has an important impact on the dying process for both the patient and the relatives,[12] we aim to provide more insight in developments in the practice of continuous deep sedation until death in the Netherlands in this paper.

Methods

Study design and data collection

In 2015, we drew a stratified sample of death certificates from the central death registry of Statistics Netherlands to which all deaths and causes of death are reported. All deaths that occurred between August and November 2015 were assigned to different strata, according to circumstances of death.

Physicians who had reported a death in a sample where an end of life-decision had been possible, received a questionnaire. The data collection procedure included anonymity of physician and patient. According to Dutch policy, the study did not require review by an ethics committee. The 2010 and 2005 studies had a similar design and similar procedures.[11, 13, 14]

Questionnaire

The attending physician was asked whether death had occurred suddenly and unexpectedly. If cases were reported as non-sudden, the physician was asked to further complete a questionnaire about the medical decision making that had preceded death. Of the 9351 questionnaires sent out, 7277 were completed and returned (78% response). The response percentage in 2010 was 74% (6363/8496) and in 2005 it was 78% (5342/6860). In 2015 and 2010, the question that pertained to continuous deep sedation was: "Was the patient continuously and deeply sedated until death?" (yes/no). In 2005, the question was: "Was the patient continuously and deeply sedated or kept in coma until death?" (yes/no). In

all years, follow-up questions were: "Which medication was given for sedation?" (midazolam, other benzodiazepine, morphine or a morphine derivative, or other types of medication); "How long before the patient's death was continuous sedation started?" (indication of the number of hours, days, weeks); and "Was artificial nutrition or hydration administered?" (yes/no). In 2015 and 2010, physicians were also asked: Continuous deep sedation, whether or not combined with the use of artificial nutrition and/or hydration, was used A. considering that death would not be hastened; B. taking into account the hastening of death; or C. with the intention to hasten death. In addition, in all studied years, the questionnaire contained questions referring to whether experts in palliative care were consulted during the month before death, and whether the patient had made an explicit request to end life that was not granted, including the reasons for not granting the request. We collected data regarding the patient's age, sex, and cause of death from the death certificate. Selection bias was probably rather limited given the high response rates. Recall bias was reduced by sending the questionnaire to the responsible physicians at most three months after the patient's death.

Analyses

The percentages reported are weighted to adjust for sampling fractions and differences in response by patients' gender, age, marital status, region of residence, and place and cause of death. After adjustment, we extrapolated the percentages to cover a 12 month period to reflect all deaths in the Netherlands in 2015. A comparable procedure was followed in 2010 and 2005.[14] We excluded missing values when these comprised less than 5% of all cases. We calculated confidence intervals for the main findings. Statistical analyses were performed with IBM SPSS Statistics 24.

Patient public involvement (PPI)

Our project involved PPI: one of the project members is a relative of a patient who received continuous deep sedation prior to death. After she has provided critical comments to our manuscript, the text was adjusted accordingly.

Results

Table 1 shows the frequency of continuous deep sedation in the Netherlands, by specialty of the physician who had attended a death. The increase in the use of continuous deep sedation occurred among all specialties. In 2015, the percentage of patients who received continuous deep sedation was 20.7% (CI 19.2-22.2) for deaths attended by general practitioners, 18.4% for deaths attended by clinical specialists (CI 16.0-21.0), and 14.3% for deaths attended by elderly care physicians (CI 12.4-16.4). Fifty-five percent of all sedations were performed by a general practitioner, 24% by a clinical specialist, and 21% by an elderly care physician (not in table).

Table 2 shows that the increase in the use of continuous deep sedation was most prominent in patients older than 80 years, especially those attended by general practitioners (20.4% of these patients received continuous deep sedation in 2015 compared to 9.4% in 2010 and 4.9% in 2005), and patients with cancer, again especially those attended by general practitioners (31.6% in 2015 compared to 18.5% in 2010 and 12.7 in 2005). Among patients who died as a result of cardiovascular diseases while being attended by a general practitioner, the use of continuous deep sedation more than doubled: 10.0% in 2015 compared to 4.2% in 2010.

Table 1. Frequency of the practice of continuous deep sedation in patients dying in 2015, 2010 and 2005 (percentages [1] of patients with 95% confidence intervals)

Deaths attended by general practitioners			Deaths attended by clinical specialist			Deaths attended by elderly care physician			Total	Total	Total
2005 N=2450	2010 N=3424	2015 N=4381	2005 N=1440	2010 N=1588	2015 N=1438	2005 N=1142	2010 N=1248	2015 N=1459	2005 N=9965	2010 N=6861	2015 n=7661
7.4 (6.4 to 8.6)	11.8 (10.6 to 13.2)	20.7 (19.2 to 22.2)	11.9 (10.0 to 14.1)	16.2 (14.1 to 18.6)	18.4 (16.0 to 21.0)	6.4 (5.1 to 8.0)	9.1 (7.5 to 10.9)	14.3 (12.4 to 16.4)	8.2 (7.4 to 9.0)	12.3 (11.4 to 13.3)	18.3 (17.3 to 19.5)

[1] Weighted for sampling fractions, non-response, and random sampling deviations.

Table 2. Frequency of the practice of continuous deep sedation in subgroups of deceased patients in 2015, 2010 and 2005 (percentages[1] of patients with 95% confidence intervals)

	General practitioners			Clinical Specialist			Elderly care physician			All physicians		
	2005 N=2450	2010 N=3424	2015 N=4381	2005 N=1440	2010 N=1588	2015 N=1438	2005 N=1142	2010 N=1248	2015 N=1459	2005 N=9965	2010 N=6861	2015 n=7661
Age at death (years):												
0-64	11.1	13.6	18.9	14.6	16.7	19.4	15.4	10.0	23.5	11.0 (9.3 to 13.0)	14.0 (12.0 to 16.3)	19.3 (16.9 to 21.8)
65-79	8.7	14.6	22.1	13.0	18.6	23.6	7.3	14.0	17.9	9.5 (8.0 to 11.2)	15.6 (13.8 to 17.6)	21.7 (19.7 to 23.8)
>80	4.9	9.4	20.4	9.1	14.5	13.2	5.4	7.4	12.7	6.2 (5.1 to 7.4)	9.7 (8.5 to 11.2)	16.2 (14.7 to 17.7)
Gender:												
Male	7.6	11.5	20.1	13.3	17.5	19.6	7.1	9.1	16.5	8.8 (7.7 to 10.1)	12.7 (11.4 to 14.2)	19.2 (17.7 to 20.8)
Female	7.3	12.5	21.2	10.3	15.3	16.9	5.9	9.2	12.9	7.6 (6.5 to 8.8)	12.0 (10.7 to 13.4)	17.6 (16.1 to 19.1)
Cause of death:												
Cancer	12.7	18.5	31.6	14.1	19.5	25.0	13.1	17.5	21.0	13.2 (11.9 to 14.5)	18.6 (17.1 to 20.1)	28.9 (27.3 to 30.6)
Cardiovascular disease	2.8	4.2	10.0	7.2	15.7	11.4	5.7	7.7	7.8	10.0 (8.1 to 12.3)	9.0 (7.2 to 11.3)	10.0 (8.1 to 12.3)
Pulmonary disease	3.2	11.5	15.9	9.0	19.6	22.1	0.8	7.1	12.6	17.5 (13.7 to 22.2)	12.9 (9.7 to 16.8)	4.9 (2.7 to 8.6)
Neurological disease	5.9	13.7	12.6	15.8	14.1	12.1	12.7	8.3	14.7	13.6 (10.8 to 17.0)	11.4 (8.4 to 15.5)	12.2 (7.3 to 19.6)
Other/ unknown	4.4	5.4	14.5	17.6	13.2	19.1	4.8	6.8	13.9	15.4 (13.2 to 17.9)	8.0 (6.2 to 10.2)	(6.3 to 10.2)

1. Weighted for sampling fractions, non-response, and random sampling deviations.

Table 3. Characteristics of the practice of continuous deep sedation in 2015, 2010 and 2005 (percentages of physicians)

	General practitioners			Clinical Specialist			Elderly care physician			All physicians		
	2005 N=220	2010 N=400	2015 N=824	2005 N=179	2010 N=260	2015 N=246	2005 N=94	2010 N=129	2015 N=218	2005 N=521	2010 N=791	2015 N= 1310
Medication administered												
Benzodiazepines	43	50	45	16	27	22	46	47	51	32	41	41
Benzodiazepines and morphine	44	48	50	60	58	58	43	49	47	51	52	52
Morphine	13	2	2	19	12	7	10	3	0	15	6	3
Other medications	0	0	3	5	3	13	1	1	2	2	1	5
Artificial nutrition and hydration withheld	95	98	99	30	46	63	98	100	100	66	79	91
Continuous deep sedation was used												
without taking into account the hastening of death	NA	52	58	NA	62	62	NA	79	65	NA	61	60
taking into account the hastening of death	NA	47	40	NA	36	37	NA	21	34	NA	38	38
with the intention to hasten death	NA	2	3	NA	2	1	NA	0	1	NA	2	2
Duration of continuous deep sedation												
0-24 hours	43	46	46	50	57	62	42	52	48	47	51	50
1-7 days	52	54	51	38	36	33	58	45	49	47	46	46
1-2 weeks	3	0	1	7	4	2	0	2	1	4	2	1

>2 weeks	2	0	1	4	3	4	0	0	2	2	1	2	
Experts involved in care in last month of life													
Palliative care expert or consultation team	20	30	27	2	10	18	5	19	11	9	20	21	
Pain specialist	7	7	4	7	6	5	2	1	1	6	5	4	
Psychiatrist or psychologist	3	3	2	4	4	5	8	16	11	5	6	5	
Chaplain	15	12	11	7	5	11	34	30	22	15	12	13	

In 2015 and in 2010, continuous deep sedation was induced with benzodiazepines, often in combination with morphine, in 93% of all cases (Table 3). The use of morphine for sedation without a benzodiazepine decreased from 6% in 2010 to 3% 2015; in 2015 this percentage was 7% for clinical specialists, 2% for general practitioners, while none of the elderly care physicians used only morphine for sedation. In 91% of the patients who received continuous deep sedation in 2015, artificial nutrition and hydration were withheld. This percentage was 79% in 2010 and 66% in 2005. There were virtually no changes over time in physicians' reports about the intention with which they used continuous deep sedation, or in their reports about the duration of the sedation. In 2015, physicians reported for 60% of all cases that they used continuous deep sedation without taking into account the hastening of death, for 38% that they took into account the hastening of death, and in 2% that their intention was to hasten death. In 2015, the patient died within 24 hours after start of continuous sedation in 50% of cases, within 1-7 days in 46%, and in 3% the patient died after one week or later. In our study, we found that palliative care experts or palliative care consultation teams were consulted in the month before death in 21% of cases in 2015 (in 27% of the cases that were attended by general practitioners), pain specialists in 4%, a psychiatrist or psychologist in 5% and a chaplain in 15%. The 2015 data on such consultation were virtually the same as in 2010.

Discussion

Summary of key findings

The increased frequency of continuous deep sedation until death involved patients in all age groups and patients with different causes of death, but was particularly notable among deaths that were attended by general practitioners, especially in patients older than 80 years and for patients dying from cancer. Over time, there were virtually no differences in how continuous deep sedation was provided: nearly all cases involved the administration of a benzodiazepine, with half of the cases having a duration of less than 24 hours, and a fifth of the cases being preceded by consultation of an expert in palliative care.

Strengths and limitations of the study

The large random samples of deaths and the high response rates in the three study years support the generalizability of our findings to all deaths in the Netherlands. Validity and reliability of our results is further strengthened by the use of a similar study design in the three study years and by guaranteed anonymity of physicians and patients. To minimize possible differences in respondents' interpretation of the concept of sedation we provided them with a descriptive definition of the practice (continuous deep sedation until death). While this study does not provide clinical characteristics of continuous deep sedation, the Dutch palliative sedation guideline recommends to use benzodiazepines as a first choice of drugs, administered subcutaneously.[7] A limitation of our study is that we did not ask about patients' symptoms and refractoriness of the suffering, nor about the request of patients or their family for CDS. Lastly, our results cannot automatically be generalized to practices outside the Netherlands. Future research should be conducted in other countries, with different models of care, different legal jurisdictions, and different practices of palliative sedation, to enhance our understanding to what extent our findings are generalizable.

Interpretation

A similar increase in the use of continuous deep sedation was observed in a Swiss study with a comparable design and questionnaire, where continuous deep sedation until death rose from 4.7% of all deaths in 2001 to 17.5% in 2013.[15] These trends contrast with Flanders (Belgium), where the initial rise of continuous deep sedation from 8.2% in 2001 to 14.5% in 2007 was followed by a decrease to 12.0% in 2013.[16, 17] As there is no indication of major shifts in demographic and epidemiological patterns of dying in the past decade in the Netherlands, we believe that explanations for the increase in its use should be sought predominantly in societal developments.

First of all, in the studied years, palliative sedation (including the use of CDS), has been increasingly debated in the Netherlands, among experts and in the news and popular media. In addition, in 2014, a large scale national program was initiated, aimed at further improving palliative care in the Netherlands through awareness campaigns and financial support.[18] Both could have led to an increased interest in palliative care and palliative sedation among physicians, patients and relatives.

Second, it could be that physicians' interpretation of the concept of "refractory symptoms", which is central in the palliative sedation guideline, has changed over time.[6] The Dutch nationwide palliative sedation guideline, issued in in 2005 and updated in 2009[7, 19] adopts a rather "open" and broad concept of refractory symptoms: a symptom is considered to be refractory "if none of the conventional modes of treatment is effective or fast-acting enough, and/or if these modes of treatment are accompanied by unacceptable side effects". The updated 2009 guideline provides two elaborations. First of all, it makes explicit that refractoriness can be context dependent. For instance, certain symptoms can be refractory in home care (where less interventions may be available) but not so in a hospital. Second, it states that existential suffering can be considered a refractory symptom as well. Indeed, Swart et al. showed in a qualitative interview study that physicians typically adopt a rather comprehensive concept of refractoriness, and often refer to a refractory "state" involving physical as well as nonphysical problems, rather than to refractory symptoms per se.[20, 21] This is in line with findings from an earlier Belgian qualitative study that found that in end of life home care, refractoriness is considered in a much broader context than just symptom based, also including patients with grave discomfort in the context of limited access to technical diagnostics and therapeutics, and pre-emptive sedation.[22] This study also showed that the decision-making process of GPs on whether to start sedation, was mostly influenced by the desire to alleviate the suffering of the patient, with the endurance of the caregivers in mind and to avoid hospital admission.[22]

Third, it may be possible that the use of continuous deep sedation until death has increasingly been used for patients *without* refractory symptoms, and as such has lost its status of "last resort option". Findings from the UNBIASED study resonate with this hypothesis: several of the interviewed Dutch physicians in that study described continuous sedation as enabling a "natural" death.[10, 23] Actual or expected suffering in the last days of life is nowadays possibly less tolerated by patients, family caregivers and clinicians, as part of an increased need to have a sense of control over the last days of life. The finding that euthanasia has increased from 1,7% to 4,5% of all deaths and intensified alleviation of symptoms from 24,7% to 35,8% in the period 2005-2015 supports this reasoning.[13] The increased need of patients to control their dying process is also illustrated by the trend of increasing patient and family demand for CDS.[10, 17]

It is important to realize that the open, broader concept of refractoriness makes it not always straightforward to judge whether a symptom is refractory.

Unanswered questions and future research

Insight in the refractory symptoms of patients who receive continuous deep sedation will add to our understanding of the practice, especially with respect to the clinical context and the role of existential suffering. As there are no major shifts in demographic and epidemiological patterns of dying, future studies should study possible explanations for the increase predominantly in societal developments, such as increased attention to sedation in education and society, a broader interpretation of the concept of refractoriness, and an increased need of patients and physicians to control the dying process. Special attention should be paid to those groups where the frequency of CDS is highest, these are patients attended by the GP, older patients, and patients with cancer. Future ethical reflections should focus on whether and under which circumstances a far reaching medical practice such as CDS until death is an acceptable response to severe suffering at the end of life. In order to achieve shared decision-making, it is also important to know what the needs and preferences of patients and their relatives are. Future studies should also address how judgment of refractory symptoms is related to physicians' experience and knowledge of palliative care, and how consultation of a palliative care expert may affect the decision-making of CDS. For instance, on the one hand, it is sometimes argued that mandatory consultation before the start of the sedation may result in fewer sedations.[24] On the other hand, it is also argued that such mandatory consultation may not be feasible.[25]

Conclusions and implications

The practice of continuous deep sedation until death has sharply increased over the past 15 years and was used in 18% of all deaths in 2015. The increase occurred in all subgroups of patients, but particularly among deaths attended by general practitioners, in patients older than 80 years and patients dying from cancer. It is important to pay attention to CDS in the training of physicians. In particular in clinical specialties where the frequency of CDS is the highest, that is, physicians working in long term care, GPs and oncologists. The focus should be on learning how to use the palliative sedation guideline, the judgment of refractory suffering, when to consult a palliative care team and on shared decision-making with patients and their relatives. The use of effective models like moral case deliberations could be used to learn physicians to apply their knowledge in clinical practice.[26]

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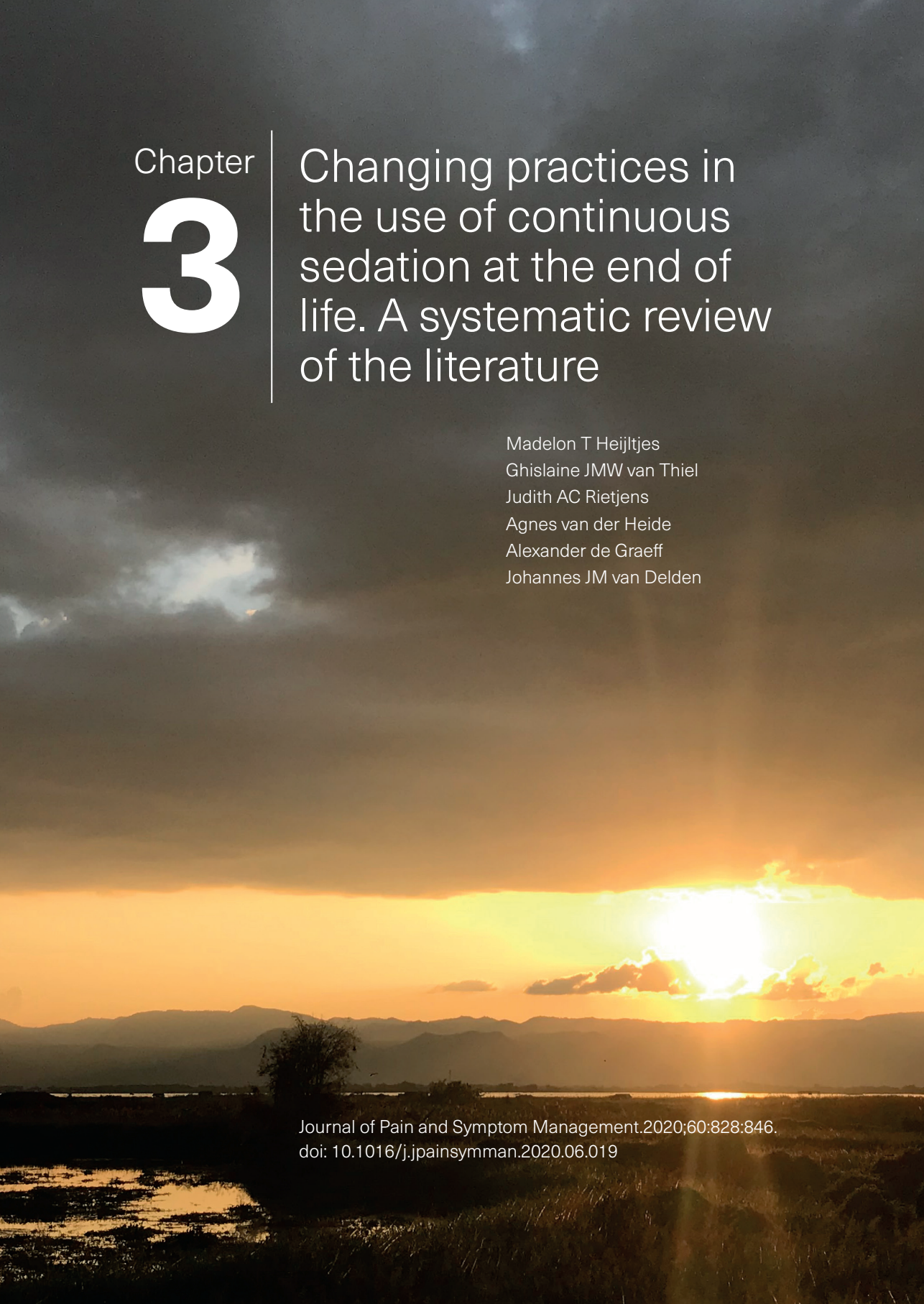

Chapter

3

Changing practices in the use of continuous sedation at the end of life. A systematic review of the literature

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Abstract

Background
The use of continuous sedation until death (CSD) has been highly debated for many years. It is unknown how the use of CSD evolves over time. Reports suggest that there is an international increase in the use of CSD for terminally ill patients.

Objective
To gain insight in developments in the use of CSD in various countries and subpopulations.

Design
We performed a search of the literature published between January 2000 and April 2020, in Pubmed, Embase, CINAHL, Psycinfo and the Cochrane Library by using the PRISMA guidelines. The search contained the following terms: continuous sedation, terminal sedation, palliative sedation, deep sedation, end-of-life sedation, sedation practice, and sedation until death.

Results
We found 23 articles on 16 nationwide studies and 38 articles on 37 subpopulation studies. In nationwide studies on deceased persons frequencies of CSD varied from 3% in Denmark in 2001 to 18% in the Netherlands in 2015. Nationwide studies indicate an increase in the use of CSD. Frequencies of CSD in the different subpopulations varied too widely to observe time trends. Over the years more studies reported on the use of CSD for non-physical symptoms including fear, anxiety, and psycho-existential distress. In some studies, there was an increase in requests for sedation of patients and their families.

Conclusions
The frequency of CSD seems to increase over time possibly partly due to an extension of indications for sedation, from mainly physical symptoms to also non-physical symptoms.

Key message
The aim of this literature review was to gain insight in the use of CSD over time in different countries and subpopulations. The frequency of CSD seems to increase, possibly (partly) due the extension of indications for sedation, from only physical symptoms to also non-physical symptoms.

Introduction

In the last phase of life, patients may suffer from severe symptoms.[1, 2] Continuous sedation until death (CSD) is a last option for these patients when intolerable suffering cannot be relieved by regular symptom treatment. The use of CSD has been highly debated for many years.[3 - 5] The inability of patients during CSD to communicate in the last phase of their lives and the potential of CSD to hasten death are important issues in this debate.[6-8] In addition, the appropriateness of CSD for symptoms of non-physical origin like fear, anxiety, and psycho-existential distress is controversial, as determining these symptoms as refractory may be subjective and complex.[8-10] It is unknown how frequencies and reasons to start CSD evolved over time in clinical practice. Reports suggest that there is an increase in the use of CSD.[4, 11, 12]

The aim of this review is two-fold. Our first aim is to explore if there is an increase in the use of CSD between 2000 to 2020. Our second aim is to provide insight in the indications to use CSD during this period. This insight is important, as it will contribute to a better understanding of current practices in end-of-life care and inform further discussion on the use of CSD.

Definitions of sedation

A variety of terms, concepts and definitions is used in the literature to describe the use of sedation for the relief of intolerable suffering at the end of patients' lives.[7, 13, 14] Continuous sedation, terminal sedation, palliative sedation, deep sedation, end-of-life sedation, and sedation until death are among these terms. The type of sedation varies from intermittent to continuous until the end of life. The depth of sedation varies from superficial to deep. Despite efforts to achieve consensus in terms and definitions of sedation, there are still many inconsistencies in the literature.[15, 16] The same holds for guidelines on the use of CSD.[17, 18] These inconsistencies complicate the debate on the use of sedation. In this literature review, we focused on continuous sedation until death.

Methods

Search strategy

On the 15th of April 2020, we performed a literature search in Pubmed, Embase, CINAHL, Psycinfo and the Cochrane Library, using the PRISMA criteria for this report.[19] The search included the following terms: continuous sedation, terminal sedation, palliative sedation, deep sedation, end-of-life sedation, sedation practice and sedation until death. The complete search, listed in supplementary table 1, was verified by our information specialist to ensure that the search was correct and complete.

The search was limited to articles in Dutch or English published between January 2000 until April 2020.

Study selection
After defining the selection criteria with all authors, study selection was performed by MH and GvT. We used the online program Rayyan for the title and abstract screening, a web application for systematic reviews.[20] We selected studies that reported frequencies of the use of continuous sedation, in English or Dutch language. Studies that described sedation as continuous, and until the end of life, or where the results of the article indicated that the sedation was given continuously, and until the end of life were included. Articles describing other forms of sedation, articles without frequencies of continuous sedation, studies with less than 100 patients and comments on articles were excluded. Conflicting judgments in article selection were resolved in discussions between MH and GvT.

Data extraction
The following data were extracted: title, first author, year of publication, period of data collection, type of study, country, number of patients, number of deaths in the study, place of death, definition of sedation, number and percentage of use of CSD, specialty of the attending physician, whether a palliative care team was involved, patients' symptoms, details on the decision-making process and characteristics of the sedation.

Synthesis
In our description of changes in the use of CSD over time, we distinguish nationwide studies from studies in subpopulations. The changes in characteristics of sedation and in patients' symptoms requiring sedation are described for all included studies.

Assessment of methodological quality
To assess the methodological quality of the reviewed studies, we used an adapted version of the Revised Cochrane risk-of-bias tool for non-randomized trials (Robins I-tool), see supplementary table 2A. The quality of the reviewed studies was assessed independently by MH and by GvT, and inconsistencies in total score of bias were discussed. The tool consists of 6 elements of the study in which bias could have occurred:

1. Bias in selection of participants of the study: The risk of bias was considered as low when a clear description of the selection of participants was given, and when patients who received continuous sedation were selected via the same procedure as patients who did not receive continuous sedation.

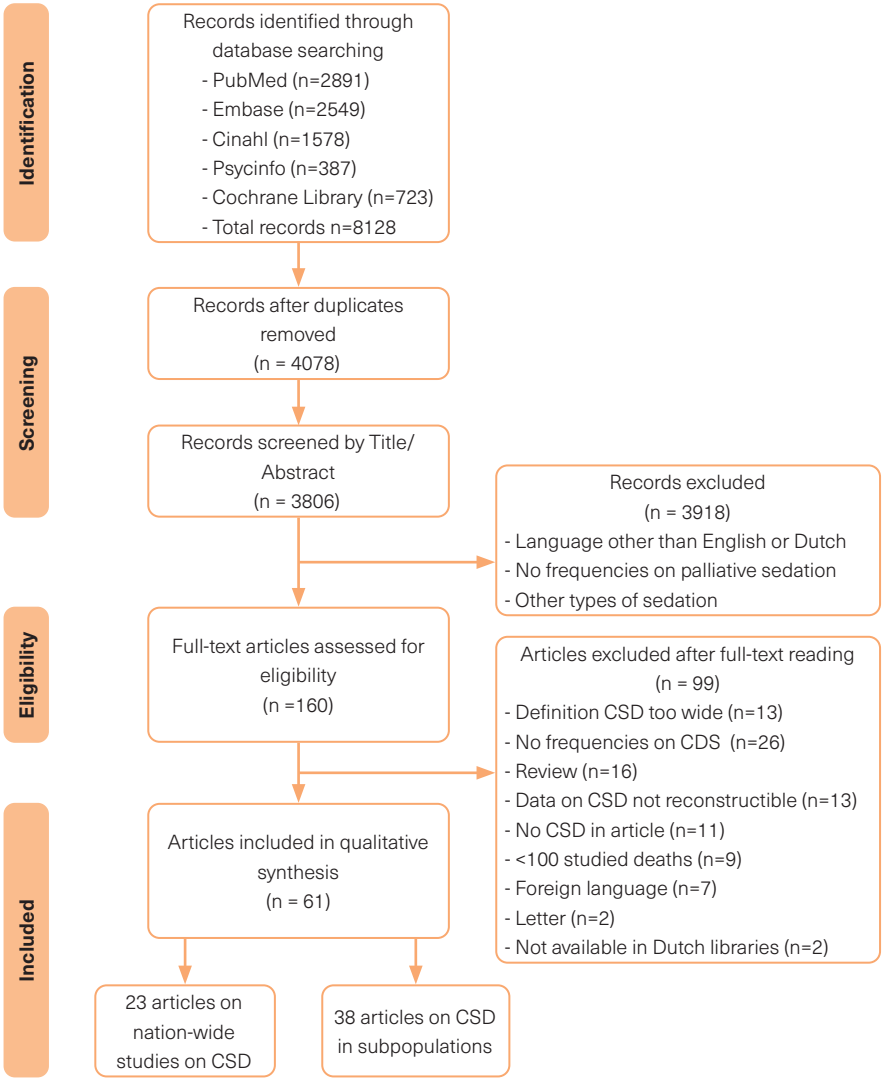
2. Bias in classification of interventions: The risk of bias was considered as low when a clear description of continuous sedation was provided, when sedation was described as continuous and until death, and when continuous sedation was clearly distinguished from intermittent sedation.
3. Bias due to missing data. The risk of bias was considered as low if there was a complete follow-up, or a loss to follow-up unlikely to introduce bias.
4. Bias in measurement of outcomes. The risk of bias was considered as low when data was collected prospectively by trained staff (physicians, nurses, researchers). The risk of bias was considered as higher when data was collected retrospectively, obtained from a database, or by self-report.
5. Bias in selection of the reported results. The risk of bias was considered as low when reported results of the study were in line with the research question and when the methods section of the study was well described.
6. Bias due to confounding: The risk of bias was considered as low when confounders were taken into account, and when these confounders were described in the article.

For each element the risk of bias was considered as low (1 point) or higher (2 points). A total score of ≤8 was considered as a low risk of bias. A total score of 9 or more was considered as a higher risk of bias.

Results

Figure 1 presents an overview of the selected articles. Initially, we found 8128 articles, and after removing duplicates, 4078 articles remained in our search. These articles were screened for eligibility based on title and abstract, which resulted in 160 articles being assessed based on the full text. 61 articles were finally included in our review, 23 articles on 16 nationwide studies, and 38 articles on 37 studies in subpopulations.[21-81] Table 1 shows the country, study period, study type, the total of patients investigated, how many patients received sedation, how sedation was defined, and the study population per study. Supplementary table 2B shows the risk of bias assessment of the included studies. We considered 22 out of 23 articles on nationwide studies to have a low risk of bias. Most studies had a retrospective design. The questionnaire studies reported a high response rate, included a description of loss to follow-up, and accounted for confounders. Only 11 out of 37 articles on subpopulation studies were considered to have a low risk of bias. In the other studies, definitions of CSD were lacking, missing data were not always described, and when comparing between subgroups confounders were not taken into account.

Figure 1. PRISMA flow diagram, overview of literature search



Frequencies of continuous sedation

We found 23 articles on 17 different nationwide studies that were performed in 7 countries: Belgium, Denmark, Italy, the Netherlands, Sweden, Switzerland and the United Kingdom (table 1). Table 2 shows characteristics of patients who received CSD in nationwide studies compared to all patients who died during the observed study period. CSD was more often applied in men than in women, in age groups below 80 years of age, in patients with cancer and in hospitals; in four of the studies these differences were statistically significant.[21, 29, 38, 43]

Frequencies of CSD were calculated in the articles by dividing the number of patients that received sedation by all deaths in the study. The frequency of CSD ranged between 3% in 2001 in Denmark and 18% in the Netherlands in 2015.[21, 38] Figure 2 displays CSD frequencies by year in each country.

Apart from the Netherlands, where the use of CSD increased from 8% of all deaths in 2005 to 12% in 2010 to 18% in 2015, an increase was also observed in Switzerland, from 5% of all deaths in 2001 to 18% in 2013.[37-39] After an initial increase in Belgium from 8% of all deaths in 2001 to 14% in 2007, the percentage decreased in 2013 to 12%.[29] For Denmark, Sweden, the United Kingdom, and Italy it was not possible to assess country-specific trends over time. The use of CSD increased in Switzerland, the Netherlands, and less clearly in Belgium between 2000 and 2020.

We found 38 studies that reported frequencies of CSD in subpopulations from 18 different countries (table 1). Subpopulations were children, patients above 80 years of age, cancer patients, patients with dementia, and patients with amyotrophic lateral sclerosis. CSD was delivered at home, in hospices, nursing homes, inpatient palliative care units and hospitals. In most subpopulation studies, the percentage of CSD was calculated by dividing the number of patients who received CSD by all patients who died during the observed period. In three studies the frequency of CSD was calculated by dividing the number of patients that received sedation by the number of all admitted patients.[51, 65, 66] In one study the percentage of sedation was calculated by dividing the number of patients who received CSD by the consultations by a palliative care team.[54] Frequencies of CSD varied in these subpopulation studies from 1% in Japan between 2005 and 2011 in cancer patients in a palliative care unit to 80% in the United Kingdom in 2010 in hospice patients.[67, 80]

Table 1. Nationwide and subpopulation studies on continuous deep sedation

Nation, year study Inclusion period (reference)	Study type	Total patients investigated	Patients who received CDS, no (%)	Definition of sedation	study population
		Nationwide studies			
Belgium, 2001 2001,06-2002,02 (21)(22)(23)(24)(25)	Questionnaire study among physicians on death certificates, stratified deaths	2950	238 (8,2)	The patient was kept in continuous deep sedation until death.	nationwide deaths
Belgium, 2005-2006 2005,01-2006,12 (26)	Questionnaire study among physicians on death certificates, stratified deaths	1629	177 (10,9)	A patient being deeply and continuously sedated or in a coma until death, by means of e.g. benzodiazepines or barbiturates (continuous deep sedation).	nationwide deaths
Belgium, 2007 2007,6-11 (23)(24)(27)(28)(29)	Questionnaire study among physicians on death certificates, stratified deaths	3623	561 (14,5)	Continuous and deep sedation until death.	nationwide deaths
Belgium, 2013 2013,01-07 (29)	Questionnaire study among physicians on death certificates, stratified deaths	3751	438 (12)	The patient was continuously and deeply sedated or kept in a coma until death by the use of one or more drugs.	nationwide deaths
Denmark, 2001 2001,06-2002,02 (21)(22)	Questionnaire study among physicians on death certificates, stratified deaths, retrospective Stratified deaths	2939	86 (2,5)	The patient received drugs, such as barbiturates or benzodiazepines, to keep him/her continuously in deep sedation or coma until death.	nationwide deaths
Italy, 2001 2001,06-2002,02 (21)	Questionnaire study among physicians on death certificates, stratified deaths, retrospective Stratified deaths	2604	314 (8,5)	The patient received drugs, such as barbiturates or benzodiazepines, to keep him/her continuously in deep sedation or coma until death.	nationwide deaths

Italy, 2007 2007 (30)	Questionnaire study among physicians, reporting on their last death, general practitioners and a random sample of hospital physicians	1376	251 (18,2)	Patient was kept continuously in deep sedation or coma until death.	nationwide non-sudden deaths
the Netherlands, 2000-2001 2000-2001 (31)	Physician interviews, Medical specialists, GPs, Nursing Home physicians	410 physician interviews	225 (10)	Medication to deeply sedate a patient or to bring him into a coma was given.	nationwide deaths
The Netherlands, 2001 2001,06-2002,02 (21)	Questionnaire study among physicians on death certificates, stratified deaths	5384	336 (5,7)	The patient received drugs, such as barbiturates or benzodiazepines, to keep him/her continuously in deep sedation or coma until death.	nationwide deaths
the Netherlands, 2005 2005,08-11 (23)(33)(36)	Questionnaire study among physicians on death certificates, stratified deaths	5342	n/a (8,2)	The patient was deeply and continuously sedated before death.	nationwide deaths
the Netherlands, 2010 2010, 08-11 (35)(36)(37)	Questionnaire study among physicians on death certificates, stratified deaths	unknown/ 6861	789 (12,3)	The patient had been deeply and continuously sedated until death.	nationwide deaths
the Netherlands, 2015 2015, 08-11 (36)(37)	Questionnaire study among physicians on death certificates, stratified deaths	unknown	n/a (18,3)	The patient was continuously and deeply sedated or kept in coma until death.	nationwide deaths
Sweden, 2001 2001,06-2002,02 (21)	Questionnaire study among physicians on death certificates, stratified deaths	3248	126 (3,2)	The patient received drugs, such as barbiturates or benzodiazepines, to keep him/her continuously in deep sedation or coma until death.	nationwide deaths

Table 1. *Continued*

Nation, year study Inclusion period (reference)	Study type	Total patients investigated	Patients who received CDS, no (%)	Definition of sedation	study population
Switzerland, 2001 2001 (21)(22)(38)	Questionnaire study among physicians on random sample of death certificates	3355	160 (4,8)	The patient received drugs, such as barbiturates or benzodiazepines, to keep him/her continuously in deep sedation or coma until death.	nationwide deaths
Switzerland, 2013 2013,8-2014-2 (38)(39)(40)(41)	Questionnaire study among physicians on random sample of death certificates	3173	557 (17,5)	The patient received drugs, such as benzodiazepines and/or other sedative substances, to keep him or her in deep sedation or coma until death.	nationwide deaths
United Kingdom, 2007 2007,11-2008,04 (23)(42)(43)	physician questionnaires reporting on their last attended death, retrospective	2782/2869	n/a (16,5)	Continuous deep sedation occurs where a patient is continuously and deeply sedated or kept in a coma before death, using a drug such as midazolam. The patient was continuously and deeply sedated or kept in a coma before death.	nationwide deaths
		Subpopulation studies			
Argentina and Spain, 2015 2015,12 (44)	Retrospective multicenter study	1447	701 (48,4)	the deliberate reduction of the patient's level of consciousness to relieve the intense suffering caused by one or more refractory symptoms.	The first 10 patients who died in the internal medicine department in 143 Spanish hospitals and 2 Argentinean hospitals

Austria, 2012-2013 2012,06-2013,06 2016)356 (71 % (45)	Retrospective cohort study, medical charts	2414	356 (14,7) Continuous sedation until death 119 (4,9) intermittent	Any sedating intervention initiated in the last two weeks of the patient's life and given continuously until his/her death (minimal duration one hour), or as intermittent sedation for more than 24 h, even when it was not given at the time of the patient's death.	patients in a palliative care unit
Belgium, 2001 2001,07-12 (46)	Physician questionnaires	2948	237 (6,9)	The patient received drugs, such as barbiturates or benzodiazepines, to keep him/her continuously in deep sedation or coma until death.	Adults, 80 years and older
Belgium, 2004-2005 2004,09-2005,04 (47)	patient reports	266	20 (7,5)	No definition of palliative sedation was imposed, because it was important to gain an insight into the practice of the use of sedatives in the PCU.	patients in a palliative care unit
Belgium, 2007 2007,06-2008,11 (48)	Questionnaire study among physicians	165	36 (21,8)	The patient was continuously kept in deep sedation or coma until death, by means of one or more drugs.	Children, 1-17years
Belgium, 2010 2010 (49)	Questionnaire study among physicians	117	11 (9,4)	The individual was kept in deep sedation or sleep continuously until death.	Dementia patients in nursing homes
Brazil, 2012-2015 2012,03-2015,01 (50	Retrospective cohort study, medical charts	374	203 (54,2)	The use of sedative drugs to reduce patient's consciousness with the intent of relieving refractory symptoms during the last hours or days of a progressive and incurable disease.	Cancer patients

Table 1. *Continued*

Nation, year study Inclusion period (reference)	Study type	Total patients investigated	Patients who received CDS, no (%)	Definition of sedation	study population
Canada, 2008 2008 (51)	Pharmacy database search	456	93 (20,4)	The definition of palliative sedation was not limited to deep sedation, but also included light levels of sedation.	patients in a palliative care unit
Canada, 2007-2015 2007,02-2015,01 (52)	Retrospective cohort study, medical charts	14360	602 (4,2) (3.3% hospital inpatient units 4,0% hospice 22,2% Intensive palliative care unit)	Continuous palliative sedation therapy involves the use of a titrated continuous infusion of midazolam to achieve deep levels of sedation.	Patients in hospitals, hospices and intensive palliative care units
China, 2007-2011 2007,03-2011,09 (53)	Retrospective cohort study, medical charts	244	82 (33,6) intermittent 20 (8,2) intermittently to continuously	The lowering of patients' consciousness using medications for the express purpose of limiting patients' awareness of suffering that is intractable and intolerable, or sufferings that patients perceive to be unbearable, which has not adequately respond to any interventions and for which additional interventions are either unavailable or impractical. Palliative sedation can be performed intermittently or continuously until death, and the depth of sedation can vary from a lower level of consciousness to complete unconsciousness.	cancer patients

Colombia, 2015 2015,01-07 (54)	patient reports	2890	66 (2,2) intermittent and continuous sedation	Two types of sedation were used according to the severity of the illness, the medical indication, or the preference of the family: intermittent (using scheduled midazolam at a 4- to 8-h interval) and continuous (use of midazolam in continuous infusion). Intermittent sedation was initially chosen when refractory symptoms where not continually present and/or when the patient or the family expressed their preference towards this kind of sedation. Continuous sedation was initiated when refractory symptoms were very frequent causing significant suffering or when the patient or the family preferred this type of sedation. Both types of sedation were titrated until symptom control was achieved.	cancer patients in hospital, attended by the palliative care team
Germany 1995-1999 (55)	Retrospective cohort study, medical charts	548 (1995-2002)	31 (10,6)	Continuous or intermittent sedation by the administration of benzodiazepines intravenously within the last 48 hours before death, achieving effective symptom control.	Patients in a palliative care unit
Germany 2000-2002 (55)	Retrospective cohort study, medical charts	548 (1995-2002)	49 (18,9)	Continuous or intermittent sedation by the administration of benzodiazepines intravenously within the last 48 hours before death, achieving effective symptom control.	Patients in a palliative care unit

Table 1. *Continued*

Nation, year study Inclusion period (reference)	Study type	Total patients investigated	Patients who received CDS, no (%)	Definition of sedation	study population
Germany, 2014-2015 2014,08-2015,07 (56)	patient reports	192	149 (78)	Palliative sedation has been defined as 'the monitored use of medications intended to induce a state of decreased or absent awareness (unconsciousness) in order to relieve the burden of otherwise intractable suffering in a manner that is ethically acceptable to the patient, family and health-care providers'.	Patients in a palliative care unit
Germany, 2015-2017 2015,01-2017,12 (57)	Retrospective cohort study, medical charts	165	26 (16)	Sedatives with a continuous effect. The terms 'sedation' or 'palliative sedation' were never identified in the examined medical records	Nursing home residents
Israel, 2012 2012,01-2013,01 (59)	Retrospective cohort study, medical charts	179	13 (7,3)	Different forms of palliative sedation were identified. Palliative sedation to unconsciousness (PSU), involved the use of deep palliative sedation, albeit given proportionally, in certain extreme circumstances, until time of death	Cancer patients in hospice

Italy 1999-2003 (60)	patient reports	129	69 (54)	A reduction of consciousness, produced by pharmacological means, to control symptoms that are refractory to ordinary palliative care approaches at the end of life. Sedation depth was continuously monitored, with the scope of keeping the patient unconscious and not awakened by strong external stimulation.	patients in a palliative care unit
Italy, 2000 2000,03-12 (61)	Retrospective cohort study, medical charts	331	47 (14,2)	A pharmacologically induced state of continuous coma lasting up until the moment of death, aimed at controlling the symptomatic state of the patient during the terminal stages of his life.	Adults in palliative care service center
Italy, 2003-2004 2003,07-2004,07 (61)	Retrospective cohort study, medical charts	744	89 (12,4)	A pharmacologically induced state of continuous coma lasting up until the moment of death, aimed at controlling the symptomatic state of the patient during the terminal stages of his life.	Adults in palliative care service center
Italy, 2010-2011 2010,02-2011,12 (62)	Longitudinal observational study	1095 Home care 1799 Hospice	161 (14,7) 370 (20,6)	Intentional reduction of the patient's level of consciousness by administration of sedating drugs to control refractory symptoms.	Home care patients Hospice patients
Italy, 2010 2010,1-7 (63)	Retrospective observational study, medical charts	104	80 (77)	Palliative terminal sedation is the pharmacological reduction of consciousness in patients faced on death.	Hemato-oncological hospice patients
Italy, 2013 2013,1-7 (63)	Retrospective observational study, medical charts	107	67 (63)	Palliative terminal sedation is the pharmacological reduction of consciousness in patients faced on death.	Hemato-oncological hospice patients

Table 1. *Continued*

Nation, year study Inclusion period (reference)	Study type	Total patients investigated	Patients who received CDS, no (%)	Definition of sedation	study population
Italy, 2014 2014, 1-7 (63)	Retrospective observational study, medical charts	104	80 (77)	Palliative terminal sedation is the pharmacological reduction of consciousness in patients faced on death.	Hemato-oncological hospice patients
Italy, 2014-2015 2014,01-2015,12 (64)	Retrospective cohort study, medical charts	326	122 (37,4)	According to the European Association of Palliative Care (EAPC), the monitored use of medications intended to induce a state of decreased or absent awareness (unconsciousness) in order to relieve the burden of otherwise intractable suffering.	Cancer patients in a hospice
japan, 1999 1999, 01-12 (65)	Retrospective cohort study, medical charts	124	63 (50,1)	A medical procedure to palliate patient symptoms refractory to standard treatment by intentionally dimming their consciousness." Therefore, palliative sedation included from mild to deep sedation. Nocturnal sedation was excluded.	Cancer patients in a palliative care unit
Japan, 1997-1998 1997, 07-1998, 10 (66)	Retrospective cohort study	248	128 (52)	A medical procedure to palliate patients' symptoms refractory to standard treatment by intentionally dimming their consciousness," which was classified into primary-secondary, intermittent-continuous, and mild-deep categories.	cancer patients in a palliative care unit

Japan, 2005-2011 2005,04-2011,8 (67)	Retrospective cohort study, medical charts	1581	22 (1,4)	Deep and continuous sedation at the end of life.	Cancer patients in palliative care unit
Japan, 2012-2014 2012,09-2014,05 (68)	Retrospective cohort study, medical charts	1827	269 (14,7)	The continuous use of sedatives to relieve intolerable and refractory symptoms by the total loss of a patient's consciousness until death.	Cancer patients in hospital, palliative care unit, home
Hong Kong, 2017 2017,07-09 (58)	Retrospective cohort study, medical charts	180	81 (45)	The monitored use of medication intended to induce a state of decreased or absent awareness (unconsciousness) to relieve the burden of otherwise intractable suffering in a manner that is ethically acceptable to the patient, family and health-care providers.	Cancer patients in palliative care unit
the Netherlands, 2011-2012 2011, 03-2012,12 (69)(70)	Prospective observational multicenter study	467	130 (28)	Palliative sedation was defined according to the Dutch national guideline, and CPS was defined as "palliative sedation 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 palliative sedation was only administered temporarily.	Hospice patients and patients in palliative care units

Table 1. *Continued*

Nation, year study Inclusion period (reference)	Study type	Total patients investigated	Patients who received CDS, no (%)	Definition of sedation	study population
the Netherlands, 2001-2005 2001,10-2005,10 (71)	Retrospective cohort study, medical charts	157	68 (43,3)	For almost all of the patients for whom sedation was used prior to death, continuous deep sedation until death was necessary. In this study, a patient was considered to have received palliative sedation when there was an annotation in the medical records of the use of "continuous deep sedation".	Cancer patients in palliative care unit
the Netherlands, 2000-2005 2000,01-2005-06 (72)	Questionnaire study among physicians and caregivers	209	31 (14,8)	The administration of drugs to keep the patient in deep sedation or coma until death.	ALS patients
the Netherlands, 2003-2008 (46) 2003,10-2008,03 (73)	Questionnaire study among physicians and caregivers	102	10 (9,8)	The administration of drugs to keep the patient in deep sedation or coma until death.	ALS patients in nursing home, hospice, hospital
the Netherlands, 2007-2011 2007-2011 (74)	Questionnaire study among physicians	330	69 (20,9)	Continuous deep sedation or sleep until death.	Dementia patients in nursing home
South-Korea , 2010-2015 2010,01-2015,10 (75)	Retrospective cohort study, medical charts	8309	1334 (16,1)	The administration of intravenous or oral sedative medication to relieve intolerable symptoms within the last 2weeks of life.	Cancer patients in tertiary medical centers

South-Korea, 2015-2017 2015,09-2017,03 (76)	Prospective cohort study	306	28 (9,2)	Intentionally inducing unconsciousness in a patient until death, clearly distincted from euthanasia	Hospice patients
Spain, 2002-2004 2002,01-2004,12 (77)	Retrospective cohort study, medical charts	245	29 (11,8)	The use of specific sedatives to relieve intolerable suffering from refractory symptoms by reducing patient's level of consciousness all patients, symptom control was achieved in a few hours, and the level of consciousness was rated as 5 or greater using the Ramsay scale within 24 hours after PS initiation.	Cancer patients at home
Spain, 2011 2011 (78)	Retrospective cohort study, medical charts	250	35 (14)	In its framework document, the European Association for Palliative Care (EAPC) defined palliative sedation as "the controlled use of medicinal products intended to induce a state of decreased or absent awareness in order to relieve suffering that is untreatable in an ethically acceptable way for patients, families, and health professionals.	Cancer patients at home
Taiwan, 1998-199 1998,08-1999,05 (79)	Prospective cohort study	251	70 (27,9)	A medical procedure to palliative patients' symptoms by intentionally making their consciousness unclear	Cancer patients in a hospice and palliative care unit

Table 1. *Continued*

Nation, year study Inclusion period (reference)	Study type	Total patients investigated	Patients who received CDS, no (%)	Definition of sedation	study population
the United Kingdom, 2010 2010, 01-12 (80)	Retrospective cohort study, medical charts	147	117 (80)	The use of a sedative medication to reduce patient awareness of distressing and intractable symptoms that are insufficiently controlled by symptom specific therapies. a sedative dose was defined as: 'The use of a minimum of 10 mg midazolam or a minimum 25 mg of levomepromazine in the 24 hours prior to death.	Hospice patients
the United Kingdom, 2011 2011, 01-03 (80)	Retrospective cohort study, medical charts	47	30 (62)	The use of a sedative medication to reduce patient awareness of distressing and intractable symptoms that are insufficiently controlled by symptom specific therapies. a sedative dose was defined as: 'The use of a minimum of 10 mg midazolam or a minimum 25 mg of levomepromazine in the 24 hours prior to death.	Hospice patients
the United Kingdom, 2010 2014, 01-03 (80)	Retrospective cohort study, medical charts	40	29 (73)	The use of a sedative medication to reduce patient awareness of distressing and intractable symptoms that are insufficiently controlled by symptom specific therapies. a sedative dose was defined as: 'The use of a minimum of 10 mg midazolam or a minimum 25 mg of levomepromazine in the 24 hours prior to death.	Hospice patients

the United States, 2004-2005 2004,01-2005,12 (81)	Retrospective cohort study pharmacy records	352	186 (41)	Palliative sedation (PS), defined as the use of a sedative medication to reduce patient awareness of distressing and intractable symptoms that are insufficiently controlled by symptom-specific therapies. The medical records of all patients who received midazolam, chlorpromazine, or lorazepam for PS were reviewed for indication(s) for palliative sedation	Cancer patients in a palliative care unit

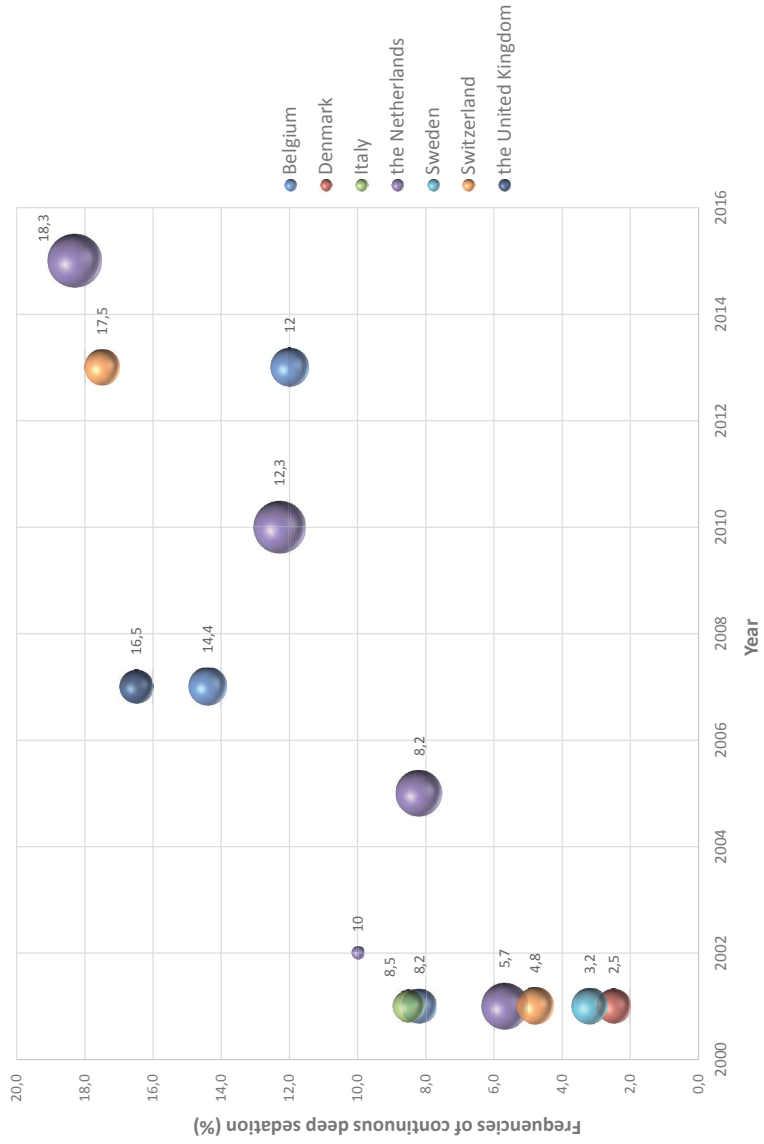


Figure 2. Frequencies of continuous deep sedation per country
* Frequencies of continuous deep sedation compared to all deaths per country
** Bell sizes in figure correlate with size studypopulation

Table 2. Characteristics of patients who received continuous deep sedation

Nation, year of data collection	Gender (%)		Age (%)				Cause of death (%)					Place of death (%)					Physician (%)		
	Male	Female	0 years	1-65 years	65-79 years	80+ years	Malignancy	Cardiovascular disease	Respiratory disease	Nervous system disease	Other, Unknown	Hospital	Home	Care Home	Hospice	Other	General Practitioner	Medical Specialist	Elderly Care Physician
Nationwide studies																			
Belgium, 2001 (21)*	9	7	11		12	5	10	8	9	7	7	13	3					x	
Belgium, 2007 (29)*	14	15	n/a	19	17	11	18	13				20	10	9	x			x	
Belgium, 2013 (29)*	12	12	n/a	17	16	9	17	10				17	9	7	x			x	
Denmark, 2001(21)	3	2	4		2	2	4	2	3	3	1	3	2					x	
Italy, 2001 (21)	9	8	14		10	6	16	5	3	15	5	8	9					x	
Italy, 2007, Non-sudden deaths (30)#	55	45	18-64: 32		48	20	71	10	5	5	10	x						x	
The Netherlands, 2000-2001 (31)#	47	53	22		42	36	54	24	22								3	6	2
The Netherlands, 2001 (21)	6	6	7		8	4	7	3	6	4	8	5	2					x	
The Netherlands, 2005 (37)º	9	8	11		10	6	13	5	5	12	8	x					7	12	6
The Netherlands, 2010 (37)º	13	12	14		16	10	19	9	13	11	8	x					12	16	9
The Netherlands, 2015 (37)º	19	18	19		22	16	29	10	18	14	15	x					21	18	14
Sweden, 2001 (21)	5	5	6		5	2	5	2	3	3	4	5	2					x	

Table 2. *Continued*

Nation, year of data collection	Gender (%)		Age (%)				Cause of death (%)					Place of death (%)					Physician (%)		
	Male	Female	0 years	1-65 years	65-79 years	80+ years	Malignancy	Cardiovascular disease	Respiratory disease	Nervous system disease	Other, Unknown	Hospital	Home	Care Home	Hospice	Other	General Practitioner	Medical Specialist	Elderly Care Physician
Switzerland, 2001, Non-sudden deaths (38)*	7	6	n/a	5	5	4	9	3	4	6	3	7	3					x	
Switzerland, 2013, Non-sudden deaths (38)*	26	23	n/a	39	27	21	28	23	26	22	22	x						x	
United Kingdom, 2007 (43)	21	16	27		19	12	22	12	19			20	20	10	13	x		x	

legend:

The table shows percentages of all patients who received continuous deep sedation compared to all studied deaths

#= These percentages are not compared to all deaths, but compared to all patients that had received CDS

X= Unknown

*= The presented nation-wide frequencies from Belgium were based on data collected in Flanders, the Dutch speaking area of the country and the presented nation-wide frequencies from Switzerland were based on data collected on the German speaking part of the country.

º= Place of death instead of attending physician.

Development of CSD in clinical practice

Figure 3 shows the reported symptoms requiring sedation over time. Over the years there was an increase in studies that reported patients' symptoms requiring sedation. The most frequently reported symptoms requiring sedation were dyspnea, agitation or delirium and pain. Fatigue was mentioned only in four studies (all after 2010). Psycho-existential distress as indication for sedation was mentioned only once in studies before 2008, and from 2008 and onwards mentioned in 9 studies with percentages ranging from 0 to 32%. Fear as indication for sedation was mentioned in six studies between 2001 and 2015, with percentages ranging from 0 to 27%. Thus, there is a clear trend for an increased use of CSD for non-physical symptoms including fear, anxiety, and psycho-existential distress.

Table 3 shows characteristics of CSD in clinical practice in repeated studies. From 1995-1999 to 2000-2002 there was an increase in requests from patients for sedation from 19% to 34% in an inpatient palliative care unit in Germany.[55] In Belgium, this number increased from 10% in 2007 to 15% in 2013.[29] During the same period the percentage of CSD on requests of the family slightly increased in Belgium from 12% in 2007 to 14% of all deaths in 2013.[29] From 2010 to 2014 there was an increase of the documentation of discussion of continuous sedation with patients, their relatives, and the medical team in a UK hospice.[80] From 2010 to 2014 there was an increase in the number of patients that was aware of their death in an Italian hospice, from 17% to more than 30% in 2014.[63]

In all countries, benzodiazepines were used for CSD in the majority of cases, with or without other medication. In the repeated studies, the use of benzodiazepines for CSD increased over time. In Belgium, the use of benzodiazepines in combination with opioids was 42% in 2007 and 46% in 2013.[29] The use of opioids as the only drug for CSD decreased from 31% to 17% of all cases during this period.[29] In the Netherlands the use of benzodiazepines for CSD increased from 60% of all cases in 2000-2001 to 93% in 2015.[37] The use of opioids decreased in the Netherlands from 36% in 2000-2001 to 3% in 2015. Over the years, CSD was more frequently provided in absence of artificial nutrition or hydration (ANH). The percentage of cases of CSD in which no ANH was provided varied from 26% in 2007 in Italy up to 91% in the Netherlands in 2015.[30, 37] Time until death was reported in studies on CSD in Belgium in 2007 and 2013, the Netherlands in 2005, 2010 and 2015, and in the United Kingdom in 2007-2008.[29, 37, 43] In all studies more than 85% of patients died within a week after starting sedation. In some cases, CSD had been performed with the intention or the co-intention to hasten a patient's death. In Belgium, the proportion of cases in which there had been a co-intention of hastening death increased from 13% in 2007 to 16% in 2013 but this rise was not statistically significant.[29]

In Italy in 2007 and in the United Kingdom in 2007-2008 the proportion of cases of CSD was higher when a palliative care team was involved or when the attending physician had followed palliative care training.[30, 43]

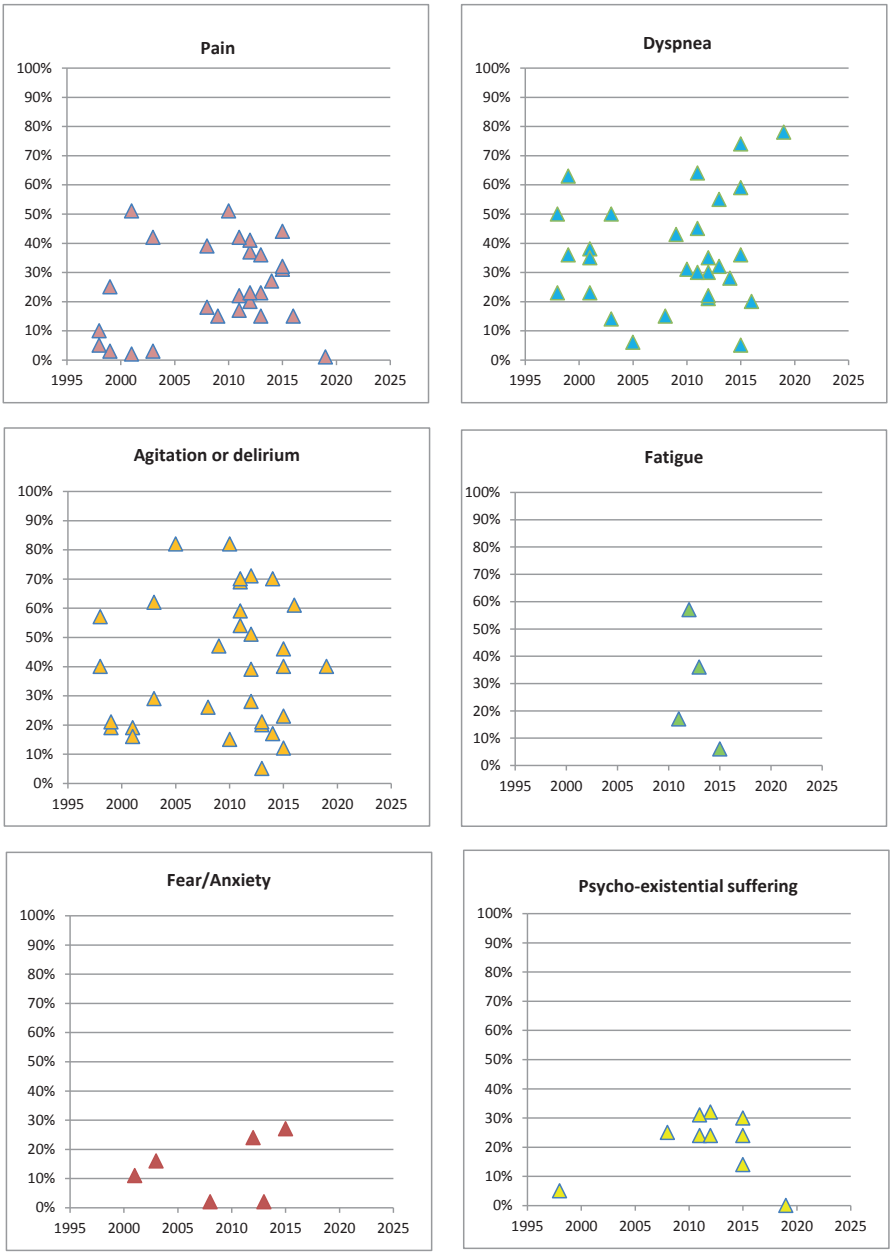


Figure 3. Percentages of patients' symptoms per study requiring sedation over time

Table 3. Characteristics of sedation

	Nationwide studies			
	Country (reference)		**Year**	
	Belgium(29)	2007	2013	
Hastening of a patient's death	Co-intention of hastening death	13	16	
	Explicit intention of hastening death	1	3	
Request	Request by patient	10	15	
	No request/consent patient but request family	12	14	
Artificial nutrition or hydration	Sedation without artificial nutrition hydration	58	62	
Duration sedation	0-24 hours	24	36	
	1-7 days	62	55	
	1-2 weeks	11	6	
	>2 weeks	2	4	
Medication used	Benzodiazepines, alone or with other medication	54	57	
		31	17	
	The Netherlands (37)	2005	2010	2015
Hastening a patient's death	Taking into account the hastening of death	x	38	38
	With the intention to hasten death	x	2	2
Consultation of palliative care expert	Consultation of palliative care expert	x	x	21
Artificial nutrition hydration	Sedation without artificial nutrition hydration	66	79	91
Duration sedation	0-24 hours	47	51	50
	1-7 days	47	46	46
	1-2 weeks	4	2	1
	>2 weeks	2	1	2
Medication used	Benzodiazepines, alone or with other medication	83	93	93
	Opioids alone	15*	3*	3*

Table 3. *Continued*

Nationwide studies			
Country (reference)		**Year**	
Subpopulation studies			
	Germany (55)	1995-1999	2000-2002
Main indication sedation	Dyspnea	36	35
	Gastrointestinal	10	6
	Bleeding	3	0
	Pain	3	2
	Delirium, agitation	19	10
	Anxiety, psychological distress	29	34
Indication sedation	Mainly somatic indication	64	45
	Mainly psychological indication	46	67
Request for sedation	Requests for sedation from patient	19	34
	Patients with request for sedation	53	45
Type of sedation	Intermittent	48	67
	Continuous	52	33
Duration sedation	Mean duration sedation (hours)	58	59
	Italy (61)	2000	2003-2004
Duration sedation (days)	1 day	66	71
	2-4 days	28	24
	5-10 days	6	6
Hydration (the administration of quantities of more than 500 cc of fluids per day)	Administration of artificial hydration	67	32
Therapy in the last 24 hours	Opioid	0	0
	Opioid + neuroleptics	0	6
	Opioids+ benzodiazepines	9	13
	Opioid +benzodiazepines + neuroleptics	71	81

Table 3. *Continued*

Nationwide studies				
Country (reference)		**Year**		
Italy (63)		2010	2013	2014
Principal refractory symptoms	Total pain	51	36	27
	Delirium	15	21	17
	Other symptoms	34	43	56
Awareness of death	No awareness	24	20	16
	Awareness of death	17	35	31
	Partial awareness	59	46	53
United Kingdom (80)		2010	2011	2014
Reason for sedation	Agitation/distress	82	70	70
	Pain	44	30	3
	Respiratory distress	31	30	28
	Risk of uncontrolled symptoms/ unable to take oral meds	16	13	11
	Observed 'discomfort/restlessness'	15	53	41
	Patient request	13	13	17
	Nausea/vomiting	9	0	3
	Not documented	13	10	3
	Unknown (started elsewhere)	x	x	3
Documented discussion	With the patient	32	37	85
	With the Family	38	80	67
	With the team	15	67	67
Hydration and nutrition	Documented hydration and nutrition	23	67	100
Dose medication	Mean dose midazolam on day of death (mg)	30	25	31
	Mean dose levomepromazine on day of death (mg)	56	55	55

Discussion

Our systematic literature review shows that CSD is used in many countries in different settings to relieve the suffering of dying patients, and suggests an increase in the use of CSD in at least some countries. Nationwide frequencies of CSD ranged between 3% and 10% in the period between 2000 and 2006, and between 12% and 18% from 2006 until June 2019.[21, 29, 31, 40] Country-specific trends in time could only be assessed for the Netherlands, Belgium and Switzerland. In the Netherlands and Switzerland frequencies rose over the period 2001-2015, but in Belgium the frequency of CSUD decreased between 2007 and 2013 after an earlier increase.[29, 37, 40] Frequencies of CSD in the different subpopulations varied too widely to observe patterns and to observe associations between subpopulations and the use of CSD. Where reported reasons to start CSD used to be mainly of physical origin, over the years more studies reported non-physical symptoms as indication for CSD such as fear or anxiety, and psycho-existential distress. Several studies showed an increased frequency of CSD on requests of patients and their families for CSD, which was notable from the beginning of 2000 and onwards.[55] Studies also showed that the use of CSD was increasingly discussed with patients, their families, and in the medical team.

Several hypotheses could explain why the use of CSD seems to increase over the years. First, the broader range of symptoms requiring sedation from only physical to also non-physical symptoms may explain the increase. Our results showed that over the years more studies reported non-physical symptoms such as fear, anxiety, and psycho-existential distress as indication to start CSD.[31, 69, 70, 80]

Second, it could be possible that improved palliative care has increased awareness among health care providers of the refractory symptoms and suffering of terminally ill patients. It could be possible that health care providers have become more acquainted with the guidelines, and that they are increasingly aware of CSD as an option to relieve suffering, resulting in a higher frequency of CSD.[82, 83]

Third, it could be possible that patients and their relatives are more aware of CSD as a relevant option at the end of life. Our review shows an increase of CSD at the request of the patient or the family. Over the years, several campaigns have been established to make people more aware of their needs and preferences for the last phase of their lives.[84, 85] A consequence of these campaigns could be that people are more aware of CSD as an option to relieve suffering in the dying phase and that they are more likely to request for CSD when they suffer of intractable symptoms.[29, 55]

Strengths and limitations

To our knowledge, this is the first review comparing frequencies and characteristics of CSD on an international level and in subpopulations over time. This review shows that patients' symptoms requiring CSD evolved over time from only physical symptoms, to both physical and psycho-existential symptoms. A limitation of our study is that most subpopulation studies were considered to have a higher risk of bias: oftentimes, definitions of CSD were lacking, missing data were not always described, and when comparing between subgroups, confounders were not taken into account. Consequently, the comparability of these included studies is limited. A second limitation is that we excluded articles written in other languages than Dutch or English in our review.

Conclusion

The frequency of CSD seems to increase over time, possibly due to the extension of indications for sedation, from only physical symptoms to also non-physical symptoms. The use of CSD appears to have become an integrated part of end-of-life care in many different countries, and it might have lost its status of "last resort". In-depth studies are needed to explore what the views, expectations and experiences of healthcare professionals, patients and families are, to better understand the changing practices and increase in the use of CSD to maintain CSD as a proportional answer to the relief of unbearable suffering of terminally ill patients.

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Supplementary table 1. Search string of literature search performed in Pubmed, EMBASE, CINAHL, Psycinfo and the Cochrane Library

Database	Search	Details	Number of results, 2020, April 15th
Pubmed	(Continuous sedation[Title/Abstract] OR continuous sedative*[Title/Abstract] OR terminal sedation[Title/Abstract] OR terminal sedative*[Title/Abstract] OR palliative sedation[Title/Abstract] OR palliative sedative*[Title/Abstract] OR deep sedation[Title/Abstract] OR deep sedative*[Title/Abstract] OR end of life sedation[Title/Abstract] OR end of life sedative*[Title/Abstract] OR end of life practice*[Title/Abstract] OR sedation practice*[Title/Abstract] OR sedation until death[Title/Abstract])	Data collection from 2000-April 15th 2020. Search on title or abstract	2891
EMBASE	('Continuous sedation ':ti,ab OR 'continuous sedative*':ti,ab OR 'terminal sedation':ti,ab OR 'terminal sedative*':ti,ab OR 'palliative sedation':ti,ab OR 'palliative sedative*':ti,ab OR 'deep sedation':ti,ab OR 'deep sedative*':ti,ab OR 'end of life sedation':ti,ab OR 'end of life sedative*':ti,ab OR 'end of life practice*':ti,ab OR 'sedation practice*':ti,ab OR 'sedation until death':ti,ab)	Data collection from 2000-April 15th 2020. Search on title or abstract Selected on article, letter, or review	2549
CINAHL	"Continuous sedation"OR "continuous sedative*" OR "terminal sedation" OR "terminal sedative*" OR "palliative sedation" OR "palliative sedative*" OR "deep sedation" OR "deep sedative*" OR "end of life sedation" OR "end of life sedative*" OR "end of life practice*" OR "sedation practice*" OR "sedation until death"	Data collection from 2000-April 15th 2020. Search on title or abstract	1578
Psycinfo	Continuous sedation.ab. OR Continuous sedation.ti. OR continuous sedative*.ab. OR continuous sedative*.ti. OR terminal sedation.ab. OR terminal sedation.ti. OR terminal sedative*.ab. OR terminal sedative*.ti. OR palliative sedation.ab. OR palliative sedation.ti. OR palliative sedative*.ab. OR palliative sedative*.ti. OR deep sedation.ab. OR deep sedation.ti. OR deep sedative*.ab. OR deep sedative*.ti. OR end of life sedation.ab. OR end of life sedation.ti. OR end of life sedative*.ab. OR end of life sedative*.ti. OR end of life practice*.ab. OR end of life practice*.ti. OR sedation practice*.ab. OR sedation practice*.ti. OR sedation until death.ab. OR sedation until death.ti.	Data collection from 2000-April 15th 2020. Search on title or abstract	387

Supplementary table 1. *Continued*

Database	Search	Details	Number of results, 2020, April 15th
The Cochrane Library	"deep sedation" OR "deep sedative*" OR "end of life sedation" OR "deep sedation" OR "deep sedative*" OR "end of life sedation" OR "end of life sedative*" OR "end of life practice*" OR "sedation practice*" OR "sedation until death" OR "continuous sedative*" OR "terminal sedation" OR "terminal sedative" OR "palliative sedation"	Data collection from 2000-April 15th 2020.	5 Cochrane reviews, 718 trials
Total of results	8128		

Supplementary table 2A. Adapted version of the Revised Cochrane risk-of-bias tool for non-randomized trials (Robins I-tool)

Bias domain	Low risk of bias (1 point)	Higher risk of bias (2 points)
1. Bias in selection of participants into the study	A clear description of the selection of participants was given. Patients who received continuous sedation were selected the same as patients who did not receive continuous sedation.	Patients who received continuous sedation were not selected the same as their controls, for example: controls who did not die, but who were visiting an outpatient clinic. Or no description of the selection process of participants was given.
2. Bias in classification of interventions	A clear description of continuous sedation was given, sedation was described as continuously and until death. Continuous sedation was clearly distinct from intermittent sedation.	Unclear if sedation was provided intermittently, or continuously, and until death, or no definition of sedation was given.
3. Bias due to missing data	A complete follow-up of all participants of the study, or a loss to follow-up of less than 20%, unlikely to introduce bias	A loss to follow-up of more than 20%, without a description of the loss, or a loss to follow-up was not reported in the article.
4. Bias in measurement of outcomes	Data was collected prospectively by adequate trained staff (physicians, nurses, researchers)	Data was collected retrospectively, or data was obtained from a database, or the data were self-reported, or it was unclear how study data were collected.
5. Bias in selection of the reported results	The reported results of the study were in line with the research question and the method was well described.	The reported results were not in line with the research question, or the method section is not clearly described.
6. Bias due to confounding	Article stated that confounders were taken into account. These confounders were well described in the article.	Article states that confounders were taken into account, but no descriptions of the confounders are given. Or confounders were not taken into account in the article.
Overall risk of bias	≤8 points; low risk of bias	9 or more points: Higher risk of bias

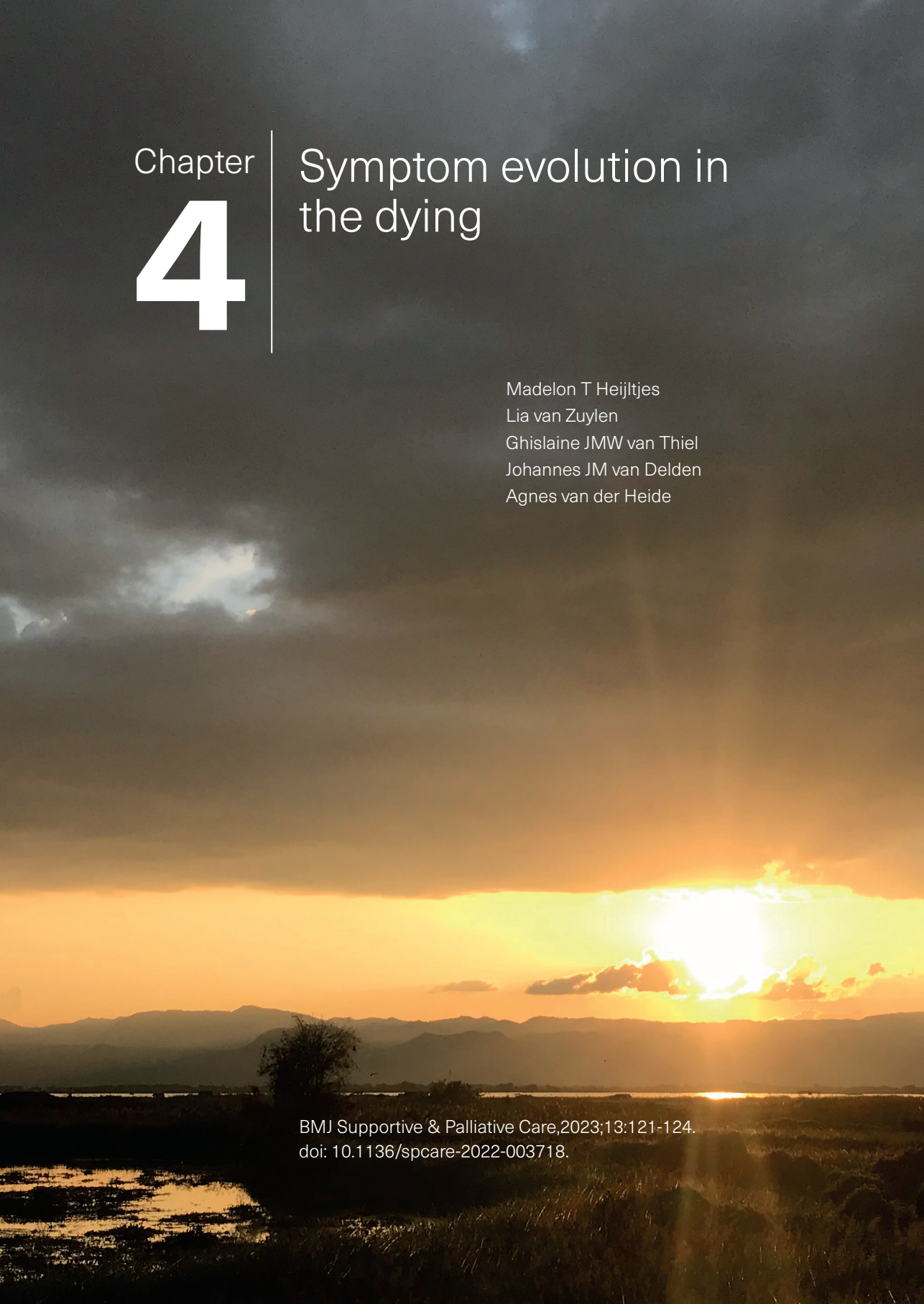
Supplementary table 2B. Adapted version of the Revised Cochrane risk-of-bias tool for non-randomized trials (Robins I-tool) per study

Reference	Bias in selection of participants	Bias in classification of interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported results	Bias due to confounding	Total score, overall risk of bias
21	1	1	1	2	1	1	7, Low risk of bias
22	1	1	1	2	1	1	7, Low risk of bias
23	1	1	1	2	1	1	7, Low risk of bias
24	1	1	1	2	2	1	8, Low risk of bias
25	1	1	1	2	2	1	8, Low risk of bias
26	1	1	2	2	2	1	9, Higher risk of bias
27	1	1	1	2	1	1	7, Low risk of bias
28	1	1	1	2	1	1	7, Low risk of bias
29	1	1	1	2	1	1	7, Low risk of bias
30	1	1	2	2	1	1	7, Low risk of bias
31	1	1	1	2	2	1	8, Low risk of bias
32	1	1	1	2	2	1	8, Low risk of bias
33	1	1	1	2	2	1	8, Low risk of bias
34	1	1	1	2	1	1	7, Low risk of bias
35	1	1	1	2	2	1	8, Low risk of bias
36	1	1	1	2	2	1	8, Low risk of bias
37	1	1	1	2	1	1	7, Low risk of bias
38	1	1	1	2	1	1	7, Low risk of bias
39	1	1	1	2	1	1	7, Low risk of bias
40	1	1	1	2	2	1	8, Low risk of bias
41	1	1	1	2	2	1	8, Low risk of bias
42	1	1	1	2	2	1	8, Low risk of bias

43	1	1	1	2	1	1	7, Low risk of bias
44	1	2	1	2	1	2	9, Higher risk of bias
45	1	1	1	2	2	1	8, Low risk of bias
46	1	1	1	2	2	1	8, Low risk of bias
47	1	2	2	1	1	2	9, Higher risk of bias
48	1	1	1	2	1	1	7, Low risk of bias
49	1	1	2	2	1	2	9, Higher risk of bias
50	1	1	1	2	1	2	8, Low risk of bias
51	2	2	2	2	1	2	11, Higher risk of bias
52	1	1	1	2	1	2	8, Low risk of bias
53	1	2	2	2	1	2	10, Higher risk of bias
54	1	1	2	1	1	n/a	5, Low risk of bias
55	1	2	1	1	2	2	9, Higher risk of bias
56	1	2	1	2	1	2	9, Higher risk of bias
57	1	2	1	2	1	2	9, Higher risk of bias
58	1	2	1	2	1	2	9, Higher risk of bias
59	1	2	1	2	1	2	9, Higher risk of bias
60	1	2	2	2	1	2	10, Higher risk of bias
61	1	1	2	2	1	2	9, Higher risk of bias
62	1	2	2	1	1	2	9, Higher risk of bias
63	1	2	2	2	1	2	10, Higher risk of bias
64	1	2	1	2	1	2	9, Higher risk of bias
65	1	2	2	2	1	2	10, Higher risk of bias
66	1	2	2	2	1	2	10, Higher risk of bias

Supplementary table 2B. *Continued*

Reference	Bias in selection of participants	Bias in classification of interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported results	Bias due to confounding	Total score, overall risk of bias
67	1	1	1	2	1	2	8, Low risk of bias
68	1	1	1	2	2	1	8, Low risk of bias
69	2	1	1	1	2	1	8, Low risk of bias
70	1	1	1	1	2	1	7, Low risk of bias
71	1	1	1	2	1	2	8, Low risk of bias
72	1	1	1	2	2	2	9, Higher risk of bias
73	1	1	1	2	2	2	9, Higher risk of bias
74	1	2	1	2	2	2	9, Higher risk of bias
75	1	1	2	2	1	2	9, Higher risk of bias
76	1	2	2	2	1	2	10, Higher risk of bias
77	1	1	1	2	1	2	8, Low risk of bias
78	1	2	1	2	1	n/a	7, Higher risk of bias
79	1	2	2	1	1	2	9, Higher risk of bias
80	1	2	2	2	1	2	10, Higher risk of bias
81	1	2	1	2	1	2	9, Higher risk of bias



Chapter

4

Symptom evolution in the dying

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Abstract

Objective
Provide insight in the prevalence of symptoms in patients who are in the last days of life.

Methods
A retrospective descriptive analysis of data on patients who died between 2012 and 2019 at the age of 18 or older in one of 20 Dutch health care facilities, including hospitals, inpatient hospices and long term care facilities (LTC). We analysed data from four-hourly registrations in the Care Program for the Dying Person, to assess for how many patients symptom-related goals of care were not achieved. We looked at the first four hour episode after the start of the Care Program and the last four hour episode prior to death.

Results
We analysed records of 2786 patients. In the first four hour episode, at least one symptom-related care goal was not achieved for 28.5-42.8% of patients, depending on the care setting. In the last four hour episode, these percentages were 17.5-26.9%. Care goals concerning pain and restlessness were most often not achieved: percentages varied from 7.3-20.9% for pain and from 9.3-21.9% for restlessness.

Conclusions
Symptom control at the end of life is not optimal in a substantial minority of patients. Systematic assessment and attention as well as further research on symptom management are of the essence.

Introduction

Many patients experience symptoms in the last phase of their life. Pain, dyspnoea, fatigue, restlessness, and discomfort are among the most common symptoms.[1-3] Little is known about how these symptoms evolve in the last days to hours of life.[4-6]

Since 2001, the Care Program for the Dying (CPD) is used in a number of healthcare organisations in the Netherlands. The CPD is started when the multidisciplinary care team expects the death of a patient to occur within hours to days and supports health care providers in systematically assessing goals of care in the physical, psychosocial and spiritual domains. The CPD consists of three parts: the first part includes items on the patient's background and goals of care at the start of the dying phase; in the second part, goals of care are evaluated by the health care provider every four hours until the patient dies; and the third part includes goals of care after death, such as care for the relatives.[7]

The aim of this paper is to provide insight in the evolvement of symptoms in patients who are in the last hours to days of life by analysing to what extent symptom-related goals of care are achieved, and to provide insight in differences in the occurrence of symptoms between different health care settings.

Methods

Study design and data collection

We performed a retrospective descriptive analysis of data from adult patients who died between 2012 and 2019. Data were provided by 20 Dutch health care facilities, including hospitals, long term care facilities (LTC), and inpatient hospices. Participating hospital wards were internal medicine wards, oncology and haematology wards, pulmonology wards, neurology wards, geriatric wards, and surgical wards. Records of all patients who were registered on the CPD were included after death. As these data were obtained after patients' death, consent was not required and obtained. The number of included patients varied from 20 to 800.per facility.

Symptom related goals of care

We analysed for how many patients symptom-related goals of care were not reported as having been achieved during the first four hour episode after the start of the CPD and during the last four hour episode prior to death. We looked at goals concerning pain, restlessness, respiratory tract secretions, nausea, vomiting and shortness of breath. Goals of care for these symptoms are formulated as follows:

Pain: the patient has no pain, as indicated by the patient, or, in case the patient is unconsciousness, by absence of pain during transfers or movements.

Restlessness: the patient is not restless, i.e. there are no signs of confusion, picking behaviour, or muscular contractions.

Respiratory tract secretions: the patient has no obstruction of breath by respiratory tract secretions, i.e. there are no signs of shortness of breath, also not when there is death rattle.

Nausea: the patient has no nausea, as indicated by the patient.

Vomiting: the patient is not vomiting.

Shortness of breath: the patient is not short of breath, as indicated by the patient.

Statistical analysis
We compared how often symptom-related goals were reported as having been achieved in the first and last episode, overall and per symptom, in the different settings, and tested the statistical significance of differences using McNemar tests.

Ethics approval
All identifying information was removed from the database before it was analysed. Under the Dutch law, this research is exempt from ethics review by a medical research ethics committee.[8]

Results

We analysed CPD records of 2786 patients. Table 1 shows the number of patients for whom goals of care were not reported as having been achieved in the first four hour episode after the start of the CPD and in the last four hour episode prior to patients' death, per setting. Sex and cause of death were known for a proportion of the patients (for 27.7 and for 40.5% respectively): 48.6% were male and 51.4% were female, 58.0% died of cancer, and 42.0% died of other underlying diseases. In the first four hour episode, care goals were most often not achieved for patients dying in the hospital setting: at least one care goal was not achieved for 42.8% of hospitalized patients, 30.5% of LTC patients, and 28.5% of hospice patients. The goal concerning pain was not achieved for 20.9% of hospitalized patients, 14.9% of LTC patients, and 13.2% of hospice patients. For restlessness these percentages were 21.9%, 14.7% and 17.2%, respectively. Care goals concerning shortness of breath and respiratory tract secretions were not achieved for 18.9% and 8.2% of hospitalized patients, respectively; not achieving these care goals

was less common for LTC patients (5.3% and 4.7%, respectively) and hospice patients (5.4% and 4.9%, respectively). Goals concerning nausea and vomiting were rarely not achieved in the first four hour episode in all settings.

In the last four hour episode prior to death, the percentage of patients for whom care goals were not achieved was generally lower than in the first four hour episode. However, the percentage of patients for whom at least one care goal was not achieved was still 26.9% for the hospital setting, 24.9% for the LTC setting and 17.5% for the hospice setting. The decrease in the percentage of patients for whom care goals were not achieved between the first and the last four hour episode was largest for the hospital setting, especially for pain, restlessness and shortness of breath. The percentage of patients for whom care goals were not achieved in LTC and hospice settings also decreased in comparison to the first hour episode, but differences were smaller than in the hospital setting. In those two settings, the percentage of patients with obstruction of breath by respiratory tract secretions increased, from 4.7% to 7.8% in the LTC setting, and from 4.9% to 5.2% in the hospice setting.

Table 1. Goals of care that were not achieved during first 4 hours episode after the start of the CPD and the last 4 hours episode prior to death, per setting

Symptom	**Hospital N=1252**		**LTC N=449**		**Hospice N=1086**	
	First four hour episode after start CPD	Last four hour episode prior death	First four hour episode after start CPD	Last four hour episode prior death	First four hour episode after start CPD	Last four hour episode prior death
Patient has no pain	262 (20.9)	140 (11.2) p<0.001	67 (14.9)	42 (9.4) p<0.001	143 (13.2)	79 (7.3) p=0.005
Patient is not restless	274 (21.9)	179 (14.3) p<0.001	66 (14.7)	53 (11.8) p=0.198	187 (17.2)	101 (9.3) p<0.001
Patient has no obstruction of breath by respiratory tract secretions	103 (8.2)	97 (7.8) p=0.679	21 (4.7)	44 (9.8) p<0.001	53 (4.9)	56 (5.2) p=0.826
Patient has no nausea	49 (3.9)	14 (1.1) p<0.001	15 (3.3)	6 (1.3) p=0.049	14 (1.3)	5 (0.5) p=0.022
Patient is not vomiting	31 (2.5)	16 (1.3) p=0.014	8 (1.8)	4 (0.9) p=0.344	13 (1.2)	10 (0.9) p=0.629
Patient is not short of breath	236 (18.9)	134 (10.7) p<0.001	24 (5.3)	14 (3.1) p=0.064	59 (5.4)	26 (2.4) p<0.001
At least one of these goals was not achieved	536 (42.8)	337 (26.9) <0.001	137 (30.5)	112 (24.9) 0.040	310 (28.5)	190 (17.5) <0.001

All P values are derived from McNemar test to assess the statistical significance of differences between the first and last four hour episode.
Differences between settings were considered statistically significant with $p \leq 0.005$

Discussion

Control of pain and other symptoms is considered important for a 'good death'.[9] Our study shows that at the start of the dying phase and in the last four hours prior death, for a substantial minority of patients at least one symptom could not be controlled. Symptom-related goals of care that were most frequently not achieved concerned pain, restlessness, and for hospitalized patients also shortness of breath. In contrast to previous studies, not achieving goals concerning nausea and vomiting was rare in all settings in our study.[10, 11]

We found that symptom-related goals of care were more often not achieved in hospitals than in other settings. This finding could be the result of patient selection, as complex symptom management during the dying phase may have been a common reason for admitting patients to the hospital.[12] Percentages of patients with uncontrolled symptoms in the dying phase in our study were lower than what has been found in other studies. Reported percentages vary between 22.2% and 52.6% for pain; between 22.1% and 41.2% for dyspnea; and between 3.9% and 25% for nausea and vomiting.[13-15]

It is unlikely that the lower percentages in our study are due to underreporting in the medical file, because the CPD is aimed at preventing underreporting of symptoms by facilitating structured observation and reporting. Use of the CPD to structure care in the dying phase may have resulted in better observation and as a consequence better treatment of symptoms, as has been suggested in a previous study.[13] However, pain and other symptoms still compromise the final hours of life of many dying patients, which may be due to suboptimal treatment or to the complex, often multifactorial origin of these symptoms.When terminally ill patients suffer severely from refractory symptoms, continuous deep sedation can be used, which is the lowering of the consciousness level of the patient by the use of sedatives. In the Netherlands, the use of continuous deep sedation has increased from 8% in 2005 up to 18% in 2015. Our finding that symptoms remain uncontrolled in the dying phase in a significant proportion of dying patients, may be part of the explanation of the frequent use of continuous deep sedation in the Netherlands.

Strengths and limitations

After a study of Ellershaw et al. in 2001, this is one of the few studies that provides insight in symptoms in patients in the last hours of life over time.[5] The use of clinical practice data of a high number of patients can be considered a strength of our study. We have limited insight in patients' characteristics, such as their underlying disease. Another limitation of our study is that we have no information about the severity of symptoms. Furthermore, we only report about patients for whom it was acknowledged that they were dying and for whom the CPD was used to monitor goals of care.

Conclusion

For a substantial minority of patients one or more symptom-related goals of care in the dying phase were not achieved. Goals of care that were often not achieved concerned pain, restlessness, and for hospitalized patients also shortness of breath. The results of this study show that symptom management in the dying phase requires ongoing attention in clinical practice and research.

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Chapter

5

Physicians' opinion and practice with the continuous use of sedatives in the last days of life

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Abstract

Context
There are few international studies about the continuous use of sedatives (CUS) in the last days of life.

Objectives
We aim to describe the experiences and opinions regarding CUS of physicians caring for terminally ill patients in seven countries.

Methods
Questionnaire study about practices and experiences with CUS in the last days of life among physicians caring for terminally ill patients in Belgium (N=175), Germany (N=546), Italy (N=214), Japan (N=513), the Netherlands (N=829), United Kingdom (N=114) and Singapore (N=21).

Results
The overall response rate was 22%. Of the respondents, 88-99% reported that they had clinical experience of CUS in the last 12 months. More than 90% of respondents indicated that they mostly used midazolam for sedation. The use of sedatives to relieve suffering in the last days of life was considered acceptable in cases of physical suffering (87-99%). This percentage was lower but still substantial in cases of psycho-existential suffering in the absence of physical symptoms (45-88%). These percentages were lower when the prognosis was at least several weeks (22- 66% for physical suffering and 5-42% for psycho-existential suffering). Of the respondents, 10% or less agreed with the statement that CUS is unnecessary because suffering can be alleviated with other measures. A substantial proportion (41-95%) agreed with the statement that a competent patient with severe suffering has the right to demand the use of sedatives in the last days of life.

Conclusion
Many respondents in our study considered CUS acceptable for the relief of physical and psycho-existential suffering in the last days of life. The acceptability was lower regarding CUS for psycho-existential suffering and regarding CUS for patients with a longer life expectancy.

Key message
This questionnaire study among physicians caring for terminally ill patients showed that many considered the continuous use of sedatives acceptable to relieve physical and psycho-existential suffering in the last days of life. Respondents' regarded the practice as less acceptable in patients with a longer life expectancy.

Introduction

Physicians who care for terminally ill patients often witness unbearable suffering in their patients. Sedatives may be considered as a last resort when this suffering cannot be relieved by standard treatment options. In particular, palliative sedation represents a treatment of last resort to relieve suffering in dying patients.[1-5] However, there is a lack of standardization regarding palliative sedation in the literature. What are the indications for sedation? How should sedation be performed? When can sedation be considered acceptable practice?[6-9]

There are many terms for the use of sedatives to relieve the suffering of terminally ill patients, including 'palliative sedation', 'continuous sedation', 'deep sedation', 'terminal sedation' and 'end of life sedation'.[6, 10, 11] The depth of sedation varies from superficial to deep, and the duration of sedation varies from intermittent to continuous until the end of life.[8, 12, 13] There is much debate on the use of sedatives, which is often complicated by a lack of consensual definitions. Empirical studies have described heterogeneous practice involving the use of sedatives for terminally ill patients in different countries and subpopulations.[4,14-16] To date, few studies have been conducted to describe medical practices and opinions of physicians in an international context.[17, 18] The aim of this study was to explore practices and opinions regarding continuous use of sedatives (CUS) of physicians caring for terminally ill patients in eight resource-rich countries: Belgium, Germany, Italy, Japan, the Netherlands, Singapore, the United Kingdom, and the United States.

Methods

Design

We designed a questionnaire study in eight countries to gain insight into the medical practices and opinions of physicians regarding CUS in the last days of life. Questionnaires were distributed among 8550 physicians in Belgium (Flanders region, n=555), Germany (n=1091), Italy (n=1083), Japan (n=734), the Netherlands (n=4000), Singapore (n=37), the United Kingdom (n=850), and the United States (n=200) between November 2018 and August 2019. Questionnaires were electronic, except for in the Netherlands and Japan where questionnaires were distributed by post. We attempted to maximize the response rate by introducing the topic at the start of the questionnaire, by the short length of the questionnaire, by personalizing the questionnaire per respondent, and by sending a reminder. Physicians received two reminders in Japan and the United States. No financial incentive was used.

Definition of sedation

We established the definition to be used in the questionnaire by discussing the terms and practices that are used in the participating countries in two face-to-face meetings, and by several subsequent rounds of email contact among the authors. It was important that the definition was acceptable and recognizable in all participating countries, applied to a broad range of patients, including those with and without capacity. We chose to use a descriptive definition: the continuous use of sedatives as a means to alleviate severe suffering in the last hours to days of life. "Continuous use" was defined as either a continuous subcutaneous/intravenous infusion or a scheduled repeated injection with the intention of producing a continuous effect.

Selection of participants

Target physicians for this study were physicians caring for terminally ill patients. The national research teams decided about whom and how to optimally recruit participants due to the very different organizational structures of palliative care in the participating countries. In Belgium, Germany, Italy, Japan, the United Kingdom, and the United States, where palliative care is a clinical specialty or sub-specialty, palliative care physicians were invited via the member lists of the national associations of palliative medicine. In Belgium, additionally, all physicians who had followed a palliative care training in the last five years prior to completion of the questionnaire were included. In the Netherlands, where there is no specific palliative care discipline, target physicians were random samples of general practitioners, geriatricians, and medical specialists. In Singapore, all physicians of major palliative care units were invited.

Development of the questionnaire

Since no validated questionnaires to survey physicians' experiences and attitudes regarding CUS were available, we developed our own questionnaire using expert opinion. Authors firstly reached a consensus on the definition of CUS. After consensus on the definition of CUS, we identified important themes and knowledge gaps about CUS in the literature. These themes concerned the type of medication, how sedation should be performed, the involvement of the patient and/or their family in the decision-making process, the goal of sedation, CUS to relieve psycho-existential suffering, CUS for patients with a life-expectancy of at least several weeks, and routine withdrawal of artificial hydration during CUS.[11,19-24]

Questions were developed by two face-to-face meetings, and by several subsequent rounds of email contact among the authors. The initial English version of the questionnaire was translated into Dutch, German, Italian, and Japanese. A pilot study was conducted in all countries with three physicians who were involved in the care of dying patients. Physicians in our pilot were asked to fill out the questionnaire, and were interviewed afterwards to identify if the

questionnaire was applicable in their country, and to identify if the questionnaire included important themes considering CUS in each participating country. This pilot test resulted in minor adjustments to the English questionnaire. The final version was translated into Dutch, German, Italian, and Japanese.

The questionnaire contained 32 questions and consisted of three parts (supplement 1). The first part enquired about physicians' backgrounds including their age, religion, self-identified specialty, work place, work experience and involvement in the care of dying patients in the last 12 months. The second part addressed physicians' practices, including their experiences with providing CUS for terminally ill patients, their medication use, their goals and intentions when providing CUS, and patient and family involvement. Answering options on frequencies were never, rarely, sometimes, often, and always. Questions considering the goal of sedation were not part of the questionnaire in Singapore. The third part of the questionnaire covered physicians' opinions regarding 12 statements about CUS, with the use of 5-point Likert scales from strongly disagree to strongly agree.

Review by ethics committee

The study protocol was approved by ethics committees in Belgium, Germany, the United Kingdom, Japan and Singapore. Approval of the study protocol by an ethics committee was not required according to national policies in Italy and in the Netherlands and therefore not obtained.[25, 26] Ethical approval for the United States respondents was also not obtained because the questionnaire was administered by the Japanese team and this was a minimal risk study involving only healthcare professionals.

Data collection and data analyses

Data were collected between March-December 2019. Data were imported into an SPSS template in each country and merged into a final dataset. Descriptive analyses were performed (i.e., calculating number and percentages per country). Statistical comparisons were not performed due to heterogeneity of respondents in different countries. Percentages were corrected for missing values for those variables that had 5% missing values or less. Responses concerning physicians' medical practices were collapsed into two categories: 'often' and 'always' vs. others. Responses concerning physicians' opinions were collapsed into two categories: 'agree' and 'strongly agree' vs. others. Results of respondents who returned empty questionnaires, and of respondents who did not fill in any questions on their medical practices or opinions on CUS were excluded from analysis. For the responses of physicians who reported that they had never provided CUS, questions concerning medical practices were excluded from further analysis. Statistical analyses were performed using IBM SPSS Statistics version 25.0.

Results

A total of 8550 questionnaires were distributed and 2543 were returned. A total of 102 questionnaires where respondents did not fill out any questions about their practices or their experiences were not eligible for further analyses. Because of the low number of participants from the United States (n=29) together with the low response rate (15%), we decided to exclude these results from further analyses, resulting in 2412 eligible questionnaires. The response rates were 13% in the United Kingdom (n=114), 15% in Germany (n=546), 20% in Italy (n=214), 21% in the Netherlands (n=829), 32% in Belgium (n=175), 57% in Singapore (n=21), and 71% in Japan (n=513); 22% overall (N=2412).

By country, the median age of respondents varied between 40-55 years, and median work experience between 16-28 years (Table 1). In line with our recruitment procedures, most German, Italian, Singaporean, and British respondents were palliative care physicians. Most Belgian respondents were general practitioners (56%), and most Dutch respondents were clinical geriatrics / elderly care physicians (27%) or general practitioners (20%). In all countries except for Japan, most respondents considered themselves Christian or non-religious. In Japan most respondents considered themselves as Buddhist or as non-religious. The median number of dying patients for whom respondents were involved in the last 12 months varied from 10 in Belgium up to 100 in the United Kingdom.

Table 1. Baseline characteristics of the respondents

Country	Belgium		Germany		Italy		Japan		The Netherlands		Singapore		United Kingdom	
No. respondents	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
	175		546		214		513		829		21		114	
Age (years)														
Median	48		53		52		55		47		40		44	
Work experience as physician (years)														
Median	20		25		21		28		19		16		20	
Gender														
Female	114	65	275	51	106	50	102	20	416	50	11	52	95	83
Male	61	35	269	49	108	51	406	80	411	50	10	48	19	17
Clinical specialty														
Palliative medicine	19	11	273	50	198	93	334	65	0	0	21	100	111	97
General practice/ Family medicine	98	56	38	7	5	2	23	5	165	20	0	0	1	1
Internal medicine	6	3	87	16	0	0	18	4	93	11	0	0	1	1
Radiotherapy	1	1	14	3	0	0	3	1	0	0	0	0	0	0
Pulmonology	8	5	36	7	0	0	13	3	93	11	0	0	0	0
Cardiology	1	1	34	6	0	0	1	0	66	8	0	0	0	0
Anesthesiology	8	5	4	1	2	1	32	6	0	0	0	0	0	0
Geriatrics[a]	13	7	4	1	5	2	4	1	227	27	0	0	0	0
Oncology	14	8	1	0	2	1	21	4	41	5	0	0	0	0
Neurology	4	2	1	0	0	0	0	0	69	8	0	0	0	0
Surgery	1	1	1	0	0	0	39	8	2	0	0	0	0	0

Table 1. *Continued*

Country	Belgium		Germany		Italy		Japan		The Netherlands		Singapore		United Kingdom	
No. respondents	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Other	2	1	53	10	2	1	24	5	71	9	0	0	1	1
Institution (multiple options possible)														
Hospital	63	36	297	54	21	10	399	78	443	53	17	81	66	58
Nursing home/Elderly care facility	26	15	29	5	5	2	18	4	192	23	0	0	1	1
Inpatient hospice	0	0	47	9	99	46	158	31	33	4	2	10	79	69
Community palliative care services	32	18	216	40	85	40	6	1	0	0	2	10	63	55
Home practice/ Family practice	106	61	121	22	2	1	86	17	168	20	0	0	2	2
Other	3	2	53	10	2	1	7	1	43	5	1	5	6	5
Religion														
Christianity	96	55	411	76	162	76	47	9	353	43	12	57	56	49
Islam	0	0	4	1	2	1	0	0	9	1	0	0	1	1
Buddhism	0	0	3	1	4	2	137	27	3	0	5	24	0	0
Judaism	0	0	0	0	0	0	0	0	4	1	0	0	1	1
No religion	77	44	117	22	46	22	304	61	443	54	1	5	51	45
Other	2	1	8	2	0	0	14	3	14	2	3	14	5	4
Number of patients in whose dying process the physician was involved in the past 12 months[b]														
Median	10		80		95		50		13		80		100	

[a] In the Netherlands these physcians were clinical geriatics and elderly care physicians

[b] Physicians who stated that they had ever provided continuous use of sedatives as a means to alleviate severe suffering in the last hours to days of life.

Table 2 presents respondents' experiences with the continuous use of sedatives as a means to alleviate severe suffering in the last hours to days of life per country. In all countries, most respondents had at least once provided CUS as a means to alleviate severe suffering in the last hours to days of life. The percentages were 82% for Belgian, 95% for German, 99% in Italian, 95% for Japanese, 97% for Dutch, 95% for Singapore, and 94% for British respondents.

In all countries, most respondents indicated that midazolam was the most frequently used medication for sedation, ranging from 91% in the United Kingdom up to 100% in Singapore. Opioids (with the intent to provide sedation) were mentioned by more than 25% of respondents in Belgium, Germany, and Italy. Levomepromazine/chlorpromazine was reported to be used as a sedative by 85% of British respondents, and haloperidol by 47% of Italian respondents. For all counties, 74% or more of the respondents indicated that they usually started low and gradually increased the dosage of the medications until the desired effect was reached. Fewer respondents indicated that they usually started high in order to reach the desired effect rapidly (≤10% in Japan and the United Kingdom; 20-32% in the other countries).

Table 2. Physicians' experiences with the continuous use of sedatives as a means to alleviate severe suffering in the last hours to days of life

Country	Belgium		Germany		Italy		Japan		Netherlands		Singapore		United Kingdom	
No. respondents[a]	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
	143		519		212		487		800		20		107	
Number of patients who were provided with the continuous use of sedatives as a means to relieve suffering in the last hours to days of life in the last 12 months[b]														
None	15	11	47	9	2	1	58	12	89	11	1	5	11	11
1-5 patients	82	58	207	40	21	10	220	45	358	45	12	60	27	26
6-10 patients	17	12	101	20	31	15	103	21	172	22	5	25	17	17
>10 patients	28	20	157	31	158	75	106	22	174	22	2	10	48	47
Medication used for the continuous use of sedatives (multiple options possible)[b]														
Midazolam	132	94	490	94	200	94	466	95	781	98	20	100	97	97
Propofol	8	6	58	11	2	1	9	2	26	3	2	11	1	1
Haloperidol	15	11	60	12	99	47	78	16	51	6	0	0	24	24
Barbiturates	8	6	21	4	9	4	65	13	7	1	0	0	19	19
Levopromazine/Chlorpromazine	8	6	124	24	56	26	34	7	58	7	8	44	85	85
Opioids (with the intent to provide sedation)	37	27	285	55	91	43	82	17	127	16	1	6	6	6
Other	13	9	61	12	11	5	24	5	18	2	0	0	3	3
Dosage of medication[b]														
I start low and gradually increase the dosage of the medications until the desired effect is reached	102	75	396	81	167	79	427	88	568	74	17	85	92	93

I start sufficiently high in order to reach the desired effect rapidly	35	26	102	21	42	20	48	10	235	32	4	21	2	2
The goal of the continuous use of sedatives is achieved[b]														
When the patient is comfortable (but not necessarily unconsciousness)	108	79	354	70	175	83	411	84	673	86	NA	NA	78	79
When the patient is unconsciousness	98	72	208	41	144	69	126	27	419	54	NA	NA	22	22

[a] Physicians who stated that they had ever provided continuous use of sedatives as a means to alleviate severe suffering in the last hours to days of life.
[b] Physicians that answered the statement with often or always

When asked about intention when providing CUS in the last hours to days of life (Figure 1), in all countries nearly all respondents indicated this was often or always to relieve suffering. Between 30% and 49% indicated their intention was often or always to decrease the patient's consciousness (except respondents from the United Kingdom, 9%). Fewer respondents expressed the intention of inducing unconsciousness. Shortening the dying process was rarely mentioned as an intention by respondents in any country, except in Belgium (12%). Table 2 further indicates that most (70-86%) respondents considered the goal of CUS as often/always achieved when the patient was comfortable but not necessarily unconscious. The percentages of the respondents who considered the goal of sedation was to induce unconsciousness was ≤17%, except for Italy and Belgium (32%).

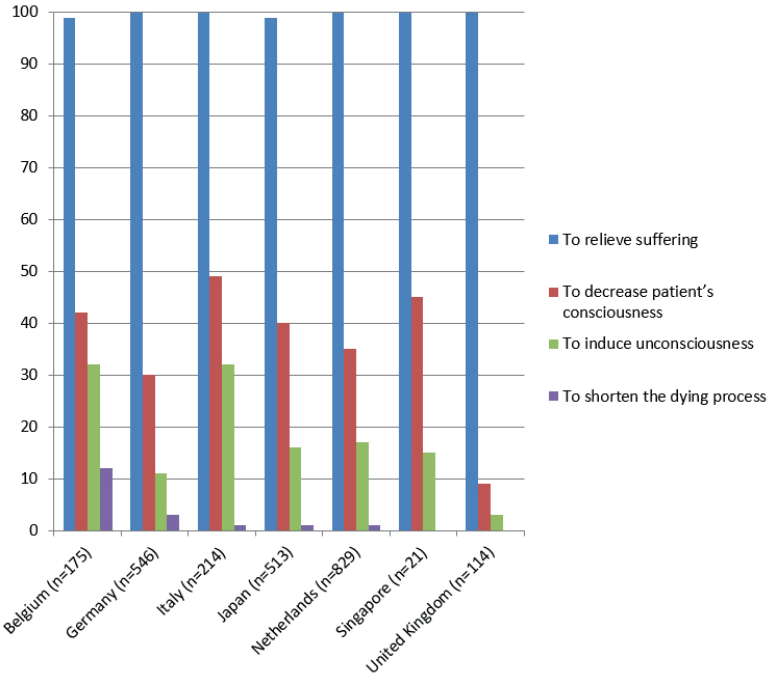

Figure 1. Percentages of physicians who answered often or always the indicated answer to the statements "What is your intention when you provide the continuous use of sedatives in the last hours to days of life"

Figure 2 shows that in all countries most (60-89%) respondents stated that the patient was often/always involved in decision-making. These percentages ranged from 91% to 100% for family involvement.

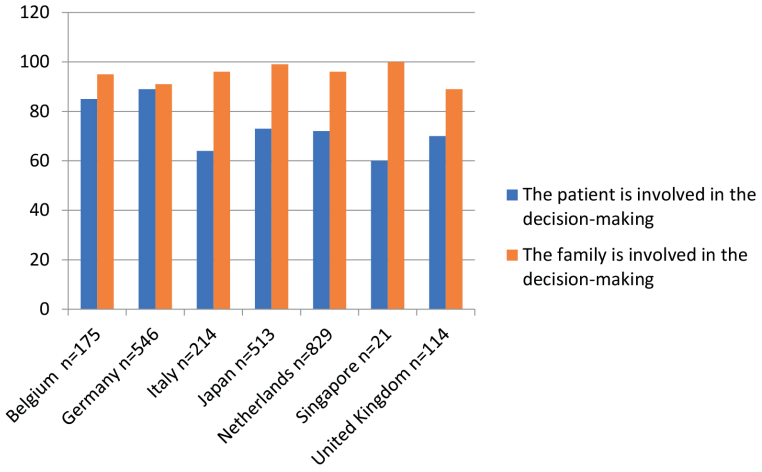

Figure 2. Percentages of physicians who often or always involved patients or families in the decision-making when providing the continuous use of sedatives as a means to alleviate severe suffering in the last hours to days of life

Figure 3 illustrates respondents' opinions about the acceptability of CUS for patients with varying symptoms and life expectancies per country. In all countries, for patients in the last hours to days of life, more than 87% of respondents considered CUS an acceptable medical practice to alleviate severe physical suffering. This percentage decreased to 45%-88% in case of severe psycho-existential suffering in the absence of physical symptoms. These percentages were lower for patients who were expected to live for at least several weeks. Agreement ranged from 22-66% in case of physical suffering and from 5-42% in case of psycho-existential suffering in the absence of physical symptoms.

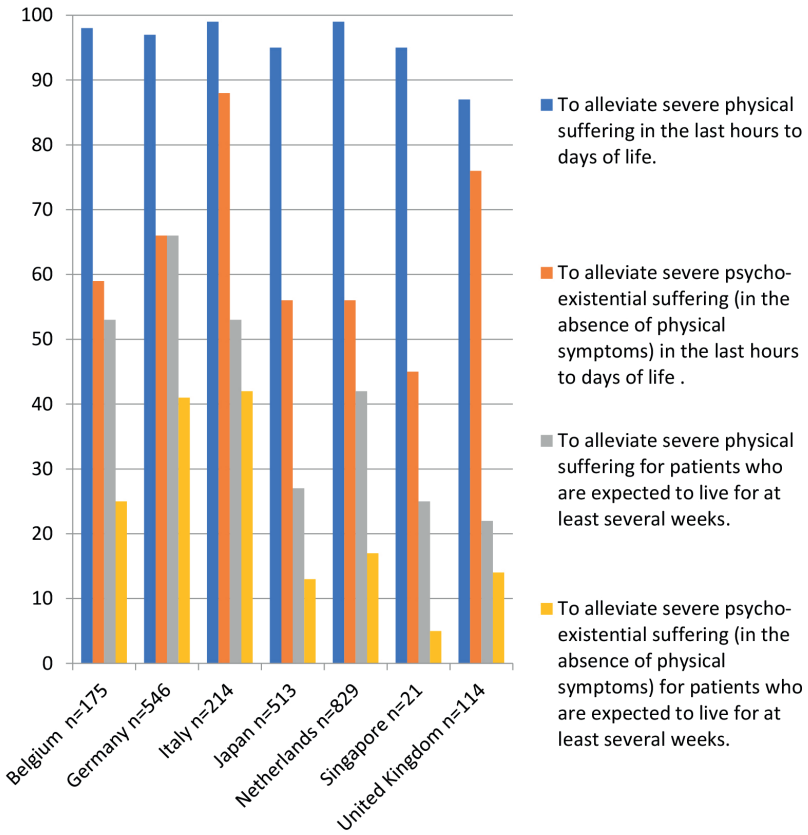

Figure 3. Percentages of physicians who (strongly) agreed with the statement that they would consider the continuous sedation use of sedatives as an acceptable medical practice in the respective situation.

Table 3 presents respondents' agreement with a set of statements. In all countries, more than 60% of respondents agreed that a competent patient with severe suffering has the right to demand CUS in the last hours to days of life, except for British respondents (41%). Relatively few respondents (≤17%) thought that CUS in the last hours to days of life shortens the duration of the dying process, except for German respondents (31%). In all countries ≤10% of the respondents agreed with the statement that CUS in the last hours to days of life is not necessary, as suffering can always be relieved with other measures. Most respondents (more than 70%) indicated that dying during sleep through CUS could be a good death, except for Japanese respondents (31%).

Table 3. Physicians' agreement with statement about the continuous use of sedatives as a means to alleviate severe suffering in the last hours to days of life (percentages indicate physicians who agreed or strongly agreed with the statement)

	Belgium		Germany		Italy		Japan		Netherlands		Singapore		United Kingdom	
No. respondents	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
	175		546		214		513		829		21		114	
1. In my opinion, a competent patient with severe suffering has the right to demand the continuous use of sedatives in the last hours to days of life.	147	89	454	83	201	94	485	95	747	91	12	60	43	41
2. The continuous use of sedatives as a means to alleviate severe suffering in the last hours to days of life is not necessary, as suffering can always be relieved with other measures.	7	4	14	3	10	5	40	8	22	3	2	10	8	8
3. The continuous use of sedatives in the last hours to days of life shortens the duration of the dying process.	25	15	167	31	8	4	41	8	141	17	1	5	4	4
4. I feel that in clinical practice the continuous use of sedatives in the last hours to days of life can be difficult to distinguish from euthanasia.	28	17	99	18	11	5	114	22	63	8	0	0	10	10
5. The continuous use of sedatives in the last hours to days of life cannot sufficiently alleviate suffering in all patients, even when patients become unresponsive.	41	25	331	61	88	41	257	50	288	35	8	40	47	45
Dying in a sleep through the continuous use of sedatives can be a good death.	143	87	487	90	174	81	157	31	758	92	14	70	77	74

Figure 4 indicates that more than 75% of the Belgian, Dutch, German and Singapore respondents considered routine withdrawal of artificial hydration an acceptable practice for patients with a life expectancy of hours to days; these percentages were lower for Japanese, British and Italian respondents (34-52%). The percentages decreased substantially for patients who were expected to live for at least several weeks.

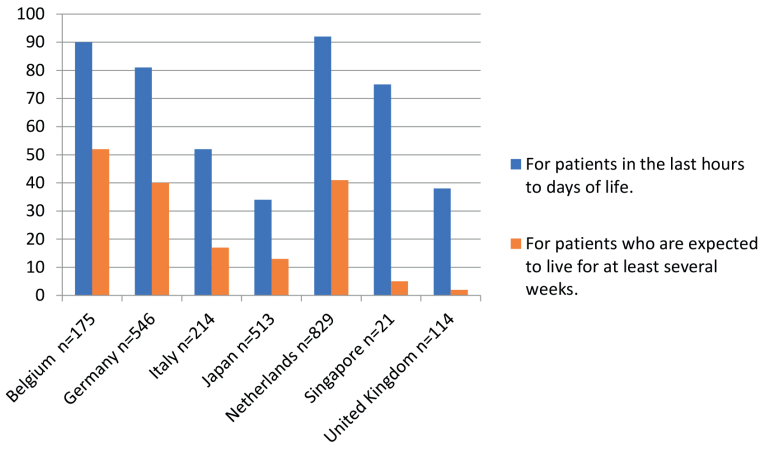

Figure 4. Percentages of physicians who (strongly) agreed with the statement that they would consider routine withdrawal of artificial hydration while providing the continuous use of sedatives to alleviate suffering as an acceptable medical practice, in the respective situation.

Discussion

In our questionnaire study we described practices and opinions regarding CUS of physicians in seven countries spanning two continents.

Strengths and limitations of the study

One of the major strengths of this study was the large number of participating physicians (more than 2400), across seven countries, all experienced in the care of dying patients. Our questionnaire used a clear definition of CUS and underwent pilot testing and modification before being used. However, there were some significant limitations to our study. In the absence of a pre-existing validated questionnaire to ascertain attitudes and practices of CUS we developed a study-specific questionnaire. We developed our study-specific questionnaire based on expert opinion and previous literature.[11, 19-24] The use of a non-validated questionnaire could be considered as a limitation. As a questionnaire based-study we relied on respondents' self-reports about CUS rather than on objective evidence about what practices actually occurred. Despite anonymity, it is possible that respondents did not always actually report their views or practices.

Our study had a low response rate in several of the participating countries and a relatively low numbers of participants, particularly in Singapore, the United Kingdom and the United States. Because no data were collected from non-respondents, we were not able to examine factors contributing to this low response rate. Because palliative care is provided by different clinicians across the participating countries, diverse recruitment strategies were used in different countries and as a result the characteristics of respondents in different countries varied substantially. Another limitation is that the results may not be directly generalizable to other countries that are less resource rich. Lastly, we did not provide a definition of psycho-existential suffering. Because of these limitations, the results of this exploratory study need confirmation in subsequent studies.

Analysis and comparison with the literature

There are many ways in which physicians influence the circumstances or timing of a patient's death. A relatively new phenomenon in the ethical discussion on end-of-life decisions is palliative sedation through the continuous use of sedatives (CUS). Often, such a decision is accompanied by the decision to forgo the provision of artificial nutrition and hydration. The combination of these two decisions has made the moral status of CUS the subject of fierce ethical debates and led to a number of conditions being made in guidelines.[22, 27-29]

Internationally, there are different perspectives towards the acceptability of withholding artificial hydration during CUS. The framework of the European Association for Palliative Care for the use of sedation emphasizes that withholding artificial hydration and providing palliative sedation are two separate decisions at the end of life and that these decisions should be taken and communicated separately.[13] At the same time the British quality standard *Care of dying adults in the last days of life* emphasizes that dehydration can lead to thirst and delirium, and may sometimes result in death, and therefore recommends to continue or to start artificial hydration for terminally ill patients, including those receiving sedation.[30] In our study, there was a consistent view (regardless of country) that withdrawal of hydration/nutrition was more acceptable when the prognosis of the patient is shorter. Furthermore, while guidelines often put limits on life expectancy,[13, 27, 28] in Belgium, Germany, Italy and the Netherlands a substantial proportion of respondents (42-66%) considered CUS as an acceptable medical practice to relieve severe physical suffering in patients with a life expectancy of several weeks.

In our study, a substantial proportion of respondents (45%-88%) considered CUS to relieve severe psycho-existential suffering in the absence of physical suffering in the last hours to days of life to be an acceptable practice.

These results seem in line with the findings of a systematic review that found that the frequency of continuous deep sedation seemed to have increased over time, possibly partly because of an extension of indications for sedation, from mainly physical symptoms to include non-physical symptoms as well.[21] In addition, a survey among Canadian palliative care physicians showed also that a third of these respondents provided continuous sedation for existential distress in the absence of physical symptoms.[31] A considerable number of respondents in our study agreed with the statement that a competent patient has the right to demand CUS. A previous study of Robijn et al. showed that in Belgium, the percentage of deaths in which sedation was used on the request of a patient had increased from 10% to 15% between 2007 and 2013.[1] A qualitative study among health care practitioners in Belgium, the Netherlands, and the United Kingdom showed that physicians in the United Kingdom typically discussed the possible use of sedation with patients and their relatives, but that they took the decision themselves, whereas in Belgium, patients more often initiated the conversation and requested the sedation and the role of the physician was more limited to evaluating if medical criteria were met. In the Netherlands, physicians emphasized the making of an "official medical decision", informed by the wish of the patient.[32] This exploratory study suggests several areas where there might be a difference in practice in use of sedatives in the last days, within and between countries. There was a wide range in reported frequency of the use of opioids, levomepromazine/chlorpromazine, and haloperidol for sedation. The appropriateness of these medications as sedative drugs should be further investigated. Also, there were diverse opinions regarding the statement that CUS cannot sufficiently alleviate suffering even when patients become unresponsive. To what degree patients receiving sedatives actually achieve symptom relief is a focus of controversy, and future studies are needed to understand how the effects and potential adverse events of CUS can be measured.[33-35]

Conclusions and implications

Insight into the practices and opinions of physicians caring for terminally ill patients regarding CUS is an important first step towards a better understanding of the current practices in the participating countries, and to support an informed debate. In the studied countries, many respondents considered CUS acceptable for the relief of physical suffering in the last days of life. Our finding that for a substantial proportion of respondents CUS is not only considered acceptable for the relief of physical, but also for psycho-existential suffering, and by a somewhat lower proportion of respondents also for patients with a life-expectancy of at least several weeks, seem in line with recent reports that suggest that the indications for the use of CUS may have widened over time, and that CUS may have lost its status as being a treatment of ''last resort''.

Future studies should explore the expectations and experiences in clinical practice of clinicians, patients, and relatives with CUS in different countries. More research is also needed to better understand how we can assess suffering in patients undergoing CUS, to measure whether CUS is sufficient assurance of comfort to maintain it as a proportional answer to the relief of unbearable suffering of terminally ill patients, and to develop effective interventions to relieve suffering in the most distressed.

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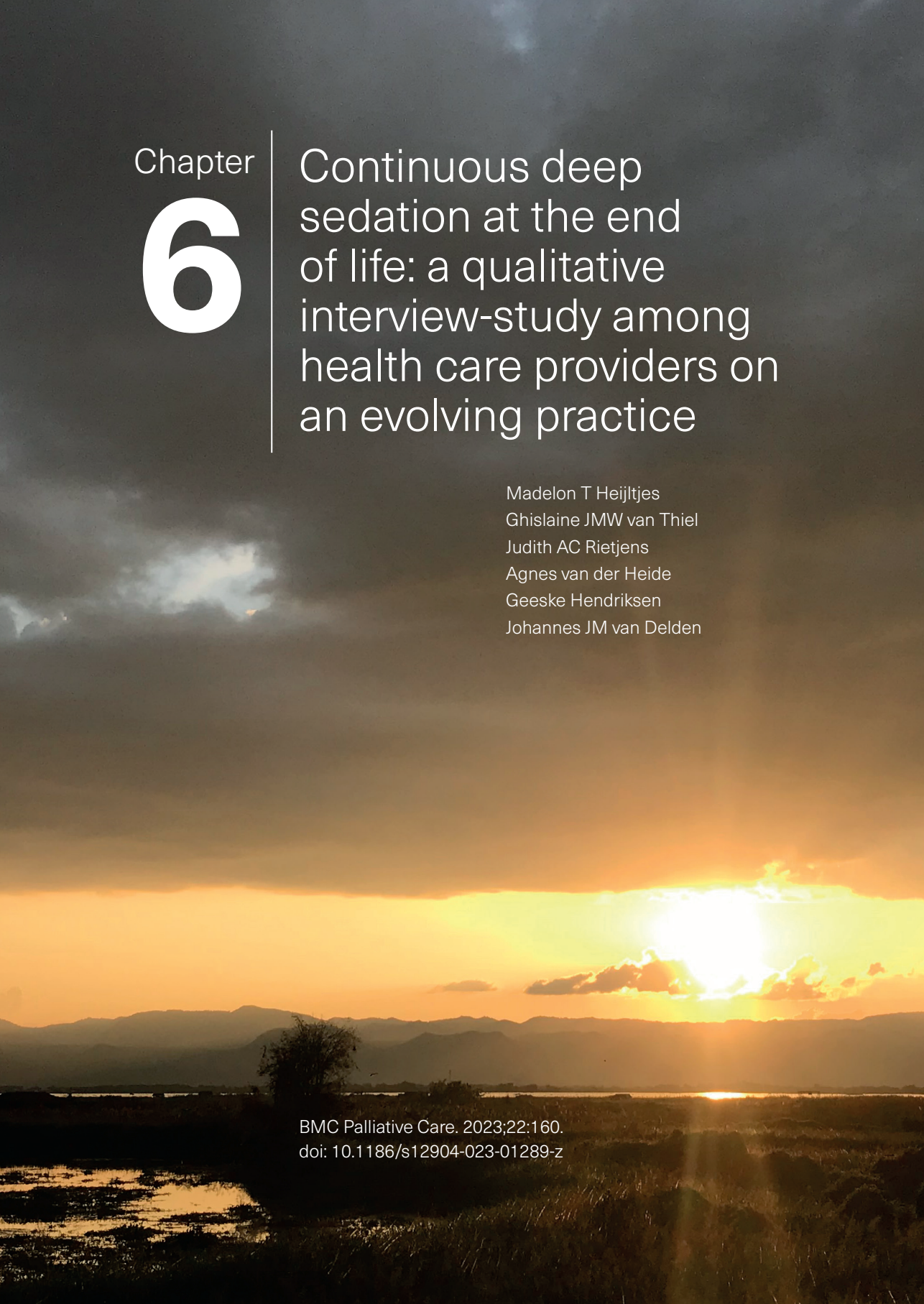

Chapter

6

Continuous deep sedation at the end of life: a qualitative interview-study among health care providers on an evolving practice

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Abstract

Background

Continuous deep sedation (CDS) can be used for patients at the end of life who suffer intolerably from severe symptoms that cannot be relieved otherwise. In the Netherlands, the use of CDS is guided by an national guideline since 2005. The percentage of patients for whom CDS is used increased from 8% of all patients who died in 2005 to 18% in 2015. The aim of this study is to explore potential causes of the rise in the use of CDS in the Netherlands according to health care providers who have been participating in this practice.

Methods

Semi-structured interviews were conducted and thematically analysed. Participants were Dutch health care providers (HCPs), working at patients' homes, hospices, elderly care facilities and in hospitals and experienced in providing CDS, who were recruited via purposeful sampling.

Results

41 Health care providers participated in an interview. For these HCPs the reason to start CDS is often a combination of symptoms resulting in a refractory state. HCPs indicated that symptoms of non-physical origin are increasingly important in the decision to start CDS. Most HCPs felt that suffering at the end of life is less tolerated by patients, their relatives, and sometimes by HCPs; they report more requests to relieve suffering by using CDS. Some HCPs in our study have experienced increasing pressure to perform CDS. Some HCPs stated that they more often used intermittent sedation, sometimes resulting in CDS.

Conclusions

This study provides insight into how participating HCPs perceive that their practice of CDS changed over time. The combination of a broader interpretation of refractory suffering by HCPs and a decreased tolerance of suffering at the end of life by patients, their relatives and HCPs, may have led to a lower threshold to start CDS.

Trial registration

The Research Ethics Committee of University Medical Center Utrecht assessed that the study was exempt from ethical review according to Dutch law (Protocol number 19-435/C).

Introduction

Patients at the end of life may suffer intolerably from severe symptoms that cannot be relieved by conventional treatment options.[1, 2] Continuous deep sedation (CDS) can be used to relieve such suffering. With CDS, the patient is deeply sedated until the end of life. This form of sedation is often distinguished from other types of palliative sedation, such as intermittent or superficial sedation.[3-6] The fact that CDS implies that patients lose their ability to communicate and the possibility that CDS could hasten a patient's death have been sources of debate about the appropriate use of this intervention for years.[7-9]

To guide a responsible practice, the Royal Dutch Medical Association issued a guideline on palliative sedation in 2005, with updated versions in 2009 and 2022.[10-12] In this guideline, different forms of palliative sedation are addressed, including CDS. Core elements of the guideline are presented in Table 1. The guideline provides information for health care providers (HCPs) about various types of palliative sedation, indications and contraindications, the appropriate medication, and practical procedures. Core elements of the guideline remained unchanged in the 2009 and 2022 versions.

In the Netherlands, the use of CDS increased from 8% of all patients who died in 2005 to 18% of all patients who died in 2015. A systematic review suggests that the use of CDS increases on an international level, and that a broadening of indications to start CDS is visible, from only physical symptoms to also symptoms of non-physical origin.[13] An international questionnaire study among physicians showed that a substantial proportion of physicians considered the use of CDS an acceptable practice to relieve symptoms of physical and non-physical origin.[14] Little is known about why the use of CDS increased in the Netherlands over the years. The aim of our study is to explore potential causes of the rise in the use of CDS in the Netherlands according to health care providers who have been participating in this practice.

Methods

Design

We performed a qualitative interview study among Dutch health care providers (HCPs) experienced in providing CDS. The interviews were conducted by the use of a topic-listThe topic list was designed for this study and was refined after three pilot-interviews (supplementary file 1). To gain insight in current practice, respondents were asked to reflect on their most recent case of CDS. In addition, respondents were asked to reflect on their general views on and practice of CDS, and if these had changed over the years. We report the study according to the COnsolidated criteria for REporting Qualitative research (COREQ).[15]

Sample of respondents

We recruited respondents via purposeful sampling, through key persons in health care organizations, and via snowballing. Via purposeful sampling we invited health care providers in our network to participate in an interview. To acquire a broad range of perspectives, we invited general practitioners, nursing home physicians, medical specialists, physician assistants, nurses, and spiritual carers involved in the care for terminally ill patients. Inclusion criteria were that these health care providers had actual experience with CDS, and that they had several years of work experience in their field so that they could reflect on changes in their use of CDS. We also recruited respondents via key persons in health care organizations. These key persons were HCPs who fulfilled a coordinating role in their organization. They worked at patients' homes, hospices, elderly care facilities and in hospitals. Inclusion criteria were that they had to be HCPs experienced with providing CDS.

Data collection

The interviews were conducted face to face and from March 2020 onwards also online due to the Covid-19 pandemic. The interviews were conducted by MH, who completed training in qualitative research. MH is a female physician, at the time working as a fulltime PhD student. MH contacted respondents prior the interview by telephone or by email, to clarify the research topic. Researcher reflexivity was enhanced by debriefing the interviews in meetings of the authors. The interviews were recorded, transcribed verbatim and anonymized. Background details of the respondents were obtained from an additional questionnaire. The Research Ethics Committee of University Medical Center Utrecht assessed that the study was exempt from ethical review according to Dutch law (Protocol number 19-435/C). Respondents provided written informed consent prior to participating in an interview.

Data analysis

We performed a thematic analysis to gain insight in different perspectives of respondents and to highlight similarities and differences.[16] The 2009 guideline of the RDMA on palliative sedation served as the conceptual framework for this study table 1). To promote rigor, credibility and trustworthiness, several transcripts were closely (re)read by the entire team during all steps. The analysis consisted of four steps and was partly deductive, as the topic-list was based on relevant themes in the literature, and partly inductive, as during the analysis new themes and subthemes arose. First, interviews were read and reread to get familiar with the data. Second, two researchers (MH and LN) independently coded the transcripts by assigning descriptive codes to interview fragments, using Nvivo 12. In addition, GvT coded five interviews. Third, MH collated the codes and merged them into themes. These themes were discussed and refined

through critical dialogue by the research team. The code tree was evaluated regularly during this second and third step. Fourth, key themes were identified and discussed in weekly meetings of MH and GvT, and in monthly meetings of all team members. Data saturation on a conceptual level was achieved, as in the last interviews with HCPs from different groups no new concepts or perspectives came up anymore.

Table 1. Core elements of the 2009 version of the RDMA guideline on the use of CDS[a]

1.	Continuous sedation is always administered in the final stage of life. The patients concerned are dying and experiencing unbearable suffering
2.	Medical indications are present when one or more intractable or 'refractory' symptoms are causing the patient unbearable suffering. A symptom is considered to be refractory if none of the conventional modes of treatment is effective or fast acting enough, and/or if these modes of treatment are accompanied by unacceptable side-effects
3.	A precondition for the use of continuous sedation is the expectation that death will ensue in the reasonably near future – that is, within one to two weeks. Next to physical suffering, existential suffering can also play a role in determining if suffering is unbearable and refractory. However, existential suffering alone cannot be an indication to start continuous sedation. When patients suffer from existential problems, it is recommended to consult an expert in psychosocial and spiritual care
4.	Palliative sedation is a medical response to a serious medical problem. A patient cannot opt for continuous sedation unless the indications and preconditions for this option are fulfilled. Only if the indications are present, in the physician's opinion, and the preconditions have been met does continuous sedation become a right that the patient may choose to exercise.
5.	The general rule is that palliative sedation should not be initiated without the consent either of the patient himself or, if he is decisionally incompetent, his representative. The patient's condition may make it necessary to administer acute sedation. This means sedating a patient in a situation in which a complication (frequently one that is life-threatening) suddenly occurs that causes unbearable suffering. In that case, the physician may decide that acute sedation is the only sound option for alleviating the patient's suffering at the point in time.
6.	Where a physician has doubts regarding his own expertise or has difficulty balancing the different considerations involved in deciding whether to start CDS, it is standard professional practice to consult the appropriate expert in good time
7.	Midazolam is the drug of choice, the use of morphine as a sedative is bad practice
8.	In principle, there is no artificial administration of fluids during the provision of continuous sedation
9.	Continuous deep sedation differs from euthanasia in that its aim is not to shorten life

[a] The 2009 version of the RDMA guideline was the actual version during the time of the interviews

Results

Between September 2019 and December 2020, we interviewed 41 HCPs. Characteristics of the HCPs are listed in table 2. The interviews lasted between 30 and 93 minutes, with a mean duration of 59 minutes. The time between the most recent case of CDS of the HCPs and the interview varied from the same day to months, and was in one case more than a year.

During the coding of the data we identified three key themes: 1) the course and performance of CDS in clinical practice.2) indications to start CDS, and 3) the decision-making process.

Table 2. Respondents' characteristics	Number N=41
Gender	
Female	27
Male	14
Age	
21-29	1
30-39	4
40-49	11
50-59	17
60-69	8
Religion	
Religious	17
Not religious	22
Unknown	2
Professional background	
General practitioner	10
Geriatrician[a]	9
Medical specialist[b]	9
Nurse	9
Nurse physician	2
Social worker	1
Medical doctor without further medical training	1
Place of work (more options possible)	
Community care	18
Hospice	10
Nursing home	13
Hospital	13

Table 2. *Continued*

Work experience as HCP	
0-9 years	4
10-19 years	7
20-29 years	18
≥ 30 years	10
Unknown	2
Followed additional training in palliative care	
Yes[c]	32
No	9
Number of patients to whom respondent has provided CDS in the last 12 months	
0	1
1-10	22
11-20	11
>20	6
Unknown	1

[a] 8 elderly care physicians, 1 cliniclal geriatrician
[b] 6 oncologists, 2 pulmonologists, 1 intensivist
[c] The additional training in palliative care varied from a course of several days to a training of multiple years

The course and performance of CDS in clinical practice.
Nearly all HCPs stated that they were familiar with the RDMA guideline on CDS and stated that they used the guideline as a reference when providing CDS. Midazolam was the medication mostly used as a sedative, administered by repeated injections or by continuous infusions.

HCPs stated that it is not always evident how the symptoms of the patient will evolve over time. Some stated that over time they increasingly used intermittent sedation, a so-called time-out, sometimes resulting in CDS. These HCPs experienced that they did not always have sufficient knowledge of the background of patients, for example during evening and night shifts. The reason to start with intermittent sedation for these HCPs was to relieve time pressure and to create space to evaluate the patient's symptoms.

> *General practitioner: "What hopefully increasingly will be used is intermittent sedation, when there is chaos and pressure, which increases the suffering of the patient. I think it can be a good solution to choose for a single dose in these situations."*

HCPs mentioned several factors they experienced as supportive in the decision-making and performance of CDS. Factors mentioned were the possibility to discuss options for supportive care and the need to start CDS with a colleague, recurrent team meetings where the use of palliative care and CDS could be discussed, increased experience and knowledge concerning palliative care and CDS, and the RDMA guideline that provides guidance in the decision-making and performance on CDS.

Some HCPs experienced that the use of CDS not always successfully relieved the suffering of a dying patient despite the fact that they increased the dosage of the sedative according the guideline.

> *Nurse: "And my last consult, there was a general practitioner who started sedation which did not succeed, it was a young man, who during sedation got up constantly and screamed for help and that he was going to die. There were young kids walking around the bed. Well, some sedations just don't succeed."*

Indications to start CDS

Reporting on their most recent case, the majority of HCPs stated that the indication to start CDS was an accumulation of multiple symptoms leading to a refractory state.

> *Nursing home physician: "it was a combination of different factors. There was not just one single symptom, so that you could say, we increase the doses of pain killers. It was not only the pain, it was the total despondency of not getting better anymore. The patient said, I am exhausted, turning in bed already costs me so much energy. I don't want this anymore, I can't take this anymore. So it was a combination of pain, which is a physical symptom, exhaustion, and existential suffering."*

Common physical symptoms mentioned were pain, dyspnoea, restlessness, delirium, fatigue, and nausea. Many HCPs stated that non-physical symptoms also played a role, including fear of dying, difficulties with accepting death and loss of dignity. Especially HCPs working at patients' homes, stated that over the years their interpretation of refractory suffering had broadened, and that non-physical symptoms more often play a role in the decision-making. For medical specialists working in hospitals, this extension of indications was less evident.
Many HCPs stated that their knowledge and experience with providing CDS increased over the years. Some stated that they use CDS more often because they recognize refractory symptoms better.

General practitioner: "In the past, when my knowledge was not sufficient enough, I remember that I was muddling along. I remember a case of a man with a delirium with motorically restlessness, and where I realized too late: what could I do? Haloperidol is working, but not on these symptoms. And very late I realized that I just needed to add a benzodiazepine. So, looking back on this case, which is more than six years ago, I let him crawl in his bed too long."

Others stated that they use CDS less often because they had experienced that CDS cannot successfully relieve suffering at the end of life in all cases.

The decision-making process

The imminent death of a patient is often discussed by HCPs with patients and their relatives in advance care planning (ACP) conversations. HCPs in our study differed in their opinion on whether CDS should routinely be discussed in these ACP conversations. Some stated that they do not always discuss CDS with patients and their relatives, certainly not when it is not a relevant option yet. Others stated that they routinely discuss the option of CDS with their patients and their relatives. The HCPs who stated that they routinely discuss the option of CDS in advance with patients, did not experience that due to such conversations they were more inclined to start CDS. These HCPs emphasized the importance of framing the decision to start CDS according the RDMA guideline, namely as a medical decision where medical criteria need to be met.

General practitioner: "What occasionally happens, is that people have certain expectations of CDS. That people say that they have discussed it with their general practitioner and that they don't choose euthanasia, but sedation instead. I then explain that it doesn't work that way, that CDS is not something you can choose, that it is something I decide about when I am their attending physician during the dying process, when I think that it is not possible to provide comfort by other palliative treatment options, and that it is not life-shortening. By giving more information I try to manage their expectations."

While most HCPs stated that they consider the decision to start CDS a medical decision, they also emphasized that it is important to involve patients and relatives in the decision-making. The extent to which patients and relatives are involved varied, from taking the initiative to start CDS to providing consent for starting CDS.

Paramedic : "Eventually the patient said that he couldn't bear it anymore. This is it, he said. The general practitioner visited the patient on a daily basis, so he just waited for the patient to be at this point. We knew that this patient would die soon. So at the moment that the patient said that he couldn't bear the pain

anymore, and was also disorientated at times as he was also suffering from a terminal delirium, he was well able to indicate that he had reached his limit."

A few HCPs stated that they had experienced a situation in which the patient or the relatives asked to start CDS while the respondent was convinced that CDS was not an option (yet), based on the criteria of the RDMA guideline.

Nursing home physician: "Once I made the mistake that I admitted a patient who had already had a conversation about euthanasia and CDS with his general practitioner. I thought, well, this is good advance care planning of the general practitioner. The patient already received palliative care, but there was absolutely no indication for CDS yet. I gave the patient a leaflet about CDS, so that if there were questions we could discuss these. Whereupon 2 days later his wife came to me and asked: when will you start?"

Most HCPs in our study felt that over the years suffering at the end of life is less tolerated by patients, their relatives, and sometimes also by other HCPs. Most HCPs experienced that they received more requests to relieve the suffering of dying patients using CDS, and a greater need for information among patients and relatives. This was sometimes experienced as pressure. Influence of the media, where dying is sometimes portrayed as a painless and almost beautiful event, was seen as contributing to the diminished tolerance of suffering.

A large minority of respondents in our study mentioned the following quote from relatives of dying patients:

"you wouldn't even let a dog suffer like this would you?".

HCPs mentioned that the involvement of many different HCPs in the care of a patient makes it difficult to manage expectations at the end of life. Pressuring factors in the decision-making reported by general practitioners occurred during evening- and nightshifts, when they also attend patients they do not know: lack of time, limited knowledge of the situation of the patient, and limited possibility to consult an expert were mentioned as causing overall pressure.

General practitioner: "At night there isn't anyone to consult. There is no palliative care consultant you can call, there is no general practitioner specialized in palliative care you can call, there is no colleague available, and the family is pressuring you to start CDS."

Furthermore, most HCPs in our study stated that for patients and relatives differences between euthanasia and CDS are often unclear. HCPs experienced that they need to explain more often what the differences between CDS and euthanasia are, and in which situations CDS and euthanasia can be used.

In some cases, euthanasia had been discussed in an earlier phase, but was no longer considered an option by the HCP, because the situation of the patient declined too rapidly. In these cases HCPs also experienced pressure to start CDS.

Nurse: "He constantly mixed it (euthanasia and CDS) up, and said: I don't care how you name it, as long as I get my injection and I don't wake up tomorrow."

Discussion

The aim of our study was to explore potential causes of the rise in the use of CDS in the Netherlands according to HCPs who have been participating in this practice. HCPs in our study mentioned several factors that could have led to a lower threshold to start CDS. The indication to start CDS is often a combination of symptoms resulting in a refractory state.[17] HCPs in our study stated that with growing experience, they had learned to better recognize a refractory state of severe suffering in terminally ill patients.

In addition, they stated that they had started to interpret the concept of refractory state more broadly and more often included symptoms of non-physical origin. Most HCPs experienced more requests to start CDS by patients, their relatives, and sometimes by other HCPs involved, and felt that over the years suffering at the end of life is less tolerated by patients, their relatives, and sometimes also by other HCPs. Some HCPs in our study experienced more pressure from patients and relatives to start CDS. HCPs also stated that for patients and their relatives differences between euthanasia and CDS may be unclear.

The RDMA guideline describes CDS as an intervention that is based on a medical decision where medical criteria need to be met.[12] The broader interpretation of refractory suffering makes it more difficult to interpret the decision to start CDS as solely a medical decision. Studies show that HCPs in other countries also seem to have embraced a broader interpretation of indications for sedation.[13, 14] There seems to be a greater acceptance for suffering of non-physical origin as a ground for starting CDS.[14]

HCPs in our study mentioned several reasons for a decreased tolerance for suffering among patients, their relatives and HCPs at the end of life. First, they mentioned the role of the media. HCPs stated that dying in the media is sometimes portrayed as a painless and beautiful event, which has also been shown in previous studies.[18, 19] Other studies proved that a substantial proportion of patients experience symptoms at the end of life, including pain, shortness of breath and fatigue.[20, 21]

It could be that due to the media, patients and their relatives incorrectly expect that they will not experience symptoms at the end of life, and when they do face such symptoms, they more often request CDS.

Second, HCPs in our study mentioned that differences between CDS and euthanasia are not always evident for patients and relatives. Since 2002 it has been established by Dutch law, that HCPs may provide euthanasia for patients under strict conditions.[22, 23] There needs to be a well-considered and voluntary request of the patient, there must be unbearable suffering without any prospect of relief, and an independent physician must assesses the patient's request.[22, 23] It could be that an increased awareness of the option of euthanasia, also increased the awareness for other options to relieve suffering at the end of life, including CDS.

Third, some HCPS stated that over the years they had discussed the option of CDS more often in ACP conversations with patients and their relatives. Little is known about the impact of these conversations on patients and their families' expectations concerning CDS. The HCPs in our study who discussed CDS in these conversations did not experience an increased number of requests for CDS. However, when HCPs discuss patient wishes regarding CDS in an earlier stage, an expectation may be created that CDS can indeed be started upon request in case of suffering.

Fourth, some HCPs stated that they increasingly used intermittent sedation to relieve suffering. The use of intermittent sedation to relieve suffering of terminally ill patients is reported in several studies, but little is known about the transition from intermittent to continuous sedation when the use of intermittent sedation is not effective.[24, 25] It could be that the use of intermittent sedation more often leads to the use of CDS when the first is not sufficiently effective.

Strengths and limitations of this study

This qualitative study is one of the few studies that provides insight in the experiences and practices of HCPs with providing CDS. The diversity of HCPs from different settings is a strength of our study. The majority of the respondents had multiple years of experience with providing CDS and were able to reflect on their evolving practices and experiences. By systematically asking details about the most recent case, we tried to get a more general insight in their practice than when we would have discussed the most memorable case. The clarity about the definition of CDS we provided at the start of the interview can also be considered a strength.

A limitation of our study is potential selection bias. Most respondents had had additional training in palliative care, worked on a daily basis with terminally ill patients, and had a special interest in the topic. They were mainly nurses and physicians. Spiritual carers were also invited, but did not participate.

Another limitation of our study is the risk of recall bias. In our study, we asked the respondents to describe their most recent case of CDS, which was for some of the respondents several months ago. Lastly, we describe practices and experiences of the use of CDS from only the HCP perspective and not from the perspective of relatives of patients who received CDS.

Conclusions and implications

This study provides insight into how participating HCPs perceive that their practice of CDS changed over time. The combination of a broader interpretation of refractory suffering by HCPs and a decreased tolerance of suffering at the end of life by patients, their relatives and HCPs, may have led to a lower threshold to start CDS. Results of our study underpin the importance of discussing the option of CDS in conversations between HCPs, patients and relatives. In future research, it would be valuable to explore patients' and relatives' experiences and expectations on the use of CDS.

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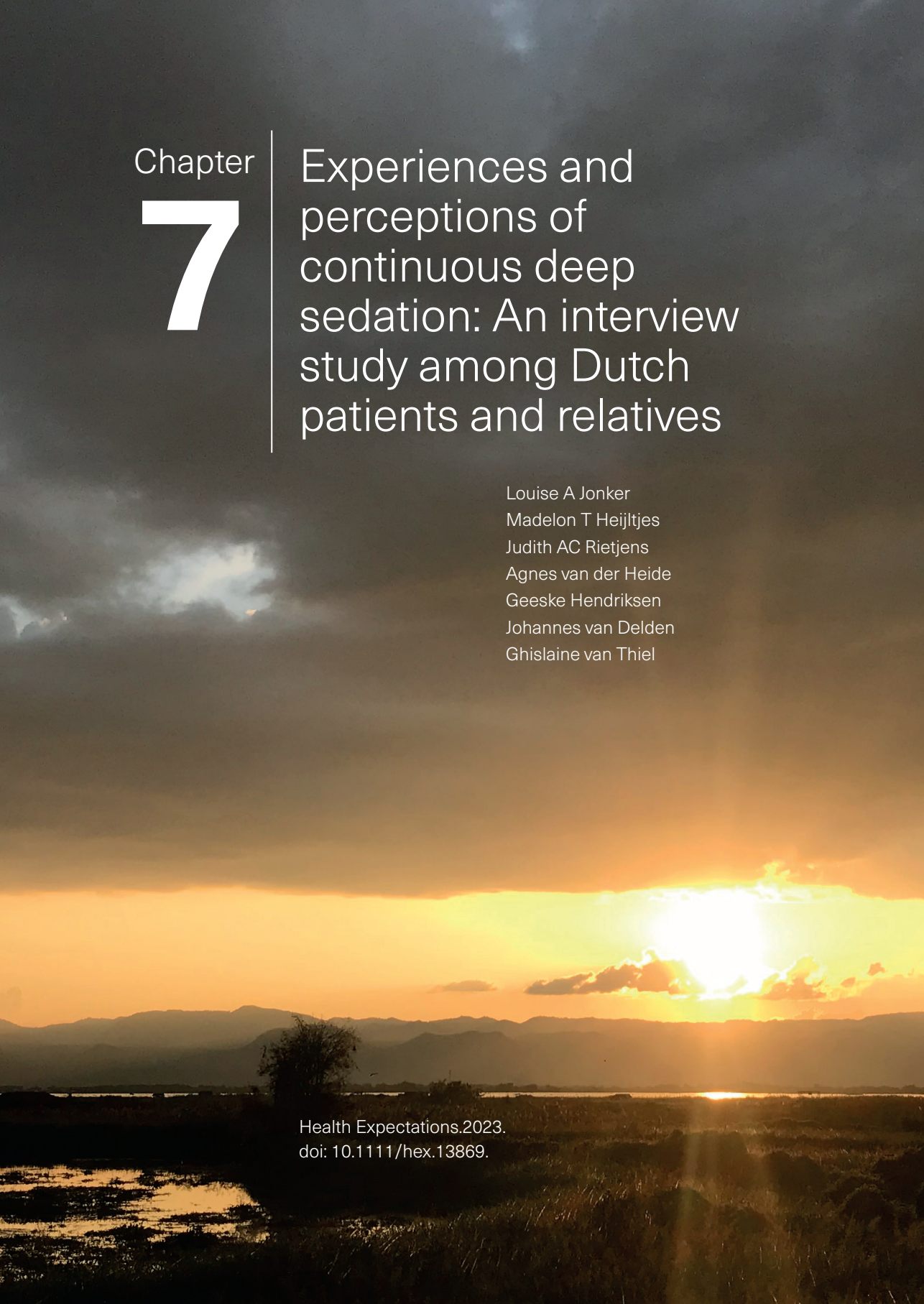
Interview guide, semi-structured interviews with health care professionals on the use of continuous deep sedation	
Definition	
Can you explain what you consider as palliative sedation? Definition of palliative sedation: In this interview we want to elaborate on the most far-reaching form of sedation: the use of continuous deep sedation until the end of life (CDS).	
Reflecting on the health care professional's most recent case of CDS	
Health care professional's most recent case of CDS	- Introduction by the health care professional of their most recent case of CDS - Wat was the reason to consider the use of CDS? - How did the decision-making take place? - Did you experience pressure? - What was the estimated life expectancy of the patient? - How did the sedation proceed? - Can you tell something about how the sedation was performed? - How do you look back on the dying process of the patient and the use of CDS?
Changed practices in the use of CDS	
CDS in clinical practice	- Did your practice of how to provide CDS change? - Do you discuss the use of CDS often with your patients? - What is your experience of what patients and their relatives know about the use of CDS? - What are their expectations of CDS? - Did your point of view on the use of CDS change? - For which indications do you mostly provide CDS? - For which patient groups do you usually start CDS? For example - Did the decision-making process change compared to 5 years ago? - Do you use the national guideline on the use of CDS?
Quotes on the opinions and experiences of the health care professionals	
Quotes	- In my opinion, CDS is not much more than a normal part of palliative care - The transition from symptom relief towards CDS is usually a slippery slope - In my opinion, it is important to discuss the use of CDS in conversations with patients on the dying process, - My patients are less able to cope with severe symptoms than 5 years before. - In my opinion patients experience greater need to be in control of their own dying process compared to 5 years before. - I experience a greater need to be in control of the dying process of patients compared to 5 years before. - A lot of my patients consider the use of CDS as a mild form of euthanasia (passive euthanasia or euthanasia light) - Over the years, I've widened my interpretation of refractory suffering - As health care professional I consider the use of CDS as a mild form of euthanasia (passive euthanasia or euthanasia light) - In my opinion, palliative sedation is a medical answer to a medical problem
Finishing the interview	



Chapter

7

Experiences and perceptions of continuous deep sedation: An interview study among Dutch patients and relatives

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Abstract

Background
The incidence of continuous deep sedation (CDS) has more than doubled over the last decade in The Netherlands, while reasons for this increase are not fully understood. Patients and relatives have an essential role in deciding on CDS. We hypothesize that the increase in CDS practice is related to the changing role of patients and relatives in deciding on CDS.

Objective
To describe perceptions and experiences of patients and relatives with regard to CDS. This insight may help professionals and policymakers to better understand and respond to the evolving practice of CDS.

Methods
Qualitative interviews were held with patients and relatives who had either personal experience with CDS as a relative or had contemplated CDS for themselves.

Results
The vast majority of respondents appreciated CDS as a palliative care option, and none of the respondents reported (moral) objections to CDS. The majority of respondents prioritized avoiding suffering at the end of life. The patients and families generally considered CDS a palliative care option for which they can choose. Likewise, according to our respondents, the decision to start CDS was made by them, instead of the physician. Negative experiences with CDS care were mostly related to loss of sense of agency, due to insufficient communication or information provision by healthcare professionals. Lack of continuity of care was also a source of distress. We observed a variety in the respondents' understanding of the distinction between CDS and other end-of-life care decisions, including euthanasia. Some perceived CDS as hastening death.

Conclusion
The traditional view of CDS as a last resort option for a physician to relieve a patient's suffering at the end of life is not explicit among patients and relatives. Instead, our results show that they perceive CDS as a regular palliative care option. Along with this normalization of CDS, patients and relatives claim a substantial say in the decision-making and are mainly motivated by a wish to avoid suffering and exercise control at the end of life. These distinct views on CDS of patients, their relatives and healthcare providers should be reconciled in guidelines and protocols for CDS.

Introduction

Continuous deep sedation (CDS) is a form of palliative sedation that relieves suffering at the end-stage of life by continuously lowering the consciousness of the terminally ill patient until death.[1] According to the Dutch guideline—of which core elements are presented in Table 1—the indication for CDS is the presence of refractory symptoms causing intolerable suffering in the last weeks or days of life. Symptoms are deemed refractory when they cannot be controlled to an acceptable degree within a reasonable time or without unacceptable side effects.[2-4] Classic examples of refractory symptoms are severe dyspnea, pain and delirium.[5] It is internationally viewed primarily as a last resort medical decision, and the patient cannot opt for CDS unless the preconditions are fulfilled in the opinion of the physician.[2, 4, 6]

In recent years, the practice of CDS in The Netherlands has expanded significantly from 8.2% of all deaths in 2005 to 18.3% in 2015. This increase was observed in all age groups and for all causes of death. However, the increase was most prominent in patients over 80 years of age and patients dying from cancer or cardiovascular disease.[7] CDS is a far-reaching intervention and many have argued that it can only be justified on serious and proportionate grounds.[8-11] The increase in its use calls for a profound understanding of current practice.

European research on CDS has mainly focused on the perceptions of healthcare providers (HCPs), whereas the experience of patients and relatives has received less attention.[12-17] Their role in the decision-making on end-of-life care has, however, been recognized as indispensable.[18] Indeed, over the last decade research shows an increasing concern of HCPs for the wishes of patients and relatives with respect to CDS, and patients desire a more active role in end-of-life decisions.[16,17,19] This stands in contrast with the 'last resort' view of CDS in which its indication is solely a medical one and the decision about its use should be made by the physician. The rise in the frequency of CDS could be associated with a change in the role of the patient in decision-making. Better insight into the views and experiences of patients and relatives may contribute to the understanding of the increase in the use of CDS in The Netherlands and may help professionals and policymakers to adequately respond to the evolving practice of CDS.

Table 1. Core elements of the 2009 version of the RDMA guideline on the use of CDS*

- Continuous sedation is the practice of intentionally lowering the consciousness of patients continually until death at the end stage of life to reduce unbearable suffering.
- Continuous sedation is always administered in the final stage of life. The patients concerned are dying and experiencing unbearable suffering.
- Medical indications are present when one or more intractable or 'refractory' symptoms are causing the patient unbearable suffering. A symptom is considered to be refractory if none of the conventional modes of treatment is effective or fast-acting enough, and/or if these modes of treatment are accompanied by unacceptable side effects.
- A precondition for the use of continuous sedation is the expectation that death will ensue in the reasonably near future—that is, within 1–2 weeks. Next to physical suffering, existential suffering can also play a role in determining if suffering is unbearable and refractory. However, existential suffering alone cannot be an indication to start continuous sedation. When patients suffer from existential problems, it is recommended to consult an expert in psychosocial and spiritual care.
- Palliative sedation is a medical response to a serious medical problem. A patient cannot opt for continuous sedation unless the indications and preconditions for this option are fulfilled. Only if the indications are present, in the physician's opinion, and the preconditions have been met does continuous sedation become a right that the patient may choose to exercise.
- The general rule is that palliative sedation should not be initiated without the consent either of the patient himself or, if he is decisionally incompetent, his representative. The patient's condition may make it necessary to administer acute sedation. This means sedating a patient in a situation in which a complication (frequently one, i.e., life-threatening) suddenly occurs that causes unbearable suffering. In that case, the physician may decide that acute sedation is the only sound option for alleviating the patient's suffering at the point in time.
- Where a physician has doubts regarding his own expertise or has difficulty balancing the different considerations involved in deciding whether to start CDS, it is standard professional practice to consult the appropriate expert in good time.
- Midazolam is the drug of choice, the use of morphine as a sedative is bad practice.
- In principle, there is no artificial administration of fluids during the provision of continuous sedation.
- Continuous deep sedation differs from euthanasia in that its aim is not to shorten life.

Abbreviations: CDS, continuous deep sedation; RDMA, Royal Dutch Medical Association.
*The 2009 version of the RDMA guideline was the actual version during the time of the interviews.

Methods

Design

We conducted a qualitative study using semistructured interviews. The interviews were guided by a topic list based on CDS literature and input by author G. H. who experienced CDS as a relative and provided us with a detailed description of her experience on current CDS practice.[20-24] The topic list was tested during three pilot interviews and adjustments were made accordingly in discussion with G. H. An English version of the topic list can be found in Supporting Information: 1. All respondents were questioned on their individual views of CDS and, if applicable, on their experience of CDS as a relative.

In our study, CDS was defined according to the definition of the Royal Dutch Medical Association (Table 1). However, respondents may not always be aware of the exact definition of CDS. To ensure respondents were discussing CDS and not another palliative care intervention, they were questioned on their understanding of the concept of CDS. In case a respondent understood CDS in ways contrary to the general definition of CDS, this was corrected during the interview using teach-back.

Study sample

We recruited a sample from an existing panel of laypersons at the University Medical Center Utrecht, The Netherlands (UMCU). This panel consisted of patients who received care at the UMCU and indicated their willingness to partake in scientific research. Additional respondents were recruited through the personal network of the researchers. Potential respondents were included if they had experienced CDS with a close relative or had contemplated CDS for themselves. Respondents participating as relatives could be a partner, family member or friend of a person who had received CDS, but not someone who took care of the patient professionally. The potential respondents were invited by email and people who expressed their interest in participation received further information, after which they were asked to give informed consent for use of their data for the purposes of this research.

Data collection

The interviews were conducted by L. A. Jonker, at that time a senior medical student, and M. T. Heijltjes, a physician working as a PhD student, who was trained in qualitative research. L. A. Jonker was supervised by M. T. Heijltjes and G. J. M. W. van Thiel, an experienced qualitative researcher. The interviews were held between November 2019 and June 2021. The interviews took place at a location suitable to the respondent, but from March 2020 onwards interviews were exclusively conducted through telephone or an online video connection, due to official regulations related to the COVID-19 pandemic.

The inclusion of respondents continued until the research group concluded that conceptual saturation was reached.

Data analysis

We conducted a thematic analysis of the data that was partly deductive and partly inductive in nature. Experiences with cases were analyzed when they had occurred after the—at the time—most recent guideline on CDS by the RMDA (2009). We excluded reports of intermittent sedation and a case in which the respondent was involved in a professional role.

The data analysis consisted of four phases; as a first step, L. A. Jonker read and reread all transcripts thoroughly. Subsequently, L. A. Jonker coded all transcripts in light of the research aim using NVivo software version 12.6. Additionally, G. J. M. W. van Thiel and M. T. Heijltjes individually read and coded four transcripts. The coding was then discussed and refined. In the third phase, the codes were categorized and bundled into overarching concepts, to create an overview of the results. Lastly, using several open and critical conversations with all authors, central themes and core categories were identified with the main purpose of answering the research question. Illustrative quotes were translated from Dutch into English.

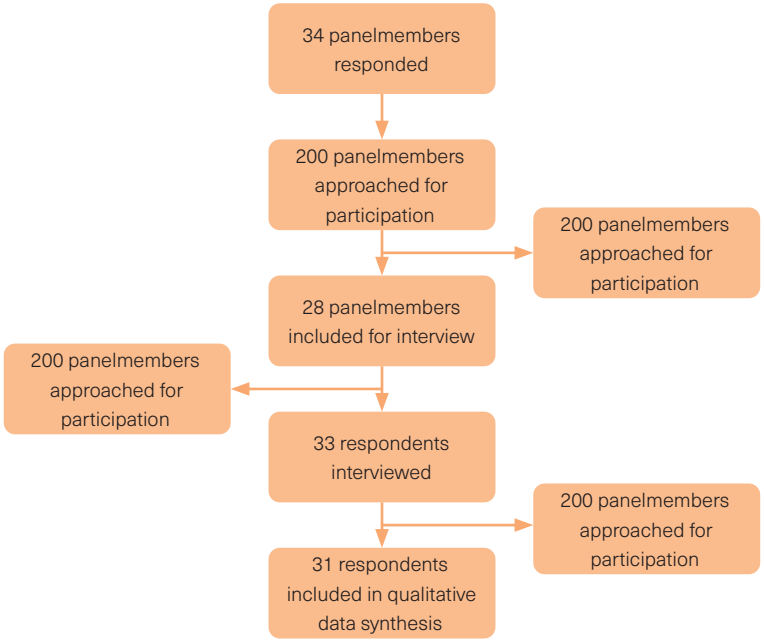
Ethics approval and reporting

The medical research ethics committee METC Utrecht confirmed that under Dutch Law, this research is exempt from review by a medical research ethics committee (protocol number 19-435/C). This study is reported according to the COmprehensive consolidated criteria for REporting Qualitative research.[25]

Results

Two-hundred members of the patient panel were invited to participate. In total, 34 panel members responded of which six were excluded. Five additional respondents were added through personal network. In total, 33 respondents were interviewed. During data analysis two respondents were excluded as we were not able to determine with certainty that the interviews were about CDS: these respondents did not demonstrate adequate understanding of CDS and did not receive a teach-back from the interviewer. All of the 31 remaining respondents displayed a correct understanding of CDS either by their own knowledge or after the teach-back provision (Figure 1).

Figure 1.



All respondents recruited via the UMCU patient panel (26) were included as patients, as they all received care for a variety of serious illnesses at the UMCU and therefore in a situation in which they had contemplated or discussed the option of CDS. Twenty-six respondents had experience as a relative of a patient for whom CDS was considered (5) or performed (31) and some respondents reported on more than one CDS case. Characteristics of the respondents and of the cases are listed in Table 2. The majority of the discussed CDS cases dated back less than five years. The duration of the interviews was between 30 and 90 min. We identified six themes relevant to our research question.

Table 2. Respondent and case characteristics (n=31)

Age	
40–49	2 (6)
50–59	6 (19)
60–69	15 (48)
70–79	8 (26)
Gender	
Female	19 (61)
Male	12 (39)
Level of education[a]	
Higher	25 (81)
Lower	6 (19)
Religion	
None	20 (65)
Christian	9 (29)
Unspecified	1 (3)
Buddhist	1 (3)
Contemplated CDS as a patient	
Yes	26 (84)
No	5 (16)
Experience with CDS as a relative[b]	
Yes	26 (84)
No	5 (16)
CDS was provided	
Yes	31 (86)
No[c]	5 (14)
Medication used to achieve CDS according to respondent	
Midazolam	17 (55)
Morphine	6 (19)
Unclear	8 (26)
Respondent present during CDS care provision	
Yes	31 (86)
No	5 (14)

Abbreviations: CDS, continuous deep sedation; HCP, healthcare providers.
[a] Level of education was defined according to the International Standard Classification of Education 2011: higher education included all individuals who had a university degree (bachelor, master or doctoral) and lower education included all individuals who had either no education, primary education alone, secondary education alone or postsecondary nontertiary education. [b] Some respondents discussed more than one CDS case. [c] In these cases CDS was discussed by the family with an HCP, but eventually, CDS was not provided due to a variety of reasons

Reasons for starting CDS

None of the respondents reported (ethical) objections to CDS. All respondents indicated the importance of a peaceful and painless deathbed. Suffering was considered unacceptable by most respondents and was the main reason for starting CDS in the discussed cases. Pain was the major source of intolerable suffering, followed by delirium, dyspnea and nausea. Existential suffering, due to fear, loss of identity, and a sense of pointlessness, was also considered unacceptable suffering and a motivation to start CDS in several cases.

> *Interviewer: What made her so uncomfortable?*
> *Respondent: Well, I think a sort of fear of death. I think not knowing what will happen, and how long it will take.*

Sometimes the relative asked to reduce suffering, which led to the decision of an HCP to initiate CDS:

> *Respondent: Well, after we specifically asked for something to calm her down, the health care workers decided to give her a butterfly needle which was used to administer morphine and midazolam.*

When discussing their own death, several respondents brought up that they would consider CDS for themselves to reduce the suffering of their relatives as a consequence of their own suffering. Other respondents mentioned the wish for CDS in case they would become severely dependent on care. For example, when admission to a nursing home is inevitable, or when there is a necessity for life supporting measures such as mechanical ventilation.

The decision-making process towards CDS

The respondents in our study generally believed that the decision for CDS was made by the patient, and not the physician. They regarded starting CDS as a matter of choice between other end-of-life care options, such as euthanasia. Physicians were valued as advisors, and guided the decision-making process but were not seen as the one making the final decision to start CDS.

> *Respondent: Yes, we discussed this with him, the doctor and me. I mean, he [the patient] had to make a decision, but we discussed it together at home.*

In case the patient was cognitively impaired, relatives made the decision together with the physician. In a few cases, the respondent reported that the physician initiated CDS without involving relatives in the decision. This was mostly experienced as frustrating by the relatives.

Respondent: At a certain moment it [CDS] was started, and then my youngest sister became very angry because it wasn't discussed with us as family. She said: this can't just be a statement [starting CDS], I want to discuss this with the treating physician!

Several respondents had asked an HCP involved in the care of their relative for measures to reduce the patient's suffering and some had explicitly asked for CDS, which was subsequently granted by the attending physician. Incidentally, relatives or HCPs convinced patients to start with CDS, as they thought that the suffering had become too intense.

Respondent: But eventually the doctor, together with her [the patient's] husband, kind of convinced her. She of course knew that things were ending. I think eventually she also felt, well, very tired. But, and I'm not saying it was against her will because then the doctor wouldn't do it of course, but they had to convince her.

The vast majority of respondents indicated that they wanted to make the decision to start CDS for themselves, in case they would need it in the future. If this were impossible, for example, due to cognitive impairment, most respondents stated that their relatives should make the decision for them.

Respondent: Look, when you're somewhat able to decide for yourself, I think you do this together with everyone involved. Well, and if that isn't an option, I have the impression that it's a decision that is made in agreement with the family and doctors. (...) But, in principle the decision is mine.

A minority of respondents thought that the physician should decide about starting CDS, as medical expertise was considered to be fundamental.

Respondent: So, his [the doctor's] medical knowledge is always decisive. And to be fair, when I think it's time, and he doesn't, well we have to discuss this because I don't want to overrule his medical knowledge. But yes, if you ask me explicitly, I think the doctor should make the assessment. Whether providing it [CDS] is rational.

The timing of conversations about CDS was also important. Respondents with experience as a relative were generally positive about early discussions on CDS, as this provided them with clear information and provided a sense of preparedness. However, in many cases, respondents said that CDS was discussed when a situation of refractory suffering was already at hand, and that it had not been a topic of conversation before that moment.

According to some, conversations on death and treatment options in the dying phase were avoided in its entirety by both patients and HCPs. In these cases, the suggestion of CDS by the treating HCP sometimes came as a surprise.

> *Respondent: In the end, we weren't included in the discussion about her treatment. At a certain point, several persons who didn't know me or my mother entered the room and injected a sedative into her. To me, this was all very disrespectful. Because this is her... well her last. and this was not specified. They never clearly discussed her dying phase with us.*
> *Interviewer: So you weren't included in the decision-making process?*
> *Respondent: No, while I was aware of what was happening due to my own knowledge. But I wasn't involved, no.*

Experiences with the provision of CDS care

All respondents mentioned the importance of adequate communication and clear information by the involved HCPs. Several respondents with experience as a relative said that inadequate information provision and communication on CDS led to distressing situations. However, when expectations were managed by the HCP and patients and families were well informed on CDS care and potential complications—such as waking up—less distress was experienced.

> *Respondent: Well, I didn't know what it [CDS] entailed and neither did my father. My father said: 'The doctor will be here soon, shall I lie down on the couch downstairs? In that way they don't have to carry me down the stairs when I'm gone'. But eventually, it took three days before he died. He just imagined it [CDS] to be something else than it was in reality. Well, the doctor administered the injections, and the home care nurses were supposed to ensure the medication would be repeated in time. But he woke up – which shouldn't have happened – and my father thought that he was gone but he wasn't. I thought that was horrible. To me, this was, very, very awful.*

Taking time to connect with the patient and relatives, listening carefully and being receptive towards their input were considered to be essential aspects of communication by HCPs. Additionally, it was considered important that the HCP ensured that both relatives and patients understood the situation and were addressed in an appropriate manner, without the use of medical jargon.

> *Respondent: Well, that was a good conversation. She was accompanied by a physician in training. And my husband asked for careful explanation because he thought it resembled euthanasia. No, it is not euthanasia, it is helping with the dying process, and she would explain it a hundred times to him.*

Most respondents who experienced CDS as a relative said that closely involved and available HCPs were of paramount importance to both the patient and themselves. In particular, mutual trust and understanding were important qualities in the relationship with the HCPs. Therefore, patients and relatives mostly preferred that their treating physician, with whom such a relationship was already established, provided CDS care.

> *Respondent: And when she was in a very poor condition, her physician went on a holiday for a week before she died. Well, we didn't like that, because we had a very good relationship with this man, and he was also the one she confided in. And on Wednesday another physician came to see her, and he said: well, we can start the palliative sedation. We can give you the sedation now. At that point, she already had morphine and such. But she didn't want that at all, because, well, she wanted to wait until her own physician returned from holiday.*

Several respondents experienced that continuity of care was compromised when care had to be transferred from one provider to another and when staffing levels were low, for example outside regular working hours. Relatives repeatedly had to ask for care, as this was not timely provided in their view.

> *Respondent: But in the weekend... yes that's horrible. When you're in labor during weekends, everything carries on, but when you die you must wait until Monday.*

Quality of dying with CDS

In almost all cases reported by the respondents, the patient died within one week after starting CDS. Respondents were largely satisfied with the quality of dying of their relatives under CDS; 'a relief' was frequently the word used to describe what they had experienced when CDS had commenced. The main reason for this was that CDS allowed the patient to die calmly, without any pain, restlessness or other suffering. Respondents often compared the dying of their relative to sleeping, which was considered comforting, and they were also appreciative of the idea of a gradual dying process during which the patient gently slides away into death.

> *Respondent: The whole night she just slept very well, and that last part was so good. You just see that she doesn't have to suffer anymore and that she was asleep, and was also not gone at once.*

In various reported cases the patient showed signs of restlessness, which was considered to be undesirable. Incidentally, the patients woke up from sedation, and this was appreciated with mixed emotions by our respondents.

For some, it was not upsetting, as they were aware that this could occur. However, others were very distressed when it happened.

> *Respondent: She moved her head restlessly from side to side, and she made fists with her hands. And her one leg moved restlessly. And her right hand was paralyzed, so we put a piece of cloth in her hand so she wouldn't hurt herself with her nails. Those kinds of things. She was just too agitated. For me, this was very difficult.*

The fact that CDS implies loss of the patient's ability to communicate was not considered problematic by the respondents. Comfort for themselves or their relative was more important. However, when relatives were not counseled properly that communication is not possible after commencing sedation, this was a source of distress.

Distinction between euthanasia and CDS

In multiple cases, relatives reported experiences of hastening the patient's death by CDS. In some cases, this was explicitly discussed with the attending HCP, and in other instances, this was the perception of the relative or of the patient themselves. Hastening death was mostly considered a desirable effect of CDS in light of the patient's terminal condition.

> *Respondent: So, my husband woke up when the doctor prepared the sedative. And my brother-in-law and I said goodbye to him. And then the medication was administered, but nothing happened. He just stayed alive. And the doctor thought that he would have died while administering the morphine. But that didn't happen. He [the doctor] said: sometimes that happens. And then he gave him the sedative. And my husband still didn't die. And then our doctor said: well, I don't know how he does it, but he's still alive.*

When discussing their views on palliative care for themselves, many respondents held the opinion that it was a matter of choice or preference whether euthanasia or CDS should be used to relieve their suffering. Respondents who preferred CDS over euthanasia mentioned that they appreciated CDS as this is a more gradual process allowing them to calmly die without needless suffering. They also thought that CDS would be more acceptable to relatives, and less difficult for physicians compared to euthanasia. Additionally, multiple respondents indicated that CDS is acceptable from a religious standpoint. Respondents who preferred euthanasia over CDS brought up that euthanasia accommodates more personal agency and avoids a potentially long and burdensome terminal phase.

Several respondents indicated that, although in general they preferred euthanasia, in certain circumstances CDS would be preferential to them.

Mainly when the procedure towards euthanasia would be too time-consuming, for example, when suffering was a result of an acute situation, or when cognitive problems would make euthanasia impossible. These were also important reasons in several of the discussed cases to revert from euthanasia to CDS. In most of these cases, the clinical situation deteriorated rapidly, leaving no time to start up the euthanasia protocol. In other cases, euthanasia was no option due to a lack of competence on the part of the patient, for example, due to stroke or dementia.

Perceptions of CDS

Most respondents were aware of the main principles of CDS. However, some of the respondents did not display a correct understanding of CDS before clarification by means of a teach-back. For example, several respondents thought that CDS comprised pain control without necessarily lowering the patient's consciousness. In a few cases, CDS was confused with starvation in the absence of lowering consciousness. In particular, respondents who were included as patients and who did not have lived experience with CDS as relatives misunderstood the concept of CDS.

Almost all respondents were aware that palliative sedation is distinguished from active life termination, but many believed that palliative sedation hastens death, for example by means of starvation or highly dosed medication.

The respondents' initial perceptions of CDS were informed through various sources, such as newspaper articles and the internet, but also through personal contacts, earlier experience with CDS and discussions with HCPs.

Discussion

Relatives were generally positive about their experience with CDS, especially when their loved-one died peacefully. Situations of unbearable suffering during the dying phase were considered unacceptable by patients and relatives, and a calm and peaceful death was seen as crucial. The suffering of a dying patient called for intervention leading to the initiation of CDS. The reported suffering of patients was mostly caused by pain, restlessness, and dyspnea. However, in several cases, existential suffering or the prevention of suffering was mentioned as the main motivation to start CDS. This potential broadening of the indication is perhaps one reason for the increased practice of CDS in end-of-life care.

In our interviews CDS was often thought of as a matter of choice by the patients and families, in which the patient decides and the physician serves as an advisor, reflecting the importance of self-agency at the end stage of life. Distress often arose from a lack of feeling in control, and especially a lack of involvement in decision-making on CDS was a major concern for relatives.

Tensions related to communication and involvement may be caused by divergent views on responsibility and decision-making about CDS among patients, relatives and HCPs. On the one hand, CDS is traditionally regarded as a 'last resort' medical decision, for which a physician is ultimately responsible.[2-4, 6] On the other hand, there is strong agreement that the key to improvement of end-of-life care is to make the care consistent with patient preferences by an individualized process of decision-making.[26, 27] In our study, respondents often said that the decision was eventually made by the patient or relative, the latter in the case of cognitive impairment of the patient. Many saw the role of physicians mainly as advising on available end-of-life care options, and on the right timing for CDS initiation. These results differ from similar research conducted ten years ago when relatives reported that the final decision was made by the attending physician.[21] Nevertheless, in recent years research has shown that HCPs put more emphasis on the wishes of patients and relatives.[16, 17, 19] A study involving HCPs from the United Kingdom, Belgium and The Netherlands showed that the Belgian HCPs tend to frame CDS as a regular end-of-life care option for which the patient can choose.[28] The dominant view among our respondents of CDS as a normal palliative care option for which they can choose instead of a last resort informed by a medical judgment on the refractory state of symptoms may contribute to an increase in requests for CDS.

The wish for a calm and peaceful death was so important that moral problems with CDS raised in the literature were of no concern to our respondents. The difference between CDS and euthanasia was recognized, but still, most respondents thought that CDS potentially hastens death—which is usually considered key to the ethical distinction between CDS and euthanasia.[2-4] However, the idea of respondents that CDS potentially hastens death was actually viewed as acceptable by them, as death was a better alternative than unbearable suffering. This relates to another ethical concern regarding the distinction between CDS and euthanasia. Namely, it has been suggested that CDS results in the social death of the patient due to loss of awareness and thus communication.[9] However, losing the ability to communicate was mostly not experienced as problematic by the relatives in our study.

In general, our respondents were satisfied with the quality of CDS and the care they received. We identified several determinants of good quality of death with CDS. First and foremost, respondents appreciated CDS when it allowed the patient to die a calm and peaceful death. It was considered 'a relieve' when the suffering of their loved one had ended due to CDS. The gradual nature of CDS, in which the patient slides away into death while seemingly asleep, was considered comforting for both patient and relative and added to a positive experience of CDS. This was often contrasted with euthanasia, which some thought to be too abrupt. Respondents valued it when continuity of care was guaranteed and when CDS was attended by their own physician.

Many of our respondents reported that CDS was appropriately discussed by HCPs, which was appreciated as it enhanced understanding and managed expectations of CDS. However, for several respondents, CDS was also a source of distress. Unmet expectations, inadequate communication and information provision, and difficulties in understanding CDS contributed to the distress and reduced the experienced quality of CDS. Adverse experiences regarding communication and information provision were also reported in other studies.[21, 23, 29, 30] This underlines the importance of timely and adequate communication on end-of-life decisions including CDS with both patients and relatives.

Most respondents were able to give an accurate description of palliative sedation and CDS, and were informed through media exposure, earlier experiences of end-of-life care, and advance care discussion with HCPs. Improved attention on end-of-life care in the public may partly explain the increase in CDS, as patients and relatives are better aware of palliative care options. However, some respondents misunderstood CDS: starvation, pain reduction and abstaining from life-prolonging measures in the absence of lowering a patient's consciousness were also considered to be palliative sedation by some. This finding corresponds with earlier research among the general public in The Netherlands, in which the term palliative sedation was also indistinct.[31] The misunderstanding was most prominent in the respondent group without lived experience of CDS as a relative. The group that experienced CDS as a relative, was mostly aware of the important principles of CDS.

When situating our results within the evolving practice of CDS, several explanations from the perspective of patients and relatives for the increase of CDS can be suggested. First, there seems to be a shift in indication assessment, as experienced patients and relatives sometimes report that CDS is currently used to relieve existential suffering. Second, patients and relatives emphasize the importance of comfort at the end-stage of life, and desire agency over the decision-making on palliative care options in this phase. Lastly, CDS may be requested more often as respondents were better informed on end-of-life care.

Strengths and limitations

The main strength of this study is that the in-depth interviews allowed uncensored insight into the experiences and perceptions of CDS of both patients and relatives within an evolving practice of CDS. However, several limitations may have influenced our results. Most importantly, some respondents—especially those without lived experience with relatives—initially misunderstood the term CDS/palliative sedation, although we corrected this in our interviews and excluded respondents who did not receive a teach-back it could be that this influenced our results. Secondly, our respondents were mainly highly educated Caucasian patients at a tertiary care center in the middle of The Netherlands.

These respondents are more likely to emphasize the importance of open communication and good quality of dying. Whereas it is known that people from non-Western cultures often have different ideas on good palliative care.[32,33] Unfortunately, we were not able to include respondents with non-Western cultural backgrounds. This raises questions on the generalizability to non-Western populations as their perceptions of CDS are probably not reflected in this study. Thirdly, potential respondents were not selected randomly, and therefore selection bias is possible, especially respondents with an interest in end-of-life may be more likely to apply for participation. Lastly, recall bias may have played a role, as the first case occurred in 2009.

Conclusion

The traditional view of CDS as a last resort option for a physician to relieve a patient's suffering at the end of life is not present among patients and relatives in our study. Instead, our results show that they perceive CDS as a regular—and not an exceptional—palliative care option. Along with this normalization of CDS, patients and relatives claim a substantial say in the decision-making and are mainly motivated by a wish to avoid suffering and exercise control at the end of life. This may result in an increase in CDS requests. The distinct views on CDS should be reconciled in guidelines and protocols for CDS. This can be done by introducing a shared-decision model in which the HCP, the patient and relatives are responsible for deciding on CDS, and not primarily the physician. By doing so, guidelines will better reflect the current practice of CDS.

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Interview guide, semi-structured interview with relatives	
Introduction interview palliative sedation	
Today we are going to discuss the topic palliative sedation, as you experienced this up close with your relative.	
When reflecting on the dying of your relative	
Your relative passed away some time ago. Can you tell how his or her last days were?	
Looking back on the dying process of the relative, structured	
Case	• **What was the reason to start considering palliative sedation?** • **When was palliative sedation discussed for the first time?** *Who initiated this conversation?* • **Which healthcare professionals were involved, and at what time?** *How was the communication with them?* • **How did the decision-making process go?** *What were the most important reasons for the decision?* *Did your relative feel involved in the decision?* *How were you as a relative involved in the decision?* • **How did the palliative sedation go?** *Did your relative wake up from the sedation at any point?* *What did you think about the performance of the medical staff*? • **Did you know how the palliative sedation was performed?** *Pumps and equipment* *Medication* *Fluids and nutrition* • **Was euthanasia an option, and how was this discussed?** • **What were your expectations of palliative sedation?** • **How do you look back on the palliative sedation and the passing of your relative?** *Was it difficult for you that you could not communicate with your relative?*
Own perceptions	
Passing of relative	How would you describe the passing of your relative in a few words?
Dying	Did the passing of your relative influence your own ideas of dying?
Palliative sedation, own perception	What do you think about giving CDS to someone who is terminally ill? Do you think palliative sedation should be applied when someone suffers unbearably from psychological symptoms at the end-stage of life?
Euthanasia vs palliative sedation	Do you thinks euthanasia differs from CDS? Why ?
Stands: My relative and me felt adequately informed on palliative sedation My relative suffered unbearably before palliative sedation commenced I think palliative sedation made dying more pleasant for my relative.	

Interview guide, semi-structured interview with patients.	
Introduction interview palliative sedation	
Today we would like to discuss palliative sedation because you have considered it, or are considering this for yourself.	
When reflecting on your thoughts	
Case	• **Can you tell what the reason was to start considering CDS?** • **What is your expectation of CDS?** *What would palliative sedation yield?* *How do you know when it is 'time' for palliative sedation, and who would indicate this?* • **What do you like about palliative sedation, and what don't you like?** *Have you discussed palliative sedation with others?* *Relavies?* → *who started this conversation* *Healthcare professionals?* → *Who initiated this conversation?* → *How is the relationship with them?* → *Are they easiliy accessible?* • **What are important elements in the decision for palliative sedation?** *Does the loss of ability to communicate with your relatives play a role in your decision?* • **Have you experienced palliative sedation with someone else before?** *Did this change your view on dying?* • **Do you know how palliative sedation is performed?** *How did you receive this knowledge?* • **What do you think about euthanasia?** *Is euthanasia an option for you?* *Is euthanasia different from palliative sedation?* • **Would you consider palliative sedation if you suffer unbearably from psychological symptoms in the last days of your life?**

Chapter

8

General discussion

Introduction

When patients suffer unbearably at the end of life, sedatives can be used to relieve their suffering. Palliative sedation is the umbrella term for this type of symptom control. The most far reaching form is continuous deep sedation (CDS), when deep sedation is provided with a continuous effect until the death.[1, 2] The use of CDS has been debated for many years.[1, 3-5] This debate is complicated by the many different terms and definitions that are used in the literature to describe the relief of the severe suffering of terminally ill patients through the use of sedatives.[6-10] In the Netherlands, the use of CDS has sharply increased, from 8.2% of all deaths in 2005 to 18.3% in 2015. Recent studies show an even further increase in its use in this country up to 23% of all deaths in 2021.[11] Study results of 2021, of death certificates from the central death registry of statistics on CDS, were not included in this thesis.

However, there is a lack of knowledge about the causes of this increase.[12] The principal aims of this thesis, therefore, was to provide insight into current CDS, to explore how its use has changed between 2005 and 2015, and to identify the causes of the increase. This general discussion starts by providing answers to the research questions as described in the introduction. This is followed by identifying the different strengths and limitations of the studies. Subsequently, the potential causes of the increase in the Netherlands which we identify are discussed in further detail, addressing, among other things, the justifications for CDS and the decision-making processes surrounding the practice.

Research question 1

What are the characteristics of the patients who receive CDS, and did these change over time?

In Chapter 2, we show results from repetitive nationwide questionnaire studies on end-of-life decision practices among physicians in the Netherlands based on a stratified sample of deaths (response rate 78%). The percentage of patients who received CDS was 20.7% for deaths attended by general practitioners, 18.4% for deaths attended by clinical specialists, and 14.3% for deaths attended by elderly care physicians. Fifty-five percent of all sedations were performed by a general practitioner, 24% by a clinical specialist, and 21% by an elderly care specialist. We observed an increase in the use of CDS in all different age groups, 0-64, 65-79, and 80 years or older, and in patients with different causes of death. The increase was the highest among elderly patients and patients with malignancies under the care of general practitioners. Of all patients, 97% died within the first seven days after the start of sedation.

Research question 2

Has the use of CDS changed internationally over recent years?

In Chapter 3, we present a systematic literature review. We aimed to explore developments in the use of CDS on an international level between January 2000 and April 2020. Furthermore, we aimed to provide insight into the indications for using CDS during this period. We included 23 articles describing 16 nationwide studies, and 38 articles about 37 sub-population studies. In the nationwide studies, the percentage of CDS ranged from 3% in Denmark in 2001, to 18.3% in the Netherlands in 2015. The nationwide studies show that the use of CDS seems to have increased on an international level over time. Over the years, an increasing number of studies reported on the use of CDS for non-physical symptoms such as anxiety and psycho-existential distress. Some studies showed an increase in requests for sedation from relatives of the patient instead of the patients themselves.

Research question 3

What are symptoms patients experience at the end of life for which CDS could be indicated?

In Chapter 4, we describe data from the Dutch Care Program for the Dying (CPD, in Dutch: *Zorgpad Stervensfase*) that provide insight into symptoms that patients experience at the end of life. We analyzed four-hourly registrations for 2,786 patients and assessed, in how many cases, the symptom-related goals of care were not achieved. The following goals of care were analyzed: pain, restlessness, respiratory tract secretions, nausea, vomiting, and shortness of breath. For a substantial proportion of the patients in the hospital, care home, and hospice, at least one symptom-related goal could not be achieved in the last hours to days of life. These percentages were, respectively, 26.9%, 24.9%, and 17.5%. Of all care goals that had not been achieved, the control of pain and an absence of restlessness were most often reported.

Research question 4

What are the perspectives of physicians who use CDS for their patients and how did their perspectives change over time?

In Chapter 5, we report a questionnaire study among physicians in eight different countries about their practices and experiences with CDS in the last hours, to days, of life. In all countries, more than 87% of the physicians considered the use of CDS an acceptable practice in cases of physical suffering in the last hours to days of life. Percentages were substantially lower, 45% to 88% in case of severe psycho-existential suffering in absence of physical symptoms. This percentage was 56% for Dutch respondents The percentages of physicians who considered the use of CDS an acceptable practice varied from 22% to 66% in case of physical suffering, and from 5% to 42% in case of psycho-existential suffering in absence of physical symptoms. These percentages were 42% and 17% for Dutch

respondents respectively. Up to ten percent of the physicians agreed with the statement that CDS is unnecessary, because suffering can always be relieved with other measures. 41% to 95% of the physicians agreed with the statement that a competent patient has the right to demand the use of CDS in the last days of life, this percentage was 91% for Dutch respondents.

In Chapter 6, we describe a qualitative interview study among Dutch health care professionals on the use of CDS. Many health care professionals mentioned that over the years they became more aware of the option of starting CDS. For health care professionals, the reason to start CDS was often a combination of symptoms, resulting in a so-called "refractory state". Health care professionals stated that over the years, symptoms of a non-physical origin have acquired a more important role in the decision to start CDS. They reported an increase in the number of requests to start CDS, and, some health care professionals, mentioned that they experienced an increased pressure from patients and relatives to start CDS. The majority of the health care professionals stated that suffering has become less acceptable to patients, their relatives, and sometimes, also by other health care professionals. The increased awareness for symptoms of a non-physical origin in combination with a lower tolerance for suffering may have led to a lower threshold to start CDS.

Research question 5

What are patients' expectations about CDS and what are the experiences of relatives of patients who received CDS?

In Chapter 7, we report on a qualitative study interviewing patients and relatives on their expectations of, and experiences with the use of CDS. Participants were patients who considered the use of CDS for their selves, and relatives who had experienced the use of CDS involving a relative. The majority of the respondents were aware of the option to start CDS, and appreciated it as a palliative care option. None of the respondents reported objections, moral or otherwise, towards CDS. An indication for CDS was reported mostly for physical symptoms, but fear and existential suffering were also mentioned as sole indications. Relatives and patients considered the decision to start CDS as their own and not as a decision of the physician. Negative experiences with CDS were mostly related to health care professionals failing to communicate properly or provide information, or due to a lack of continuity of care. We observed differences in respondents' understanding of the concept of CDS and of the distinction between it and other end-of-life decisions, including euthanasia. Patients and relatives consider the use of CDS as a regular palliative care option. The traditional view of CDS as an option of last resort is not explicit among patients and relatives. Together with the move towards CDS becoming standard practice, patients and their relatives also now claim a substantial say in the decision making. They are motivated mainly by a wish to avoid suffering and to exercise control at the end of their lives.

Strengths and limitations of the studies:
The combination of different study designs provided a comprehensive picture in this thesis of the practice, and the increase in the use of CDS in the Netherlands. A systematic literature review, in combination with complementary qualitative and quantitative research data, contributed to a better understanding of the increase in CDS. National and international trends in the use of CDS were observed. This thesis sought to find explanations for the increase in CDS, not only in demographic and epidemiological patterns of dying, but also in societal developments, such as increased attention for CDS.

Despite the combination of different research methods, a clear single cause for the increase in CDS could not be identified. However, the systematic literature review, questionnaire studies with physicians, and analyses of the Care Program for the Dying allowed us to gain insight in a large number of cases. A limitation of this broader view was that it was not possible to go into more detail on individual cases. Neither was any information available on the use of CDS in the analysis of the Care Program for the Dying. The interview studies, however, provided more insight into the distinct views and considerations of health care professionals, patients, and their relatives. These were though all based on self-reported practices so there could be a discrepancy between actual and reported practices. In the interview study with health care professionals selection bias could have occurred as nearly all had followed additional training in the field of palliative care, worked on a daily basis with terminally ill patients, and had a special interest in the topic. In the interview study with patients and relatives, selection bias could also have occurred as patients who participated were recruited via a patient panel, in which we presume, all were entirely empowered to share their opinions.

The increase in the use of CDS in the Netherlands
It can be concluded, based on the findings of this thesis that different factors may have contributed to the increase of CDS in the Netherlands.[13-17] Firstly, there has been an increased awareness of the option of starting CDS among health care professionals and among the public. In the interviews with health care professionals, they stated that they were more aware of this option in cases of refractory suffering and thus more often started CDS compared with several years before.[16] They also mentioned that they were more experienced in applying CDS for terminally ill patients, and more often discussed the option to start CDS with patients and their relatives. It could be that the introduction of the national guideline on CDS in 2005 contributed to this increased awareness.[18]

Secondly, health care professionals experienced that, compared with several years before, patients, relatives, and sometimes even other health care professionals are increasingly inclined to raise the subject of CDS in cases of severe suffering.[16] Previous studies also showed that Dutch physicians sometimes experience pressure to start CDS.[19] This pressure was also described

in the decision making about euthanasia. This is especially true for physicians who refused a euthanasia request, or in cases of patients aged 80 years or older, those with diseases other than cancer, and those with a life expectancy of more than six months.[20-22]

Thirdly, there has been a broadening of the indications to start CDS.[16, 17, 23] Previous studies showed that the indication to start CDS is often based on a combination of physical, psychological, and existential symptoms, which is called a refractory state.[24] Where previously indications for sedation were based on symptoms of a physical origin, increasingly, in recent years, symptoms of non-physical origin, such as fear and existential suffering, more often play a role in the decision to start CDS.[14,16]

Several decades ago Cassell provided a definition of suffering. He mentioned that suffering is experienced by persons and has it source in challenges that threaten the intactness of the person as a social and psychosocial entity.[25] Suffering can include pain, but is not limited to it.[25] However, studies showed that there is no consensus among physicians of when CDS should be started in cases of existential suffering.[26] In the literature, existential suffering is described as a loss of meaning and purpose in life, fear of death, loss of dignity, hopelessness, and regret, predominantly in patients who are at the end of their lives.[27-29] But there is no uniform definition of existential suffering.[28,30] The change of indications for CDS for only physical symptoms, towards a combination of physical and non-physical symptoms could be related to a changed attitude towards suffering. Where suffering used to be interpreted as physical, indications to start CDS expanded towards symptoms of non-physical origin. The 2022 guideline of the Royal Dutch Medical Association (RDMA) on CDS does pay attention to existential suffering in relation to the use of CDS. But, for physicians, it can be difficult to identify existential symptoms as contributing to such a refractory state. The Dutch guideline emphasizes that expertise in the area of psychosocial and existential suffering is needed to evaluate this suffering properly in relation to the how far symptoms amount to a refractory state.[18]

Fourthly, the general opinion is that there is no need for a dying patient to suffer at the end of life, as symptoms can always be relieved, if necessary by the use of sedatives. Most physicians consider CDS as, sometimes, a necessary option to relieve severe suffering at the end of life.[17] In our interview study with health care professionals, they stated that suffering is less accepted by patients, their relatives, and sometimes also by other health care professionals.[16] Dying while sleeping is often considered a peaceful death by patients, relatives, but also by health care professionals.[13, 16, 31] Health care providers mentioned that the death of a patient is often pictured as a beautiful event. They suggested the media may here have played a role. In the interviews, patients and relatives mentioned that they had heard about CDS either in the media or from other relatives.[13] There has been increased attention for CDS in Dutch media over several years.

Patients and relatives can also find more information from public websites.[32,33] Patients who considered CDS for themselves considered it as a means to help achieve a peaceful and painless death.[13] Relatives of patients who died during CDS had, overall, a positive memory of its use and considered CDS as a relief.[13] A systematic literature review showed that patients considered control of pain and symptoms, clear decision making, a feeling of closure, being seen as a person, preparation for death, and still being able to give something to others as important elements of a good death.[34]

In the literature, suffering is described as unique and inherently different for each person. Therefore, its assessment should pay attention to complex multi-dimensional, subjective experiences.[35] A person's experience with dying is also culturally determined. Cultural ideas, patterns, rituals, or practices play a role in people's experiences of dying.[36, 37] Studies showed that people who suffer can sometimes pass through their suffering to a new equilibrium that gives meaning to their experience.[38-40] A greater appreciation of life, a change in priorities, and changes in relationships with others are mentioned in the literature.[39,40] Nevertheless, our analyses of the Care Program for the Dying showed that symptoms in the last hours to days of life cannot always be relieved.[23] These symptoms are most often pain and restlessness.[23]

The justification for CDS

CDS could be justified by the physician's moral duty to relieve suffering. CDS could also be justified by the preferences of patients and their relatives whom, in the interview study raised no moral objections to CDS.[13] Some relatives stated that they felt stress in such situations. This was, in particular, when they were not informed about how the sedation would proceed, or when the sedation proceeded differently from how they had expected it to.[13] These results are in line with previous studies which found that relatives were distressed by the use of sedation.[44] In the judgement on the severity of symptoms, patients themselves play an important role as they determine, to what degree, they are capable of coping with these symptoms. A 2014 systematic literature review of CDS guidelines showed that the role of different stakeholders was not specified.[45] The updated 2022 version of the RDMA guideline describes the role of different stakeholders and emphasizes that, when criteria are met, the decision to start CDS is one that can be made by patients and their relatives, supported by the health care professionals.[18] It could be possible that for health care professionals, the use of CDS is also preferred as it enables them to control the dying process. The use of CDS could, therefore, be justified given these different perspectives. By involving different stakeholders, the guideline connects with the current zeitgeist, where patients, relatives, and health care professionals collaborate in the decision to commence CDS.

Debates on the circumstances in which CDS could be considered a morally

acceptable practice go back several decades.[3, 9, 46] Dying under CDS is often considered a painless and peaceful death. However, the disadvantages of commencing CDS is that it ends someone's conscious life and possibly shortens their biological one.[47-49] The disadvantage of CDS is that patients lose their ability to communicate with others, while these last moments of contact can be valuable for patients and their relatives.[13] By the use of CDS patients lose their ability to participate in any daily activities.

Kouwenhoven et al. claim that, regarding euthanasia, when autonomy is considered a patient's right, the physician's window to provide end-of-life care, other than euthanasia, is narrowed.[21] This could also apply to CDS. The interview studies with patients and relatives showed that these had no moral objections towards CDS.[13] Nevertheless, previous studies showed that relatives found it difficult to accept that there were no options to communicate anymore when sedation was started.[54]

It is argued that CDS has the potential to shorten life.[51, 52] Opponents of its use argue that it can be compared to euthanasia, due to this potential life-shortening effect.[53] The moral distinction, however, between CDS and euthanasia is based on the intention of the actor.[53-55] According to the guidelines on CDS, the intention of the physician in cases of CDS is to relieve the intolerable suffering of the terminally ill patient. Whereas, in euthanasia, it is the intention to end life.[18, 53, 56-58] Then again, studies have shown that, for some physicians, the intention of starting CDS was to hasten a patient's death.[59-61] The danger of CDS is that it could hasten death due to the side effects of the treatment.[53] It is also feared that CDS is used as an alternative route to euthanasia for ending a patient's life.[62,63] According to the doctrine of double effect, an action is acceptable if the intention of the effect is good, even it has an unintended side-effect.[64] But for a justification of CDS, under the formal doctrine of the double effect, the act being performed must be ascertained to be good, or at least neutral, without reliance on the anticipated consequences.[1, 2] You intend only the good effect.[3] The bad effect must not be the means to the good.[4] The good effect must outweigh the bad one. This is sometimes explained in terms of 'proportionality' or 'sufficient reason'.

In the case of CDS, it is argued that the doctrine of double effect could apply. The good effect could be the relief of symptoms by the use of sedatives. The bad effect could be the reduction of the patient's consciousness, and the possibility of shortening their life. However, this doctrine of double effect is criticized in the literature on ethics.[65] One of the criticisms is that the principle relies on the intentions of the health care professional, and that these intentions are difficult to objectify.[59] It is argued that it reflects physicians' discomfort with the complex moral, intentional, and causal aspects of end-of-life care.[64, 66] The common view in medical ethics is that the principles of subsidiarity and proportionality, in combination with the duty of the physician to relieve suffering, morally justify the use of CDS. The principle of subsidiarity, in relation to CDS, means that there

are no other options that are sufficiently effective to relieve symptoms, or no other options that have a sufficiently rapid effect. The principle of proportionality requires that the use of CDS should be reasonably balanced by the suffering of the patient. However, in our studies, we found that multiple factors have led to a lower threshold for starting CDS. This could indicate that these principles are interpreted in more lenient ways than before.

Some remarks can be made to this lower threshold of starting CDS. The first is about expectations, where conflicts may occur when health care professionals have to adhere to guidelines and criteria to start, and where patients and relatives think they may request for sedation when desired.[55] The second remark is the disadvantage of CDS, where patients lose their ability to communicate with others, while these last moments of contact can be valuable for patients and their relatives.[13] The third is about when the life-expectancy of the patient is uncertain, or exceeds two weeks. In these cases it will be hard to discriminate between CDS and euthanasia, as in these cases CDS will also have a life-shortening effect. In case of euthanasia, a review committee evaluates if the euthanasia is performed in compliance with the law and protocols.[67] In case of CDS there are no such safeguards to guarantee a performance of CDS according the guidelines and protocols. Fourth, this lower threshold for starting CDS could, be problematic as it entails and increasingly medical approach to the dying process.

The implications for practice and further research

CDS used to be an option of last resort, but in recent years it has increasingly become a more conventional option to relieve the suffering of terminally ill patients. Initially, physicians considered the decision to start CDS as theirs, informed by the patient and their relatives.[68] Our studies showed that today several patients and relatives consider the decision to commence CDS as their own and not as a decision of the physician.[13,16] This change in attitudes underlines the importance of adequate information for patients and their relatives on the use of CDS. Furthermore, it would be valuable to pay attention to the use of CDS and communication about both CDS and other end-of-life decisions in health care professionals' training curricula. The updated guideline on the use of CDS in the Netherlands reflects this change in attitudes and addresses the role of the patient and relatives in the decision making.[18]

It would be valuable for health care professionals to discuss the use of CDS more frequently in conversations about the end of life, for example during advance care planning (ACP) conversations. In discussions on ACP, patients and their relatives have the opportunity to discuss their wishes, values, and expectations with their health care professional. The goal of these discussions is to improve the quality of care at the end of life and to ensure that the care provided meets the wishes of the patient.[69] During these discussions about ACP, it is important for health care professionals to focus not only on the wishes of the patients and

their relatives, but also on the possibilities of, and limitations on when CDS can be offered as an option to relieve symptoms. Health care professionals need to explain the differences between euthanasia and CDS, as these differences are not always clear for patients and relatives.[13,16] Health care professionals may explain at what point symptoms may be considered refractory. They can provide realistic perspectives for patients and relatives about when CDS can be an option to relieve suffering at the end of life.

For health care professionals, it is important to realize that there has been an extension of indications for CDS. Over the years, existential suffering has played a more important role in the decision to commence CDS. In cases of existential suffering, the Dutch guideline states that expertise in the field of psychosocial and existential suffering is needed.[18] There is, however, no uniform definition in the literature of existential suffering. It would be valuable to research further what health care professionals consider as existential suffering and how they relate this to the use of CDS.

Lastly, it is often said, or thought, that all symptoms can be controlled at the end of life. Our studies showed that a substantial number of patients suffer from pain and restlessness when nearing death. To empower patients and their relatives better, it would be valuable to improve palliative care further. For health care professionals it is important to collaborate with patients, their relatives, and other health care professionals in order to provide the best care for the dying patient.

Future challenges

The health care landscape in Western countries has changed over recent years. The majority of these countries face an ageing population.[70] This comes with challenges for the health care system, through the increase in patient numbers, costs, as well as pressures on staffing numbers.[71] Future Dutch policy plans for the elderly people with comorbidities to live longer in their homes and to receive more care there.[72] But, in the interview studies with professionals, they reported that it was sometimes difficult to organize care at home for their terminally ill patient.[16] It will be challenging for the near future to organize this care for the dying patient and to help support patients and their relatives. With the increasing pressure on the health care system, technical resources, and trained health care professionals, it could become increasingly challenging for health care providers in the future to deliver sufficient care, including CDS, for terminally ill patients. Thus CDS and care for patients at the last phase of life in general, may come under pressure. For health care professionals, the problems that they experience in organizing care for terminally ill patients may be part of a longer trend that has already begun.[73, 74] Given the complexity and vulnerability of the clinical practice, it would be valuable to research further the use of CDS in this changing health care landscape.

Conclusion

The increasing use of CDS demonstrates that what was originally seen as an exceptional option to relieve severe refractory suffering, has now become a more common practice in physicians end-of-life care for terminally ill patients. This lower threshold for CDS has been driven by a greater awareness of the option to commence CDS, an extension of its indications for treatment, the positive image of CDS, and the common view that there is no need for dying patients to suffer. CDS is, therefore, no longer considered as an option of last resort, but as an accessible option to relieve suffering at the end of life.

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Addendum

Summary

At the end of life, patients may suffer from severe symptoms like pain, dyspnea, fatigue, and restlessness. When these symptoms cannot be controlled by conventional treatment options, palliative sedation can relieve suffering. The most far reaching form of sedation is continuous deep sedation (CDS), which involves lowering the consciousness level of a dying patient deeply and continuously until the end of life. The acceptability of CDS has been highly debated in the past decades. Its moral sensitivity stems from the fact that CDS may shorten a patient's life. Moreover, it may end someone's biographical life since patients lose the ability to communicate with their relatives.

In the Netherlands, end-of-life practices have been studied approximately every 5 years from 1990 onwards. Stratified samples of deaths are drawn from the national death registry, and physicians who are involved in these deaths are invited to fill out a questionnaire. The use of CDS is a topic of research in these repetitive nationwide questionnaire studies since 2005. These studies showed that the use of CDS has increased from 8.2% to 18.3% of all deceased people between 2005 and 2015. The latest report even shows a frequency of 23%. This increase has raised questions about its background and about how this increase should be valued. The aim of this thesis is to provide insight in current practices of CDS, to explore how the use of CDS has changed in the Netherlands between 2005 and 2015, and to identify reasons for the increase of the use of CDS.

Terms and definitions of sedation

A variety of terms is used for the lowering of the consciousness level of dying patients by the use of sedatives. Continuous sedation, deep sedation, end-of-life sedation, palliative sedation, terminal sedation and sedation until death are more or less commonly used terms in the literature. The many different forms of sedation make the discussion on the use of sedatives complex: the depth of sedation may vary from superficial to deep, and the duration may vary from intermittent to continuous sedation until the end of life. The focus of this thesis will be on continuous deep sedation until the end of life (CDS). CDS is the most far reaching form of sedation, as sedatives are provided with a continuous effect and the patient is deeply sedated until the end of life.

The regulation of CDS in the Netherlands and the guideline Palliative Sedation

Physician assisted dying and euthanasia are regulated by the Termination of Life on Request and Assisted Suicide (Review Procedures) Act in the Netherlands since 2002. Under this law, the practice of physician-assisted suicide and euthanasia by physicians is reviewed by a committee, which assesses in retrospect if all due care criteria were met. It has been argued that CDS should

also be reviewed by such an external committee. It was argued that starting CDS and simultaneously withholding nutrition and hydration could result in the death of the patient, and that CDS therefore should be evaluated in the same way as euthanasia. To guide responsible practice, the Royal Dutch Medical Association in 2005 developed a national guideline in the Netherlands to clarify questions and misunderstandings about palliative sedation on a conceptual level and in actual practice. The guideline was updated in 2009, and more recently in 2022. The premise of the guideline is that the use of palliative sedation is, under certain circumstances, to be considered as normal medical practice. The guideline distinguishes different forms of sedation, and describes that continuous palliative sedation is administered in the final stage of life to patients who are dying and experiencing unbearable suffering. The RDMA guideline describes that the use of CDS differs in its aim from euthanasia because the aim of CDS is to relieve suffering and not to shorten a patient's life. Preconditions to start continuous sedation are that the patient suffers from one or more refractory symptoms, and that the patient's death is nearby, what means that the life-expectancy of the patient does not exceed more than two weeks. A symptom can be called refractory when there are no treatment options to relieve the suffering, or when treatment options do not work quickly enough.

Knowledge gaps regarding to the current use of CDS

The use of CDS increased in the Netherlands between 2005 and 2015 from 8.2% to 18.3%. Not much is known about how the use of CDS has been changed in the Netherlands over the years. It is also unknown why the use of CDS has increased over the years, and how this increase should be interpretated. Insight in the use of CDS is important as the societal acceptation of CDS depends on the moral carefulness by which CDS is used. It could be possible that health care professionals started to use CDS more often for specific patient subgroups. CDS is used in many different countries in different settings. It could be possible that the use of CDS is also increasing in other countries, apart from the Netherlands. An increase in other countries apart from the Netherlands could provide more generalizable explanations for the increase in use of CDS. Symptoms that often require sedation are pain, dyspnea and restlessness. Not much is known about the background of symptoms for which CDS has taken place. It is also unknown if the symptoms for which CDS is used had changed over the years. At last, insight in the experiences opinions and expectations of health care professionals, patients and relatives on the us of CDS is limited.

Research questions addressed in this thesis:
The previous paragraphs point to several knowledge gaps that lead to a number of research questions. The research questions of this thesis are:

1. What are the characteristics of the patients who received CDS, and did the characteristics of these patients change over the years?
2. Did the use of CDS change over the years on an international level?
3. What are symptoms that patients experience at the end of life for which CDS could be indicated?
4. What are the perspectives of health care professionals who use CDS for their patients and how did their perspectives change over the years?
5. What are patients' expectations about CDS and what are the experiences of relatives of patients who received CDS?

Answer to research question 1:
In Chapter 2, we show results from repetitive nationwide questionnaire studies on end-of-life decision practices among physicians in the Netherlands based on a stratified sample of deaths (response rate 78%).The percentage of patients who received CDS was 20.7% for deaths attended by general practitioners, 18.4% for deaths attended by clinical specialists, and 14.3% for deaths attended by elderly care physicians. Fifty-five percent of all sedations were performed by a general practitioner, 24% by a clinical specialist, and 21% by an elderly care specialist. We observed an increase in the use of CDS in all different age groups, 0-64, 65-79, and 80 years or older, and in patients with different causes of death. The increase was the highest among elderly patients and patients with malignancies under the care of general practitioners. Of all patients, 97% died within the first seven days after the start of sedation.

Answer to research question 2:
In Chapter 3, we present a systematic literature review. We aimed to explore developments in the use of CDS on an international level between January 2000 and April 2020. Furthermore, we aimed to provide insight into the indications for using CDS during this period. We included 23 articles describing 16 nationwide studies, and 38 articles about 37 sub-population studies. In the nationwide studies, the percentage of CDS ranged from 3% in Denmark in 2001, to 18.3% in the Netherlands in 2015. The nationwide studies show that the use of CDS seems to have increased on an international level over time. Over the years, an increasing number of studies reported on the use of CDS for non-physical symptoms such as anxiety and psycho-existential distress. Some studies showed an increase in requests for sedation from relatives of the patient instead of the patients themselves.

Answer to research question 3:
In Chapter 4, we describe data from the Dutch Care Program for the Dying (CPD, in Dutch: *Zorgpad Stervensfase*) that provide insight into symptoms that patients experience at the end of life. We analyzed four-hourly registrations for 2,786 patients and assessed, in how many cases, the symptom-related goals of care were not achieved. The following goals of care were analyzed: Pain, restlessness, respiratory tract secretions, nausea, vomiting, and shortness of breath. For a substantial proportion of the patients in the hospital, care home, and hospice, at least one symptom-related goal could not be achieved in the last hours to days of life. These percentages were respectively, 26.9%, 24.9%, and 17.5%. Of all care goals that had not been achieved, the control of pain and an absence of restlessness were most often reported.

Answer to research question 4:
In Chapter 5, we report a questionnaire study among physicians in eight different countries about their practices and experiences with CDS in the last hours, to days, of life. In all countries, more than 87% of the physicians considered the use of CDS an acceptable practice in cases of physical suffering in the last hours to days of life. Percentages were substantially lower, 45% to 88% in case of severe psycho-existential suffering in absence of physical symptoms. This percentage was 56% for Dutch respondents The percentages of physicians who considered the use of CDS an acceptable practice varied from 22% to 66% in case of physical suffering, and from 5% to 42% in case of psycho-existential suffering in absence of physical symptoms. These percentages were 42% and 17% for Dutch respondents respectively. Up to ten percent of the physicians agreed with the statement that CDS is unnecessary, because suffering can always be relieved with other measures. 41% to 95% of the physicians agreed with the statement that a competent patient has the right to demand the use of CDS in the last days of life, this percentage was 91% for Dutch respondents.

In Chapter 6, we describe a qualitative interview study among Dutch health care professionals on the use of CDS. Many health care professionals mentioned that over the years they became more aware of the option of starting CDS. For health care professionals, the reason to start CDS was often a combination of symptoms, resulting in a so-called “refractory state”. Health care professionals stated that over the years, symptoms of a non-physical origin have acquired a more important role in the decision to start CDS. They reported an increase in the number of requests to start CDS, some health care professionals, mentioned that they experienced increased pressure from patients and relatives to start CDS. The majority of the health care professionals stated that suffering has become less acceptable to patients, their relatives, and sometimes, also by other health care professionals. The increased awareness for symptoms of a non-physical origin in combination with a lower tolerance for suffering may have led to a lower threshold to start CDS.

Answer to research question 5:
In Chapter 7, we report on a qualitative study interviewing patients and relatives on their expectations, and experiences with the use of CDS. Participants were patients who considered the use of CDS for their selves, and relatives who had experienced the use of CDS involving a relative. Most of the respondents were aware of the option to start CDS, and appreciated it as a palliative care option. None of the respondents reported objections, moral or otherwise, towards CDS. An indication for CDS was reported mostly for physical symptoms, but fear and existential suffering were also mentioned as sole indications. Relatives and patients considered the decision to start CDS as their own, and not as that of the physician. Negative experiences with CDS were mostly related to health care professionals failing to communicate properly or provide information, or due to a lack of continuity of care. We observed differences in respondents' understanding of the concept of CDS and of the distinction between it and other end-of-life decisions, including euthanasia. Patients and relatives consider the use of CDS as a regular palliative care option. The traditional view of CDS as an option of last resort is not explicit among patients and relatives. Together with the move towards CDS becoming standard practice, patients and their relatives also now claim a substantial say in the decision making. They are motivated mainly by a wish to avoid suffering and to exercise control at the end of their lives.

Strengths and limitations of the studies:
The combination of different study designs provided a comprehensive picture in this thesis of the practice, and the increase in the use of CDS in the Netherlands. A systematic literature review, in combination with complementary qualitative and quantitative research data, contributed to a better understanding of the increase in CDS. National and international trends in the use of CDS were observed. This thesis sought to find explanations for the increase in CDS, not only in demographic and epidemiological patterns of dying, but also in societal developments, such as increased attention for CDS.

Despite the combination of different research methods, a clear single cause for the increase in CDS could not be identified. However, the systematic literature review, questionnaire studies with physicians, and analyses of the Care Program for the Dying allowed us to gain insight in a large number of cases. A limitation of this broader view was that it was not possible to go into more detail on individual cases. Neither was any information available on the use of CDS in the analysis of the Care Program for the Dying. The interview studies, however, provided more insight into the distinct views and considerations of health care professionals, patients, and their relatives. These were though all based on self-reported practices so there could be a discrepancy between actual and reported practices. In the interview study with health care professionals selection bias could have occurred as nearly all had followed additional training in the field of palliative

care, worked on a daily basis with terminally ill patients, and had a special interest in the topic. In the interview study with patients and relatives, selection bias could also have occurred as patients who participated were recruited via a patient panel, in which, we presume, all were entirely empowered to share their opinions.

The increase in use of CDS in the Netherlands

It can be concluded, based on the findings of this thesis, that different factors may have contributed to the increase of CDS in the Netherlands. Firstly, there has been an increased awareness of the option of starting CDS among health care professionals and among the public.

Secondly, health care professionals experienced that, compared with several years before, patients, relatives, and sometimes even other health care professionals are increasingly inclined to raise the subject of CDS in cases of severe suffering. Previous studies also showed that Dutch physicians sometimes experience pressure to start CDS.

Thirdly, there has been a broadening of the indications to start CDS. Previous studies showed that the indication to start CDS is often based on a combination of physical, psychological, and existential symptoms, which is called a refractory state. Where, previously, indications for sedation were based on symptoms of a physical origin, increasingly, in recent years, symptoms of non-physical origin, such as fear and existential suffering, more often play a role in the decision to start CDS.

Fourthly, the general opinion is that there is no need for a dying patient to suffer at the end of life, as symptoms can always be relieved, if necessary by the use of sedatives. Most physicians consider CDS as, sometimes, a necessary option to relieve severe suffering at the end of life. Patients who considered CDS for themselves considered it as a means to help achieve a peaceful and painless death. Relatives of patients who died during CDS had, overall, a positive memory of its use and considered CDS as a relief.

Remarks towards the increase in use of CDS

Some remarks can be made to this lower threshold of starting CDS. The first is about expectations, where conflicts may occur when health care professionals have to adhere to guidelines and criteria to start, and where patients and relatives think they may request for sedation when desired. The second remark is the disadvantage of CDS, where patients lose their ability to communicate with others, while these last moments of contact can be valuable for patients and their relatives. The third is about when the life-expectancy of the patient is uncertain, or exceeds two weeks. In these cases it will be hard to discriminate between CDS and euthanasia, as in these cases CDS will also have a life-shortening effect. In case of euthanasia, a review committee evaluates if the euthanasia is performed in compliance with the law and protocols. In case of CDS there are no such

safeguards to guarantee a performance of CDS according the guidelines and protocols. Fourth, this lower threshold for starting CDS could, be problematic as it entails and increasingly medical approach to the dying process. In the use of CDS. Shared decision making has become more important in the use of CDS. It is of great value for patients and relatives to discuss together with health care professionals until what extent the suffering of the patient is tolerable and to consider together if CDS can be a useful option the relieve the suffering of the patient.

Implications for practice and further research

CDS used to be an option of last resort, but in recent years it has increasingly become a more conventional option to relieve the suffering of terminally ill patients. Initially, physicians considered the decision to start CDS as theirs, informed by the patient and their relatives. Our studies showed that today several patients and relatives consider the decision to commence CDS as their own and not that of the physician. This change in attitudes underlines the importance of adequate information for patients and their relatives on the use of CDS. Furthermore, it would be valuable to pay attention to the use of CDS and communication about both CDS and other end-of-life decisions in health care professionals' training curricula. The updated guideline on the use of CDS in the Netherlands reflects this change in attitudes and addresses the role of the patient and relatives in the decision making.

It would be valuable for health care professionals to discuss the use of CDS more frequently in conversations about the end of life, for example during advance care planning conversations (ACP conversations). In discussions on ACP, patients and their relatives have the opportunity to discuss their wishes, values, and expectations with their health care professional. The goal of these discussions is to improve the quality of care at the end of life and to ensure that the care provided meets the wishes of the patient. During these discussions about ACP, it is important for health care professionals to focus not only on the wishes of the patients and their relatives, but also on the possibilities of, and limitations on when CDS can be offered as an option to relieve symptoms. Health care professionals need to explain the differences between euthanasia and CDS, as these differences are not always clear for patients and relatives. Health care professionals may explain at what point symptoms may be considered refractory. They can provide realistic perspectives for patients and relatives about when CDS can be an option to relieve suffering at the end of life.

For health care professionals, it is important to realize that there has been an extension of indications for CDS. Over the years, existential suffering has played a more important role in the decision to commence CDS. In cases of existential suffering, the Dutch guideline states that expertise in the field of psychosocial and existential suffering is needed. There is, however, no uniform definition in

the literature of existential suffering. It would be valuable to research further what health care professionals consider existential suffering and how they relate this to the use of CDS.

Lastly, it is often said, or thought, that all symptoms can be controlled at the end of life. Our studies showed that a substantial number of patients suffer from pain and restlessness when nearing death. To empower patients and their relatives better, it would be valuable to improve palliative care further. For health care professionals it is important to collaborate with patients, their relatives, and other health care professionals in order to provide the best care for the dying patient.

Future challenges

The health care landscape in Western countries is changing. The majority of these countries faces with an ageing population, which comes with challenges for the health care system, with an increase in patient numbers, costs, as well as pressures on staffing numbers. These challenges will have an inevitable impact on the end-of-life care for terminally ill patients. In the interview studies with professionals, they reported that it was sometimes difficult to organize care at home for their terminally ill patient. In the near future, it could become increasingly challenging for health care professionals to deliver sufficient care for terminally ill patients, including CDS.

Conclusion

The increasing use of CDS demonstrates that what was originally seen as an exceptional option to relieve severe refractory suffering, has now become a more common practice in physicians end-of-life care for terminally ill patients. This lower threshold for CDS has been driven by a greater awareness of the option to commence CDS, an extension of its indications for treatment, the positive image of CDS, and the common view that there is no need for dying patients to suffer. CDS is, therefore, no longer considered as an option of last resort, but as an accessible option to relieve suffering at the end of life.

Nederlandse samenvatting

Aan het einde van het leven lijden patiënten soms aan ernstige symptomen, zoals pijn, benauwdheid, uitputting, en rusteloosheid. Wanneer deze symptomen niet verlicht kunnen worden door conventionele behandelopties, kan palliatieve sedatie mogelijk dit lijden verlichten. De meest vergaande vorm van sedatie is continue diepe sedatie (CDS), waarbij het bewustzijn van een patiënt continu en diep wordt verlaagd tot aan het einde van het leven. De aanvaardbaarheid van CDS staat ter discussie in de laatste decennia. De morele sensitiviteit komt voort uit dat CDS mogelijk iemands leven bekort en bovenal iemands biografische leven eindigt, waarbij patiënten de mogelijkheid om te kunnen communiceren verliezen.

In Nederland worden medische beslissingen rondom het levenseinde circa iedere 5 jaar onderzocht vanaf 1990 tot nu. Gestratificeerde steekproeven van overlijdens worden getrokken via het Centraal Bureau voor Statistiek en zorgverleners die betrokken waren bij een overlijden krijgen een uitnodiging om een vragenlijst in te vullen. De toepassing van CDS is een onderwerp in deze recidiverende nationale vragenlijststudies sinds 2005. Deze studies toonden aan dat de toepassing van CDS in Nederland is gestegen van 8.2 naar 18.3 van alle overlijdens tussen 2005 en 2015. Recente cijfers laten zelfs een stijging zien naar 23%. Deze stijging roept vragen op over hoe deze stijging moet worden gewaardeerd. Het doel van dit proefschrift is om inzicht te krijgen in de huidige praktijk van CDS, om te exploreren hoe de toepassing van CDS is veranderd in Nederland tussen 2005 en 2015 en om redenen voor de stijging van de toepassing van CDS te achterhalen.

Termen en definities van sedatie

Een verscheidenheid aan termen wordt gebruikt in de literatuur voor het verlagen van het bewustzijn van patiënten met het gebruik van sedativa. Continue sedatie, diepe sedatie, terminale sedatie, palliatieve sedatie zijn termen die frequent worden gebruikt in de literatuur. Het gebruik van veel verschillende termen en definities maken de discussie rondom het toepassen van CDS complex. De diepte van sedatie varieert van oppervlakkige sedatie tot diepe sedatie en de lengte van de sedatie varieert van tijdelijke, intermitterende sedatie, tot continue sedatie tot aan het einde van het leven. De focus van dit proefschrift ligt op de meest vergaande vorm van sedatie: continue diepe sedatie tot aan het einde van het leven (CDS).

De regulering van continue diepe sedatie in Nederland en de richtlijn Palliatieve Sedatie

In Nederland worden hulp bij zelfdoding en euthanasie gereguleerd volgens de levenseindewet sinds 2002. Volgens deze wet dient het handelen van een zorgverlener bij deze praktijken getoetst te worden dor een toetsingscommissie, welke retrospectief bekijkt of aan alle criteria is voldaan. Eerder werd erover gediscussieerd dat CDS ook door een commissie zou moeten worden getoetst omdat het onthouden van vocht en voeding ook zou kunnen resulteren in het overlijden van een patiënt. In 2005 werd de Nederlandse KNMG richtlijn Palliatieve Sedatie in gebruik genomen waarin de verschillen tussen palliatieve sedatie en euthanasie uiteen werden gezet. De richtlijn is een leidraad voor zorgverleners in de praktijk en werd in 2009 en 2022 geüpdatet. In tegenstelling tot hulp bij zelfdoding en euthanasie, wordt palliatieve sedatie onder bepaalde voorwaarden zien als normaal medisch handelen. De ene voorwaarde is dat het overlijden van een patiënt dichtbij is, dit wil zeggen binnen 1 tot 2 weken. De andere voorwaarde is dat de patiënt lijdt aan 1 of meer refractaire symptomen. Dit zijn symptomen waarbij er geen behandelopties mogelijk zijn om het lijden te verlichten, of geen van de behandelopties werkt snel genoeg.

Kennislacunes ten aanzien van de huidige toepassing van CDS

Het aantal gevallen waarbij CDS werd toegepast is tussen 2005 en 2015 gestegen van 8.2 naar 18.3%. Onbekend is op welke manier de praktijk van het toepassen van CDS in Nederland is veranderd. Ook is niet bekend is waardoor de stijging van het aantal gevallen waarbij CDS werd toegepast tot stand is gekomen en hoe deze stijging moet worden gewaardeerd. Inzicht in deze stijging is van belang omdat de maatschappelijke acceptatie van CDS afhangt van de morele zorgvuldigheid en de gepastheid waarmee CDS wordt ingezet. Mogelijk zijn zorgverleners voor specifieke patiëntengroepen vaker CDS gaan toepassen. CDS wordt in verscheidene landen in verschillende settingen gebruikt om het lijden van zieke patiënten aan het einde van het leven te verlichten, mogelijk vindt deze stijging ook buiten Nederland plaats. Een stijging in meerdere landen zou een meer generaliseerbare verklaring kunnen bieden voor de stijging van CDS. Symptomen waarbij frequent palliatieve sedatie wordt toegepast zijn pijn, benauwdheid en rusteloosheid. Er is weinig bekend over aan welke symptomen patiënten in de laatste uren tot dagen van het leven leiden, dus tegen welke achtergrond de stijging van continue diepe sedatie plaats heeft gevonden. Verder is onbekend of de symptomen waarvoor continue diepe sedatie wordt toegepast veranderd zijn in de loop der jaren. Als laatste is er weinig inzicht in de opvattingen en ervaringen van zorgverleners patiënten en naasten zijn ten aanzien van CDS.

Onderzoeksvragen
Naar aanleiding van de bovengenoemde kennislacunes worden in dit proefschrift de volgende onderzoeksvragen geformuleerd:

1. Wat zijn de karakteristieken van patiënten bij wie CDS werd toegepast en zijn de patiëntkarakteristieken van deze patiënten veranderd over de jaren?
2. Is de toepassing van CDS in de loop der jaren veranderd op een internationaal niveau?
3. Wat zijn symptomen die patiënten ervaren aan het einde van het leven waarvoor CDS geïndiceerd zou kunnen zijn?
4. Wat zijn perspectieven van zorgverleners wie CDS toepassen bij hun patiënten en hoe zijn hun perspectieven veranderd in de loop der jaren?
5. Wat zijn de verwachtingen van patiënten over CDS en wat zijn de ervaringen van naasten van patiënten bij wie CDS werd toegepast?

Antwoord op onderzoeksvraag 1:
In hoofdstuk 2 tonen we de resultaten van een nationale vragenlijststudie over levens einde beslissingen in Nederland onder artsen over een gestratificeerde groep overlijdens (response-rate 78%). Het percentage patiënten bij wie CDS werd toegepast was 20.7 voor patiënten onder de zorg van de huisarts, 18.4% voor patiënten onder de zorg van de medisch specialist, en 14.3% voor patiënten onder de zorg van de specialist ouderengeneeskunde. 55% van alle sedaties werd uitgevoerd door een huisarts, 24% door een medisch specialist en 21% door een specialist ouderengeneeskunde. We merkten een stijging op in het aantal gevallen waarbij CDS werd toegepast in alle leeftijdsgroepen, 0-64, 65-79, en 80 jaar en ouder, onder patiënten met verschillende doodsoorzaken. De stijging was het meest prominent onder ouderen en patiënten met maligniteiten onder de zorg van de huisarts Van alle patiënten overleed 97% binnen de eerste 7 dagen na de start van de sedatie.

Antwoord op onderzoeksvraag 2:
In hoofdstuk 3 presenteren we een systematische literatuur review. Het doel van deze studie was om ontwikkelingen in de toepassing van CDS te onderzoeken tussen januari 2000 en april 2020. Daarnaast was het doel om inzicht te krijgen in de indicaties voor het toepassen van CDS gedurende dezelfde periode. We includeerden 23 artikelen, waaronder 16 landelijke studies en 38 artikelen over 37 subpopulatie studies. In de landelijke studies varieerde het percentage waarbij CDS werd toegepast van 3% in Denemarken in 2001 tot 28.3% in Nederland in 2015. De landelijke studies laten zien dat de toepassing van CDS lijkt te stijgen in de loop der tijd. Over de jaren rapporteerde een toenemend aantal studies over de toepassing van CDS voor niet fysieke symptomen zoals angst en psycho-existentiële stress. Sommige studies vonden een toename in het aantal verzoeken voor sedatie vanuit patiënten of vanuit de familie zelf.

Antwoord op onderzoeksvraag 3:
In hoofdstuk 4 hebben we gegevens uit het zorgpad stervensfase geanalyseerd. Het doel hiervan was om inzicht te krijgen in symptomen die patiënten ervaren aan het einde van het leven. We analyseerden 4-uurs registraties van 2,786 patiënten en bekeken hierbij in hoeveel gevallen de symptoom gerelateerde doelen niet werden bereikt. De volgende zorgdoelen werden geanalyseerd: afwezigheid van pijn, afwezigheid van rusteloosheid, afwezigheid van hinderlijke slijmvorming in de luchtwegen, afwezigheid van misselijkheid, afwezigheid van overgeven en afwezigheid van kortademigheid. Voor een substantieel deel van de patiënten in het ziekenhuis, verpleeghuis en hospice kon ten minste een symptoom gerelateerd zorgdoel niet worden bereikt in de laatste dagen tot uren van het leven. Deze percentages waren 26.9%, 24.9% en 17.5% respectievelijk. Van alle zorgdoelen die niet werden bereikt, waren controle van pijn en afwezigheid van rusteloosheid het meest frequent gerapporteerd.

Antwoord op onderzoeksvraag 4:
In hoofdstuk 5 rapporteren we over een vragenlijststudie onder artsen in 8 verschillende landen over hun ervaringen en handelingen met het toepassen van CDS in de laatste uren tot dagen van het leven. In alle landen vond meer dan 87% van de artsen vond de toepassing van CDS acceptabel in het geval van fysiek lijden in de laatste dagen van het leven. Percentages waren lager, 45 tot 88% in het geval van ernstig psycho-existentieel lijden in afwezigheid van fysieke symptomen. Dit percentage was 56% voor Nederlandse artsen. De percentages van artsen die CDS acceptabel vond voor CDS met een levensverwachting van ten minste enkele weken varieerde van 22 tot 66% voor fysiek lijden en van 5 tot 42% voor psycho-existentieel lijden in afwezigheid van fysieke symptomen. Deze percentages waren respectievelijk 42% en 17% voor de Nederlandse artsen. Tot tien procent van de artsen was het eens met de stelling dat CDS onnodig is, omdat lijden altijd op andere manieren kan worden verlicht. 41 tot 95% van de artsen was het eens met de stelling dat een wilsbekwame patiënt het recht heeft om CDS te vragen in de laatste dagen van het leven. Dit was 91% voor Nederlandse artsen.

In hoofdstuk 6 beschrijven we een kwalitatieve interview studie onder Nederlandse zorgverleners over de toepassing van CDS. Veel zorgverleners noemden dat ze zich over de jaren meer bewust waren geworden van de optie om CDS toe te passen. Voor zorgverleners was de reden om CDS toe te passen veelal een optelsom van symptomen, een refractair toestandsbeeld. Zorgverleners noemden dat over de jaren symptomen van niet fysieke origine een grote rol in besluitvorming om CDS toe te passen heeft ingenomen. Ze noemden een stijging in het aantal verzoeken om CDS toe te passen. Sommige zorgverleners noemden dat ze een toegenomen druk van patiënten en naasten

ervaarden in de besluitvorming om CDS toe te passen. De meerderheid van de zorgverleners noemde dat lijden minder geaccepteerd wordt door patiënten, naasten en soms ook door andere zorgverleners. Het toegenomen bewustzijn voor symptomen van niet fysieke origine in combinatie met een lagere tolerantie voor lijden heeft mogelijk geleid tot een lagere drempel om CDS in te zetten.

Antwoord op onderzoeksvraag 5:
In hoofdstuk 7 beschrijven we een kwalitatieve interview studie met patiënten en naasten over hun verwachtingen en ervaringen met CDS. Deelnemers waren patiënten die CDS voor henzelf overwogen en naasten van patiënten waarbij was toegepast of waarbij overwogen was CDS toe te passen. De meerderheid van de respondenten was zich bewust van de optie om CDS toe te passen en apprecieerde deze optie als palliatieve zorg interventie. Geen van de respondenten had (morele) bezwaren tegen de toepassing van CDS. Fysieke symptomen werden het meest genoemd als indicatie om CDS toe te passen, maar angst en existentieel lijden werden ook genoemd. Naasten en patiënten zagen de optie om CDS toe te passen als een beslissing van hen zelf en niet zozeer als een beslissing van de zorgverlener. Negatieve ervaringen met CDS gingen vooral over onvoldoende voorlichting door zorgverleners en over een gebrek aan continuïteit in zorgpersoneel. We observeerden een wisselend begrip van het concept van CDS en het onderscheid tussen andere levenseinde beslissingen zoals euthanasie tussen respondenten. Patiënten en naasten zagen het toepassen van CDS als een reguliere palliatieve zorg optie. De traditionele visie van CDS als laatste redmiddel was niet evident onder patiënten en naasten. Met de normalisatie van CDS nemen patiënten en naasten in de besluitvorming een belangrijke positie in, gemotiveerd door een wens om het lijden van een patiënt in de laatste levensfase zoveel mogelijk te vermijden en door de wens om regie te behouden.

Sterke en zwakke punten
Dit proefschrift heeft een veelomvattend overzicht gegeven van de toepassing en stijging van CDS in Nederland. In dit proefschrift worden verklaringen voor het toenemend inzetten van CDS niet alleen gezocht in demografische en epidemiologische patronen van overlijden, maar ook in sociale ontwikkelingen zoals een toegenomen aandacht voor CDS.

Ondanks de combinatie van onderzoeksmethoden kon er niet een eenduidige oorzaak voor de stijgende toepassing van CDS worden geïdentificeerd. De systematische literatuurreview, vragenlijststudies met artsen, en analyse van het zorgpad stervensfase geven inzicht in een groot aantal sterfgevallen. Een beperking aan deze bredere manier van onderzoeken is dat het niet mogelijk is om meer gedetailleerd naar individuele gevallen te kijken. De interview studies geven daarentegen een uitgebreider inzicht in de opvattingen en ervaringen

van zorgverleners, patiënten en hun naasten. Deze waren gebaseerd op zelf gerapporteerde praktijken, dus er zou een discrepantie kunnen zitten tussen de actuele en zelf gerapporteerde praktijken. In de interview studie met zorgverleners zou daarnaast selecte bias kunnen voorkomen, omdat alle zorgverleners een additionele training hadden gevolgd op het gebied van palliatieve zorg, deze zorgverleners op dagelijkse basis met terminaal zieke patiënten werkten en bovendien een speciale interesse in het onderwerp hadden. In de interview studies met patiënten en naasten heeft mogelijk ook selectie bias plaatsgevonden, aangezien patiënten en naasten werden geworven via een patiënten panel, waarbij de deelnemers goed in staat waren tot in het delen van hun opvattingen en ervaringen.

De stijging van de toepassing van CDS in Nederland

Gebaseerd op de bevindingen uit dit proefschrift kan worden geconcludeerd dat verschillende factoren een rol hebben gespeeld bij de stijging van CDS in Nederland. Ten eerste, er is een toegenomen bewustzijn van de optie om CDS in te zetten onder zorgverleners en onder de Nederlandse bevolking.

Ten tweede, zorgverleners ervaren dat patiënten, naasten en soms andere zorgverleners in vergelijking tot een aantal jaar ervoor toenemend geneigd zijn om het onderwerp CDS te benoemen in geval van ernstig lijden. Eerdere studies toonden ook aan dat Nederlandse artsen soms ook een druk ervaren om CDS toe te passen.

Ten derde, heeft er een verbreding van indicaties om CDS toe te passen plaatsgevonden. Eerdere studies toonden aan dat de indicatie om CDS toe te passen vooral is gebaseerd op een combinatie van fysieke, psychologische en existentiële symptomen, wat bij elkaar leidt tot een refractair toestandsbeeld. Waar voorheen indicaties voor sedatie voornamelijk gebaseerd werden op een enkel (fysiek) symptoom, zijn over de jaren symptomen van niet fysieke origine zoals angst en existentieel lijden een grotere rol gaan spelen in de besluitvorming om CDS toe te passen.

Ten vierde is er de algemene visie dat lijden aan het einde van het leven niet meer nodig is, omdat lijden altijd verlicht kan worden, indien nodig met het gebruik van sedativa. De meerderheid van de artsen beschouwt CDS als een optie die soms nodig is om ernstig lijden aan het leven te verlichten. Sterven in een diepe slaap onder de toepassing van CDS wordt regelmatig als een vredig overlijden gezien. Patiënten die CDS overwogen voor henzelf zagen CDS als een middel om vredig en pijnvrij te kunnen sterven. Naasten van patiënten bij wie CDS was toegepast hadden over het algemeen ook een positief beeld van CDS.

Kanttekeningen ten aanzien van de stijging van CDS

Enkele kanttekeningen kunnen bij de stijging van het aantal gevallen van CDS worden gemaakt. De eerste kanttekening gaat over verwachtingen. Wanneer zorgverleners gebonden zijn aan de richtlijn waarin wordt beschreven dat CDS kan worden toegepast bij refractaire symptomen; als andere behandelingen niet effectief zijn of naar verwachting niet snel genoeg het gewenste effect hebben, terwijl patiënten en naasten de verwachting hebben dat ze een verzoek kunnen doen tot het toepassen van CDS wanneer gewenst, leidt dit mogelijk tot conflicten. Voor zorgverleners is het van belang om duidelijk uit te leggen wanneer CDS wel, maar ook wanneer CDS geen optie zou kunnen zijn om het lijden te verlichten, bijvoorbeeld in advance care planningsgesprekken. De tweede kanttekening is dat het belangrijk is om te realiseren dat patiënten tijdens het toepassen van CDS niet of nauwelijks meer interactie kunnen hebben met hun naasten en dat door de toepassing van CDS heldere momenten mogelijk worden ontnomen voor de patiënt. Dit kan als een verlies worden ervaren. De derde kanttekening is dat het belangrijk is om te realiseren dat wanneer de levensverwachting onzeker is, of mogelijk langer dan twee weken betreft, het lastig is om CDS te onderscheiden van euthanasie, aangezien CDS in deze gevallen ook een levensbekortend effect kan hebben. De vierde kanttekening is dat de lagere drempel om CDS toe te passen kan zorgen voor een verdere medicalisering van het stervensproces. Bij het toepassen van CDS is de gezamenlijke besluitvorming steeds belangrijker geworden. Het is waardevol voor patiënten en hun naasten om samen met zorgverleners te kunnen bespreken welke mate van discomfort nog draaglijk is en om samen de afweging te maken of CDS een zinvolle manier kan zijn om het lijden van de patiënt te verlichten.

Implicaties voor de praktijk en aanbevelingen voor verder onderzoek

Waar CDS eerst werd gezien als een laatste redmiddel, is CDS door de jaren heen een meer gangbare optie geworden om het lijden van terminaal zieke patiënten te verlichten. Initieel zagen zorgverleners de beslissing om CDS toe te passen als een eigen beslissing, geïnformeerd door patiënten en naasten. Onze studies toonden aan dat patiënten en naasten de beslissing om CDS toe te passen vooral zagen als een eigen beslissing en niet zozeer als een van de zorgverlener. Deze veranderingen onderstrepen het belang van adequate informatie voor patiënten en naasten over de toepassing van CDS. De in 2022 herziene KNMG richtlijn Palliatieve sedatie sluit aan bij deze veranderingen en benoemen het belang van de betrokkenheid van patiënten en hun naasten in de besluitvorming. Het is waardevol om aandacht te besteden aan de toepassing van CDS en de communicatie hierover in onderwijscurricula.

Het zou waardevol zijn voor zorgverleners om CDS frequenter te bespreken in conversaties over het levenseinde, bijvoorbeeld in advance care planningsgesprekken (ACP gesprekken). In discussies over ACP hebben patiënten

en naasten de mogelijkheid om hun wensen, eigen waardes en verwachtingen te bespreken met hun zorgverlener. Het doel van deze gesprekken is de kwaliteit van zorg aan het levenseinde te verbeteren en om zorg te bieden die zo goed mogelijk aansluit bij de wensen van de patiënt. Gedurende deze gesprekken is het belangrijk voor zorgverleners om niet alleen te focussen op de wensen van patiënten en hun naasten maar ook op de mogelijkheden en beperkingen over wanneer CDS als optie kan worden geboden om symptomen te verlichten. Daarnaast is het van belang dat zorgverleners de verschillen tussen euthanasie en CDS uitleggen, omdat deze verschillen niet altijd duidelijk zijn voor patiënten en hun naasten. Zorgverleners kunnen uitleggen op welk punt een symptoom als refractair kan worden gezien en zorgverleners kunnen realistische perspectieven bieden over wanneer CDS een optie kan zijn om ernstig lijden te verlichten aan het einde van het leven.

Voor zorgverleners is het belangrijk zich bewust te zijn van de verbreding van indicaties voor het toepassen van CDS. Over de jaren is existentieel lijden een grotere rol gaan spelen in de besluitvorming om CDS toe te passen. De KNMG richtlijn Palliatieve Sedatie noemt hierbij het belang van expertise op het gebied van psychosociaal en existentieel lijden. Echter, een uniforme definitie van wat existentieel lijden precies om vat ontbreekt in de literatuur. Het kan waardevol zijn om het begrip existentieel lijden verder te onderzoeken, wat zorgverleners zien als existentieel lijden en hoe ze dit relateren aan het toepassen van CDS.

Als laatste wordt veelal gedacht dat alle symptomen aan het einde van het leven verholpen kunnen worden. Onze studies toonden aan dat een substantieel deel van de patiënten aan het einde van het leven klachten blijft houden van symptomen zoals pijn en rusteloosheid. Zorgverleners kunnen dit meenemen in gesprekken met patiënten en hun naasten over het naderende levenseinde.

Toekomstige uitdagingen

Het zorglandschap in Westerse landen is aan verandering onderhevig. De meerderheid van deze landen heeft te maken met een vergrijzende populatie, waarbij een toename in zorgkosten en een gebrek aan zorgpersoneel voor uitdagingen zorgt. Deze uitdagingen hebben onvermijdelijk invloed op de levenseindezorg voor terminaal zieke patiënten. Zorgverleners in de interviewstudies noemden dat het soms een uitdaging was om passende zorg te regelen voor terminaal zieke patiënten thuis. In de toekomst zal het waarschijnlijk een nog grotere uitdaging zijn om de zorg voor terminaal zieke patiënten goed te blijven organiseren, waaronder ook de toepassing van CDS.

Conclusie

De stijging in de toepassing van CDS illustreert dat waar CDS eerst werd gezien als een uitzonderlijke optie om het lijden te verlichten, nu een gangbare optie is in het bieden van levenseindezorg door zorgverleners voor terminaal zieke patiënten. Deze lagere drempel wordt gevormd door een grotere bewustwording van de optie om CDS te starten, een verbreding van indicaties, de positieve beeldvorming van CDS en de gemeenschappelijke visie dat het niet nodig is om te lijden in de laatste levensfase. CDS wordt daarom niet langer gezien als laatste redmiddel, maar als een toegankelijke optie om het lijden te verlichten aan het einde van het leven.

Dankwoord

In dit dankwoord wil ik graag iedereen van harte bedanken die aan de totstandkoming van dit proefschrift heeft bijgedragen. Zonder jullie was het afronden van dit proefschrift nooit gelukt.

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Daarnaast wil ik alle zorgverleners die in dit onderzoek hebben deelgenomen bedanken. Tijdens een interview deelden jullie je opvattingen en ervaringen met het toepassen van continue diepe sedatie in de praktijk. In jullie verhalen kwam jullie warme betrokkenheid en aandacht voor patiënten en diens naasten naar voren, dat blijft me bij.

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Curriculum Vitae

Madelon Tessa Heijltjes was born in 1991 on June the 25th in Hoeven, in the Netherlands. In 2009 she obtained her Gymnasium diploma at Markland College in Oudenbosch. After high school, she studied medicine in Leiden. At the end of her study, Manon was interested in oncology. During her Masters, she did her scientific internship in the lab, in the field of colorectal cancer, in Galway, Ireland. Furthermore, Manon did internships abroad in Suriname and in Sri Lanka. After she finished her study, Manon started to work as a physician in the Antoni van Leeuwenhoek Hospital in Amsterdam. She saw that patients at the end of their lives were sometimes suffering of intractable symptoms. Sometimes continuous deep sedation relieved these symptoms. Manon became interested in end-of-life care and in the use of continuous deep sedation. After working in the Antoni van Leeuwenhoek Hospital, Manon worked at the Prinses Maxima Center for Pediatric Oncology at the later outpatient clinic, where people who cured of childhood cancer received their check-up appointments. In June 2018 Manon started with her PhD on the use of continuous deep sedation in the Netherlands. During her research period Manon gained more experience with quantitative and qualitative research methods. Manon obtained interviews with patients, relatives, and health care professionals. During these period, Manon got inspired by the elderly care specialists who were passioned about their work. While finishing her PhD thesis, Manon started to work in the nursing home as a physician in November 2021, and from March 2022 and onwards as elderly care physician in training. Manon lives together with Marvin. Together they are parents of Felien and Tijn and expect their third child to be born in May 2024.

List of publications

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