Review Article

Changing Practices in the Use of Continuous Sedation at the End of Life: A Systematic Review of the Literature

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Abstract

Context. 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.

Methods. 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 Preferred reporting items for systematic review and meta-analysis protocols 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 frequencies of CSD in deceased persons 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 nonphysical symptoms including fear, anxiety, and psycho-existential distress. In some studies, there was an increase in requests for sedation of patients from their families.

Conclusions. The frequency of CSD seems to increase over time, possibly partly because of an extension of indications for sedation, from mainly physical symptoms to also nonphysical symptoms. J Pain Symptom Manage 2020;■:■−■.

Key Words

Continuous sedation, terminal sedation, palliative sedation, deep sedation, end-of-life sedation

Key message

The aim of this literature review was to gain insight into the use of continuous sedation until death over time in different countries and subpopulations. The frequency of continuous sedation until death seems to increase, possibly (partly) because of the extension of indications for sedation, from only physical symptoms to also nonphysical symptoms.

Introduction

In the last phase of life, patients may suffer from severe symptoms.[1,2] Continuous sedation until death

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(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 nonphysical origin such as 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 and 2020. Our second aim is to provide insight into 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 are 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 CSD.

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 preferred reporting items for systematic review and meta-analysis protocols 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 Appendix 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 M.T.H. and G.J.M.W.v.T. 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 M.T.H. and G.J.M.W.v.T.

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 nonrandomized trials (Robins I-tool), see Appendix Table 2. The quality of the reviewed studies was assessed independently by M.T.H. and G.J.M.W.v.T., 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 were collected prospectively by trained staff (physicians, nurses, researchers). The risk of bias was considered as higher when data were 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. Sixty-one articles were finally included in our review, 23 articles on 16 nationwide studies, and 38 articles on 37 studies in subpopulations.[21–30,31–45,46–55,56–65,66–75,76–81]

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. Appendix Table 3 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.

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, and in patients with cancer and hospitalized; 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 older than 80 years, 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 patients with cancer in a palliative care

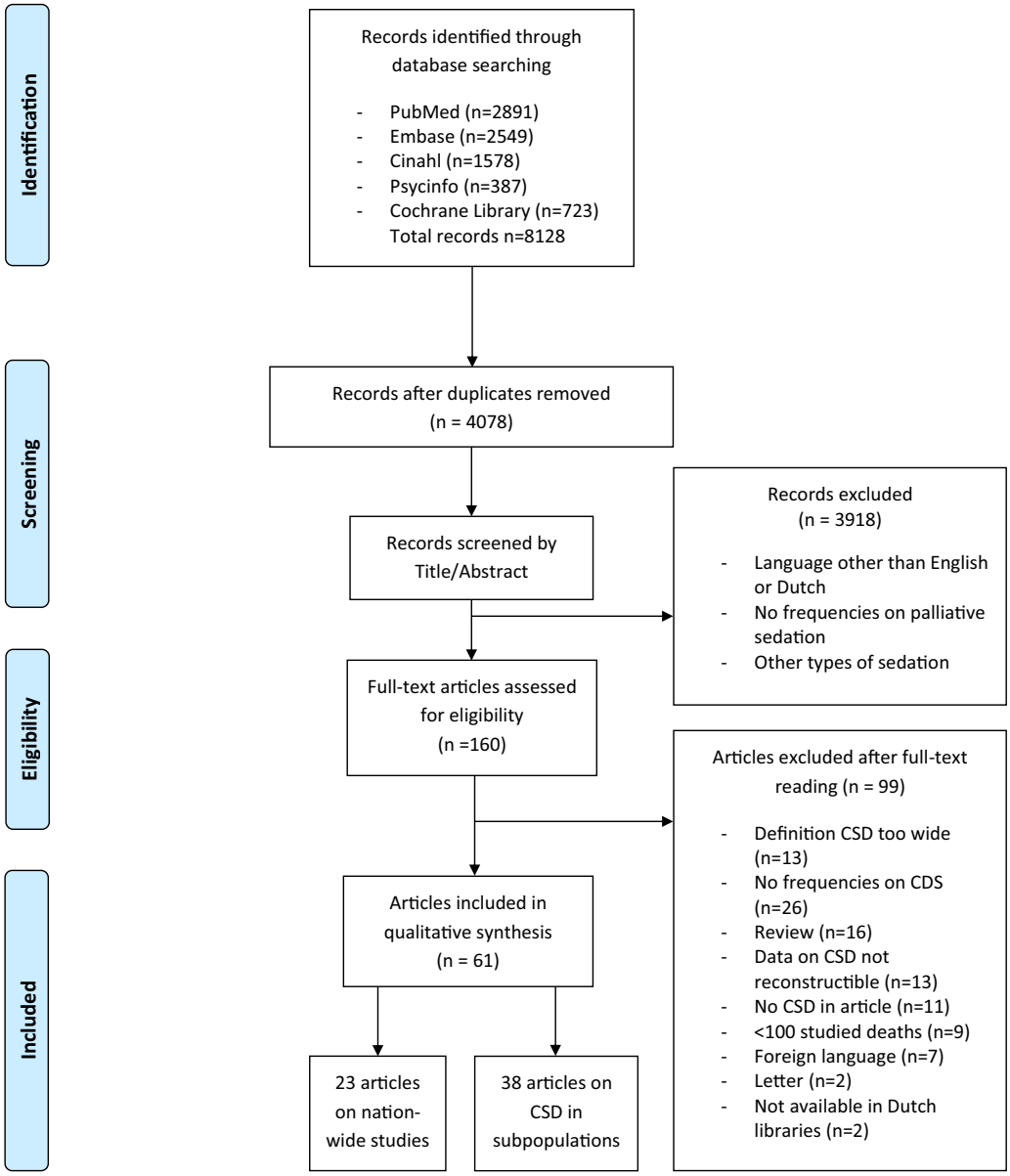

Fig. 1. PRISMA flow diagram, overview of literature search. CSD = continuous sedation until death; PRISMA = Preferred reporting items for systematic review and meta-analysis protocols.

unit to 80% in the United Kingdom in 2010 in hospice patients.[67,80]

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 an indication for sedation was mentioned only once in studies before 2008, and from 2008 and onwards, it was mentioned in 9 studies with percentages ranging from 0 to 32%. Fear as an 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 nonphysical symptoms including fear, anxiety, and psycho-existential distress.

Table 3 shows characteristics of CSD in clinical practice in repeated studies. From 1995 to 2002, there was an increase in requests from patients for sedation from 19% to 34% in an inpatient palliative care unit

Table 1
Nationwide and Subpopulation Studies on Continuous Deep Sedation

Nation year Study Inclusion Period (Reference)	Study Type	Total Patients Investigated	Patients Who Received CSD, No (%)	Definition of Sedation	Study Population
Nationwide studies					
Belgium, 2001 2001,06-2002,02[21–25]	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[23,24,27–29]	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, 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, 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 (nonsudden) 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 nonsudden deaths
The Netherlands, 2000-2001 2000-2001[31]	Physician interviews among medical specialists, general practitioners, and 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[35–37]	Questionnaire study among physicians on death certificates, stratified deaths	6363	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	7277	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
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	Nationwide deaths

(*Continued*)

Table 1
Continued

Nation year Study Inclusion Period (Reference)	Study Type	Total Patients Investigated	Patients Who Received CSD, No (%)	Definition of Sedation	Study Population
				sedation or coma until death.	
Switzerland, 2013 2013,8-2014-2[38–41]	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]	Questionnaire study among physicians, reporting on their last attended death	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[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 hours, 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]	Questionnaire study among physicians on random sample of death certificates	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, aged 80 years and older
Belgium, 2004-2005 2004,09-2005,04[47]	Prospective multicenter study	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 palliative care unit.	Patients in a palliative care unit
Belgium, 2007 2007,06-2008,11[48]	Questionnaire study among physicians on death certificates, all physicians signing the death certificates of all patients aged 1-17 were invited to participate.	165	36 (21.8)	The patient was continuously kept in deep sedation or coma until death, by means of one or more drugs.	Children, 1-17 years
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	Cancer patients

				progressive and incurable disease.	
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	14,360	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 responded 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]	Descriptive prosepective study	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-hour 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 toward 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

(*Continued*)

Table 1
Continued

Nation year Study Inclusion Period (Reference)	Study Type	Total Patients Investigated	Patients Who Received CSD, No (%)	Definition of Sedation	Study Population
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
Germany, 2014-2015 2014,08-2015,07[56]	Retrospective cohort study, medical charts	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) 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]	Retrospective cohort study, medical charts	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	Home care patients Hospice patients

				control refractory symptoms.	
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
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) 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, reanalysis of data collected for other prospective studies	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, andcontinuous palliative sedation was defined as "palliative sedation administered until death." This definition excluded situations in which	Hospice patients and patients in palliative care units

(*Continued*)

Table 1
Continued

Nation year Study Inclusion Period (Reference)	Study Type	Total Patients Investigated	Patients Who Received CSD, No (%)	Definition of Sedation	Study Population
				medication was administered in normal doses to relieve insomnia and/or anxiety, where sedation was an unintended side effect of medication or where palliative sedation was only administered temporarily.	
The Netherlands, 2001-2005 2001,10-2005,10[71]	Retrospective cohort study, medical charts	157	68 (43.3)	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.	Patients with amyotrophic lateral sclerosis
The Netherlands, 2003-2008 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.	Patients with amyotrophic lateral sclerosis 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 2 weeks of life.	Cancer patients in tertiary medical centers
South-Korea, 2015-2017 2015,09-2017,03[76]	Prospective observational 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. In 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 at home 191 at the hospital	35 (14) 93 (49)	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 care professionals.	Cancer patients at home

Taiwan, 1998-1999 1998,08-1999,05[79]	Prospective observational 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
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 before 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 before death.	Hospice patients
The United Kingdom, 2014 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 before death.	Hospice patients
The United States, 2004-2005 2004,01-2005,12[81]	Retrospective cohort study, pharmacy records	352	186 (41)	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

CSD = continuous sedation until death; n/a = not available; PS = palliative sedation.

Table 2
Characteristics of Patients Who Received CSD

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	Care Home	Home	Hospice	Other	General Practitioner	Medical Specialist	Elderly Care Physician
Nationwide studies																			
Belgium, 2001[21,a]	9	7	11		12	5	10	8	9	7	7	13	3				x		
Belgium, 2007[29,a]	15	15	n/a	19	17	11	18	13				20	10	9	x		x		
Belgium, 2013[29,a]	12	12	n/a	17	16	9	17	10				17	9	7	x		x		
Denmark, 2001[21]	3	2	4		3	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,b]	55	45	18-64: 32		48	20	71	10	5	4	10	x					x		
The Netherlands, 2000-2001[31,b]	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,c]	9	8	11		10	6	13	10	18	14	15	x					7	12	6
The Netherlands, 2010,[37,c]	13	12	14		16	10	19	9	13	11	8	x					12	16	9
The Netherlands, 2015,[37,c]	19	18	19		22	16	29	10	5	12	8	x					21	18	14
Sweden, 2001[21]	4	3	6		5	2	5	2	3	3	4	5	2				x		
Switzerland, 2001, Non-sudden deaths,[38,a]	7	6	n/a	10	8	6	10	4	4	8	6	8	7	5	x		x		
Switzerland, 2013, Non-sudden deaths,[38,a]	26	23	n/a	39	27	21	28	23	26	22	22	33	14	19	36	x	x		
United Kingdom, 2007[43]	21	16	27		19	12	22	12	19			20	22	8	11	14	x		

CSD = continuous sedation until death; n/a = not available; x = unknown.
The table shows percentages of all patients who received continuous deep sedation compared to all studied deaths.
[a]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.
[b]These percentages are not compared to all deaths, but compared to all patients that had received CSD.
[c]Place of death instead of attending physician.

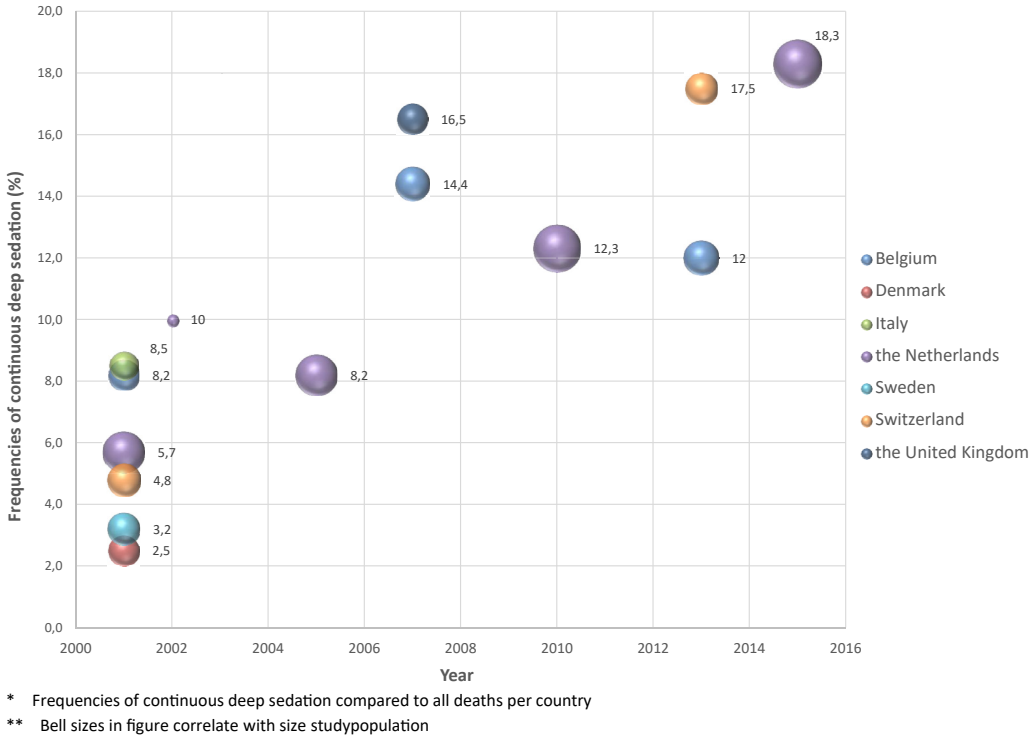

Fig. 2. Frequencies of continuous deep sedation per country.

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 most 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 alone or in combination with opioids was 54% in 2007 and 57% 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 morphine without a benzodiazepine for sedation decreased in The Netherlands from 15% in 2005 to 3% in 2015. Over the years, CSD was more frequently provided in the absence of artificial nutrition or hydration. The percentage of cases of CSD in which no artificial nutrition or hydration was provided varied from 33% in 2000 in Italy 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 cointention to hasten a patient's death. In Belgium, the proportion of cases in which there had been a cointention of hastening death increased from 13% in 2007 to 15% 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]

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 CSD decreased between

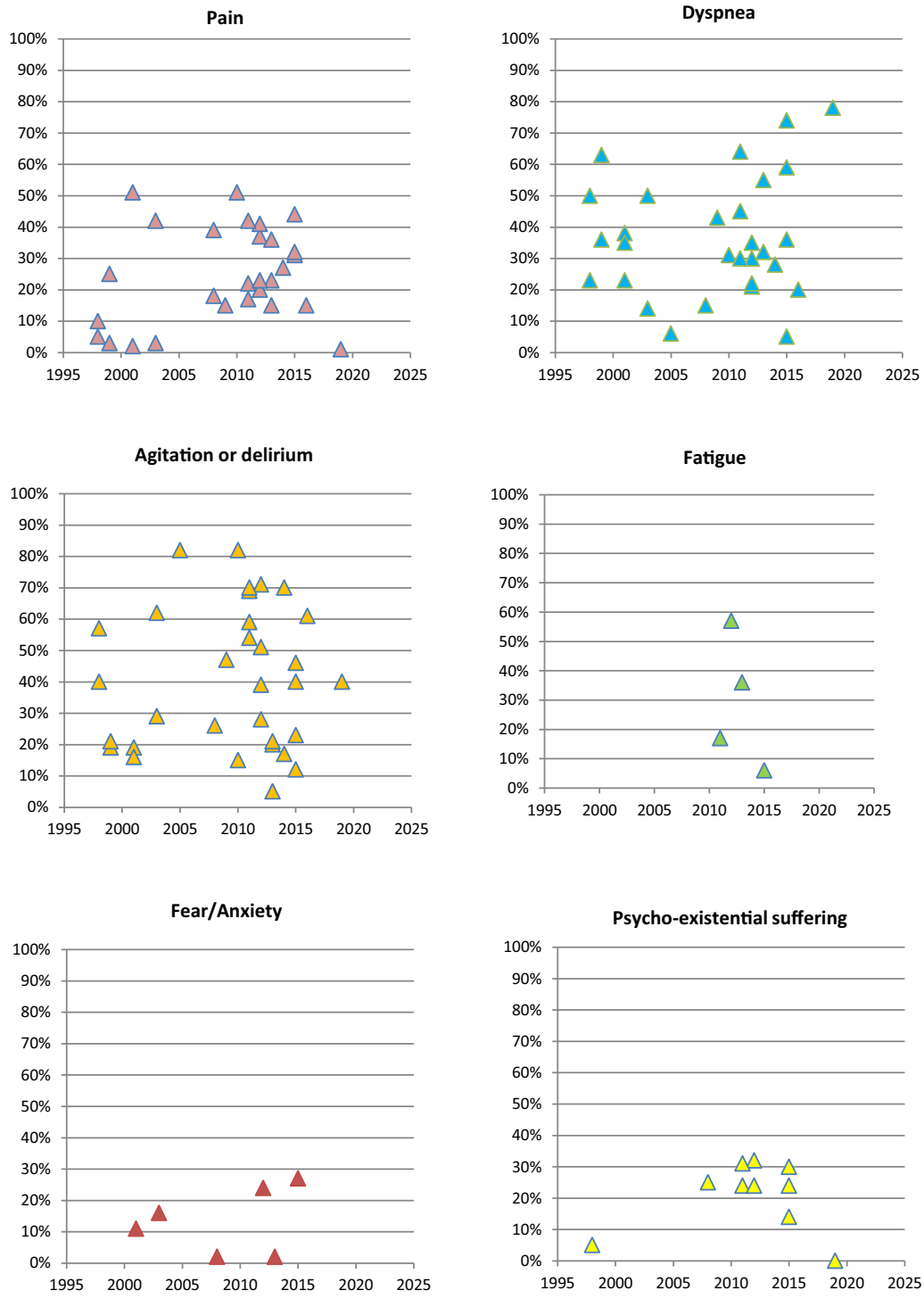

Fig. 3. Percentages of patients' symptoms per study requiring sedation over time.

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 nonphysical symptoms as indication for CSD such as fear, anxiety, or 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

Table 3
Characteristics of Sedation

Nationwide Studies				
Country (Reference)			Year	
Belgium[29]			2007	2013
Hastening of a patient's death	Cointention of hastening death		13	15
Request	Explicit intention of hastening death		1	3
Artificial nutrition or hydration	Request by patient		10	15
Duration sedation	No request/consent patient but request family		12	14
Medication used	Sedation without artificial nutrition hydration		58	62
	0-24 hours		24	36
	1-7 days		62	55
	1-2 weeks		11	6
	>2 weeks		2	4
	Benzodiazepines, alone or with other medication		54	57
	Only opioids		31	17
The Netherlands[37]		2005	2010	2015
Hastening a patient's death	Taking into account the hastening of death	x	38	38
Consultation of palliative care expert	With the intention to hasten death	x	2	2
Artificial nutrition hydration	Consultation of palliative care expert	9	20	21
Duration sedation	Sedation without artificial nutrition hydration	66	79	91
Medication used	0-24 hours	47	51	50
	1-7 days	47	46	46
	1-2 weeks	4	2	1
	>2 weeks	2	1	2
	Benzodiazepines, alone or with other medication	84	93	93
	Morphine without a benzodiazepine	15	6	3
Subpopulation studies				
Germany[55]		1995-1999		2000-2002
Main indication sedation	Dyspnea	36		35
Indication sedation	Gastrointestinal	10		6
Request for sedation	Bleeding	3		0
Type of sedation	Pain	3		2
Duration sedation	Delirium, agitation	19		10
	Anxiety, psychological distress	29		47
	Mainly somatic indication	64		45
	Mainly psychological indication	46		67
	Requests for sedation from patient	19		34
	Patients with request for sedation	53		45
	Continuous	48		67
	Intermittent	52		33
	Mean duration sedation (hours)	58		59
Italy[61]		2000		2003-2004
Duration sedation (days)	1 day	66		71
Hydration (the administration of	2-4 days	28		24
quantities of more than	5-10 days	6		6
500 cc of fluids per day)	Administration of artificial hydration	67		35
Therapy in the last 24 hours	Opioid	0		0
	Opioid + neuroleptics	20		6
	Opioids + benzodiazepines	9		13
	Opioid + benzodiazepines + neuroleptics	71		81
Italy[63]		2010	2013	2014
Principal refractory symptoms	Total pain	51	36	27
Awareness of death	Delirium	15	21	17
	Other symptoms	34	43	56
	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
Documented discussion	Pain	44	30	3
Hydration and nutrition	Respiratory distress	31	30	28

(*Continued*)

Table 3
Continued

United Kingdom[80]		2010	2011	2014
Dose medication	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
	With the patient	32	37	85
	With the Family	38	80	67
	With the team	15	67	67
	Documented hydration and nutrition	23	67	100
	Mean dose midazolam on day of death (mg)	30	25	31
	Mean dose levomepromazine on day of death (mg)	56	55	55

x = unknown.
The table shows percentages compared to all patients who received continuous deep sedation during the observed period.

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 nonphysical symptoms may explain the increase. Our results showed that over the years, more studies reported nonphysical 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 because of the extension of indications for sedation, from only physical symptoms to also nonphysical 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 health-care 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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Appendix

Appendix 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 to 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 to 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 to 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 to April 15th 2020. - Search on title or abstract	- 387
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 to April 15th 2020.	- 5 Cochrane reviews, 718 trials
Total of results	8128		

Appendix Table 2

Adapted Version of the Revised Cochrane Risk-of-Bias Tool for Nonrandomized 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 were collected prospectively by adequate trained staff (physicians, nurses, researchers)	Data were collected retrospectively, or data were 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

Appendix Table 3

Adapted Version of the Revised Cochrane Risk-of-Bias Tool for Nonrandomized 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
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