Review Article

Clinical Aspects of Palliative Sedation in Prospective Studies. A Systematic Review

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Abstract

Context. Near the end of life when patients experience refractory symptoms, palliative sedation may be considered as a last treatment. Clinical guidelines have been developed, but they are mainly based on expert opinion or retrospective chart reviews. Therefore, evidence for the clinical aspects of palliative sedation is needed.

Objectives. To explore clinical aspects of palliative sedation in recent prospective studies.

Methods. Systematic review was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and registered at PROSPERO. PubMed, CINAHL, Cochrane, MEDLINE, and EMBASE were searched (January 2014−December 2019), combining sedation, palliative care, and prospective. Article quality was assessed.

Results. Ten prospective articles were included, involving predominantly patients with cancer. Most frequently reported refractory symptoms were delirium (41%−83%), pain (25%−65%), and dyspnea (16%−59%). In some articles, psychological and existential distress were mentioned (16%−59%). Only a few articles specified the tools used to assess symptoms. Level of sedation assessment tools were the Richmond Agitation Sedation Scale, Ramsay Sedation Scale, Glasgow Coma Scale, and Bispectral Index monitoring. The palliative sedation practice shows an underlying need for proportionality in relation to symptom intensity. Midazolam was the main sedative used. Other reported medications were phenobarbital, promethazine, and anesthetic medication—propofol. The only study that reported level of patient's discomfort as a palliative sedation outcome showed a decrease in patient discomfort.

Conclusion. Assessment of refractory symptoms should include physical evaluation with standardized tools applied and interviews for psychological and existential evaluation by expert clinicians working in teams. Future research needs to evaluate the effectiveness of palliative sedation for refractory symptom relief. J Pain Symptom Manage 2021;61:831−844. © *2020 The Authors. Published by Elsevier Inc. on behalf of American Academy of Hospice and Palliative Medicine. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Key Words

Palliative sedation, sedation, deep sedation, palliative medicine, palliative care, terminal care, terminally ill, hospice care, systematic review, prospective studies

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Key Message

This article explores clinical aspects of palliative sedation in prospective studies. The results show there is room for improvement on assessment, including clinical expertise, interdisciplinary team dialogue, and specifying assessment tools used. There may be more than one refractory symptom at once. One study measured improvements in patient discomfort as outcome.

Introduction

There are symptoms that are common at the end of life as disease progresses. These symptoms, such as pain, delirium, dyspnea, and others, can become distressing and even intolerable for patients and their families. Different treatment options are available to manage symptoms. However, in some cases, the available standard treatments are no longer effective, the benefits are not reached in sufficient time, or treatments provoke more negative effects than benefits.[1] In cases where symptoms are very burdensome, no longer tolerable for the patient and can be considered refractory, palliative sedation may be considered as a therapeutic option. Among the most common symptoms that can become refractory are agitated delirium, dyspnea, pain, and convulsions.[2] No consensus exists about the appropriateness of using palliative sedation for psychological or existential distress[3] although it is being used occasionally.[4–7]

The European Association for Palliative Care (EAPC) defines palliative sedation 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.[8(p581)] The EAPC aimed to facilitate the development of national guidelines by presenting a 10-point framework based on pre-existing guidelines, literature, and extensive peer review. Palliative sedation may be delivered intermittently or given continuously until death. The level of sedation, after administration of sedatives to alleviate suffering, can be classified as mild, intermediate, or deep.[9]

Clinical guidelines for palliative sedation have been developed to guide medically appropriate and ethically acceptable practices, but they are mainly based on expert opinion because of the limited available evidence from prospective clinical studies.[10]

In a previous study conducted in several European countries, the percentages of reported continuous palliative sedation based on death registries ranged from 2.5% in Denmark up to 8.5% in Italy.[11] More recent articles state that the overall incidence of palliative sedation varied between 7% and 18% of deaths of palliative care patients.[12,13] However, the incidence of palliative sedation is not easily interpreted because of the existence of several definitions and alternative terms.[12,14,15]

In addition, other articles suggest that the practice varies not only across countries[15] but also across clinical settings.[11] Variation relates to prognosis, whether both physical and existential symptoms are considered refractory or not,[16] and the expertise of the health professionals to deal with difficult symptoms.

In 2015, a systematic review was conducted focusing on the medications used for palliative sedation,[17] whereas another earlier review focused on the tools used to assess palliative sedation and symptom control.[18] Both reviews showed very limited evidence based on prospective data as most of the included articles were retrospective chart reviews, guidelines, or literature reviews. However, prospective data provide information over time collected at regular intervals and minimize recall errors. A review based on prospectively collected data could fill this research gap. Therefore, we sought to investigate this to inform a prospective international multicenter clinical project on palliative sedation.[19] The aim of this review was therefore to explore clinical aspects of palliative sedation in recent prospective studies.

Methods

A systematic review was conducted. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline was considered,[20] and it was registered with PROSPERO,[21] registration number CRD42019136326.

Research Question

The overall review question is: What is the clinical practice regarding palliative sedation in palliative care reported in prospective studies?

The specific questions are as follows:

1. What are the refractory symptoms related to palliative sedation in adults with advanced incurable illness?
2. What are the treatment strategies applied for palliative sedation in adults with advanced incurable illness?
3. What are the assessment strategies applied for palliative sedation in adults with advanced incurable illness?

Search Strategy

PubMed, CINAHL, Cochrane, MEDLINE, and EMBASE databases were searched. The search strategy

Table 1
Search Strategy

Database	Concepts and Combinations				
	Sedation		Palliative Care		Prospective
PubMed	Sedation (Title)	AND	Palliative care (MeSH)	AND	Prospective (MeSH)
MEDLINE (WoS)	Sedation (Title)	AND	Palliative care (MeSH)	AND	Prospective studies (topic)
EMBASE	Palliative sedation (title)	AND	Palliative care (abstract)	AND	Prospective (all files)
CINAHL	Sedation (Title)	AND	palliative care (abstract)	AND	Prospective (abstract)
Cochrane library	Sedation (Title, abstract, and key word)	AND	palliative care (title, abstract, and key word)	AND	Prospective

MeSH = Medical Subject Headings; WoS = Web of Science.
Limits: English language; published between January 2014 and September 2019.

combined three main concepts: sedation, palliative care, and prospective (studies) adjusting for each database (Table 1) and considering the suitability of using Medical Subject Headings (MeSH) or thesaurus terms. Palliative sedation as a MeSH term was not used, as the definition provided for it focused only on continuous deep sedation. The focus of the review sought to take a more inclusive view of palliative sedation.

The search was limited to the English language, and articles were published between January 2014 and December 2019. The 2014 year was chosen as there is a Cochrane review up to then about the benefit of palliative pharmacological sedation on quality of life, survival, and specific refractory symptoms.[17] Search strategies and strings were revised with an expert librarian in biomedical databases.

Selection Criteria

Articles were screened by title and abstract to determine eligibility through assessment of inclusion/exclusion criteria (Table 2). Two researchers independently performed eligibility assessment using Covidence software which is operated by Veritas Health Innovation Ltd, registered in Australia (ABN 41 600 366 274). This software allows blind reviewing of titles and abstracts. Disagreements between reviewers were resolved by the researchers discussing each article in question (M.A. and A.B.). All included articles were citation tracked, and their reference lists were checked to identify further articles.

Data Collection and Analysis Process

Data extraction and quality assessment were conducted by two researchers (M.A. and A.B.). Each researcher was responsible for the data extraction in 50% of the articles and independently extracted data on 10% of the articles of the other reviewer to ensure data extraction was done rigorously.[22] No substantial differences were found between researchers, but discussion between reviewers helped further data extraction.

A predefined data template was used after being piloted in three articles and adjusted (Table 3). The section on decision making is presented in another submitted article. Extracted data were coded in seven areas that are the focus of this article: 1) general data and study design; 2) study objectives; 3) participating setting and sample/patient characteristics; 4) refractory symptoms; 5) sedation outcomes; 6) monitoring and documenting; and 7) the quality of articles assessed using the Critical Appraisal Skills Programme tool (CASP, 2019).[23] In cases where important data were missing, the original authors were contacted and asked for additional information.

The CASP tool enabled systematic assessment of the trustworthiness, relevance, and results of the published articles,[23] specifically, the cohort studies

Table 2
Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Prospective clinical studies on palliative sedation for refractory symptoms	Studies that do not use a prospective methodology
Studies conducted in any type of settings	Studies that focus on other health professionals' perspectives and do not report data about patients
Studies of terminally ill persons aged older than 18 yrs (cancer and noncancer)	

Table 3
Data Extraction Sheet

Area	Item
General data	Author, year, country, and study design
Objective	Protocols, optimal sedation, effects, survival, and level of consciousness
Methodological strength, CASP	CASP items
Sample characteristics	Setting, patients, disease, age, gender, performance scales, and status
Refractory symptoms	Registered refractory symptoms
Decision making	Team work, PC teams, primary care physicians, protocols, and guidelines
Monitoring and documenting	Prior, baseline, and during the palliative sedation, and treatment strategy
Sedation results	Duration, survival, and effects (scales for measuring effects)

CASP = Critical Appraisal Skills Programme tool; PC = palliative care.

checklist was used to assess articles. A score was assigned to each of the 12 items assessed (1: response is affirmative, 0: response is unknown or negative) obtaining a maximum score of 12.[24] The score was used to provide an overview of the quality of the articles, not to exclude.

Results

A total of 43 articles were identified through the database searches. There were no additional records identified through citation tracking and reference list checking. After removing duplicates, 19 articles were screened by title and abstract, seven were excluded (Table 4), resulting in 12 articles for full-text assessment. Finally, 10 articles met the inclusion criteria and were included in the systematic review (Fig. 1).

Study Characteristics

Studies were conducted in Belgium,[25,26] Italy,[27,28] Japan,[29,30] The Netherlands,[31,32] Colombia,[33] and Mexico.[34] Two articles pertain to the same study,[31,32] so results have been reported as one study.

Table 4
List of Excluded Articles

Title	Exclusion Reason
The minimal clinically important difference of the Richmond Agitation-Sedation Scale in patients with cancer with agitated delirium	Irrelevant for the review: secondary analysis of a randomized controlled trial to compare the effect of lorazepam vs. placebo as an adjuvant to haloperidol for persistent agitation in patients with delirium
Interdisciplinary research in palliative care units: together we thrive	Irrelevant for the review: Review the structure, processes, and outcomes of acute palliative care units. Highlight the role of interdisciplinary teamwork in two prospective studies (investigating the process of dying; RCT on agitated delirium) in palliative care units
Psychological Support Based on Positive Suggestions (PSBPS) on Mental Health Morbidity and Cognitive Function	Irrelevant for the review: identifying causal factors and designing interventions to treat and ideally prevent postintensive care syndrome
Le droit à la sédation profonde et continue: réflexions et pistes prospectives (The right to deep and continuous sedation: reflections and prospective tracks)	Does not use a prospective methodology: French article with reflections
Sedation by Propofol for Painful Care Procedures at the End of Life: A Pilot Study. PROPOPAL 1	Irrelevant for the review: Verify whether propofol could allow us to administer care without causing major pain to patients with refractory pain at the end of life. (Uses propofol to control pain to do some care)
Discussions about palliative sedation in hospice: frequency, timing, and factors associated with patient involvement	Does not use a prospective methodology: It is a retrospective study and focus on investigating whether and when PS was discussed with hospice patients with cancer and/or with their families and factors associated with patient involvement in such discussions
Palliative sedation in specialized palliative care—a study of current practise	Does not use a prospective methodology: It is a retrospective study of patient's records to explore the use of PS in specialized palliative home care and inpatient care

RCT = randomized controlled trial; PS = palliative sedation.

The methodological quality evaluation of each article using CASP appraisal questions is shown in Table 5. The quality is between good and excellent except for two articles with lower scores (scores of 6 of 12).[28,33] The two articles of van Deijck et al.[31,32] (same prospective study) are outstanding for their excellence (CASP 11 of 12). Strengths identified in the articles are recruitment across several settings, data collected during a year,[29–32] and assessment of specific outcomes and measurement times.[29] Some of the limitations identified in the articles include a small sample size;[26,29,33,34] lack of clarity about the assessment tools used,[26,27,29,30,33,34] timing, and follow-ups;[25] inability to ensure that study reports are truly comparable at baseline;[28] and lack of a uniform standardized protocol for sedation among settings.[30]

Study designs used are longitudinal studies with follow-up lengths ranging from one to four months,[25,27,31,32] three observational studies,[28,33,34] two cohort studies,[29,30] and one mixed-method study.[26] Most of them are multicenter studies except for two that were recruited from one center.[29,34]

The studies were conducted in palliative care services. Regarding the specific palliative care services involved, there was considerable variety: palliative care teams in hospitals,[30,33] palliative home care services,[26,27,28,30] hospices,[25,27,31,32] nursing home-based palliative care units,[31,32] and palliative care units.[25,29,30,34]

Study Participant Characteristics

In most articles, participants were patients with cancer,[25,27–30,33,34] but two articles also included noncancer patients ($n = 2$[26]; $n = 14$[31]). The information about the diagnoses of noncancer patients is limited. Patients could have more than one diagnosis, including heart failure, dementia, chronic lower respiratory diseases, cerebrovascular diseases, Parkinson disease, and diabetes mellitus.[32]

The sample size of sedated patients ranged from 23[26] to 531.[27] There were larger sample sizes in the studies by Caraceni et al. ($n = 531$),[27] Maeda et al. ($n = 269$),[30] and van Deijck et al. ($n = 130$).[31,32] These studies are multicenter or even national studies. The

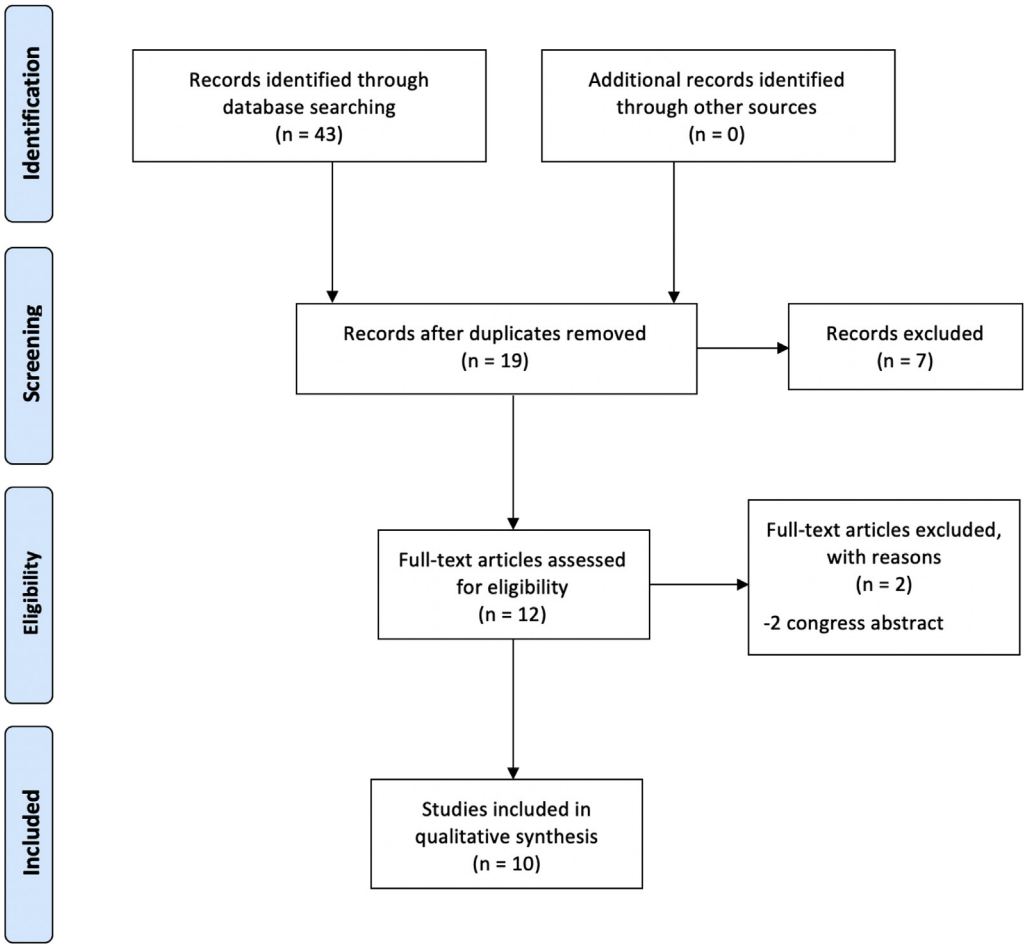

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart from the search strategy.

Table 5
CASP Score of the Included Articles

Study	(1) Focused	(2) Recruitment	(3) Exposure Measurement	(4) Outcome Measurement	(5a) Confounding Factors	(5b) Confounding Factors	(6a) Follow-Up	(6b) Follow-Up	(7) Results	(8) Results Precision	(9) Credibility	(10) Application	(11) Adjustment	(12) Implications	Overall Assessment
Caraceni et al., 2018[27]	Y	Y	Y	Y	U	U	Y	Y	Y	Y	Y	N	U	Y	9/12
Claessens et al., 2014[25]	Y	Y	U	Y	N	U	U	Y	Y	Y	Y	U	Y	U	7, 5/12
Imai et al., 2018[29]	Y	Y	Y	N	U	U	Y	Y	Y	Y	U	Y	U	U	7/12
Maeda et al., 2015[30]	Y	Y	U	Y	U	U	Y	Y	Y	U	Y	Y	Y	Y	9/12
Mercadante et al., 2014[28]	Y	Y	U	U	U	U	Y	Y	Y	U	Y	Y	U	U	6/12
Monreal-Carrillo et al., 2017[34]	Y	N	Y	Y	U	U	Y	N	Y	U	Y	Y	Y	Y	8, 5/12
Parra Palacio et al., 2018[33]	Y	U	U	U	Y	U	U	U	Y	U	Y	Y	Y	U	5, 5/12
Pype et al., 2018[26]	Y	U	Y	Y	U	U	Y	Y	Y	Y	Y	U	U	U	7/12
van Deijck et al., 2016 a[31]	Y	Y	Y	Y	U	U	Y	Y	Y	Y	Y	Y	Y	Y	11/12
van Deijck et al., 2016 b[32]	Y	Y	Y	Y	U	U	Y	Y	Y	Y	Y	Y	Y	Y	11/12

CASP = Critical Appraisal Skills Programme tool.
CASP appraisal questions: 1) Did the study address a clearly focused issue? 2) Was the cohort recruited in an acceptable way? 3) Was the exposure accurately measured to minimize bias? 4) Was the outcome accurately measured to minimize bias? 5a) Have the authors identified all important confounding factors? 5b) Have they considered of the confounding factors in the design and/or analysis) 6a) Was the follow-up of subjects complete enough? 6b) Was the follow-up of subjects long enough? 7) What are the results of this study? 8) How precise are the results? 9) Do you believe the results? 10) Can the results be applied to the local population? 11) Do the results of this study fit with other available evidence? and 12) What are the implications of this study for practice?
CASP scoring: Y (yes) = 1; U (unclear) = 0; N (no) = 0. When assessment item included two questions, each one was scored 0.5 points.

other six articles had much smaller samples, ranging from 20 to 66 sedated patients.[26,29,33,34]

Most of the articles provided characteristics about sedated patients, such as age, gender, and some information about performance status.[26,27,29–34] In some articles, there was a predominance of male sedated patients,[26,27,29,30] whereas in others, females were predominant.[31,33,34] The age of sedated patients tends to be around 65 years or older,[29–32] but in two articles, lower mean ages were reported: 61 years (range 24–87)[33] and 41 years (range 29–71).[34]

Regarding the information on the performance status of sedated patients, the scores on the Karnofsky Performance Status tend to be mainly below 50 points[27,31,33] and on the Eastern Cooperative Oncology Group Performance Status above three or four indicating a severely impaired functional capacity (capable of only limited self-care or completely disabled).[29,30]

What Refractory Symptoms Are Indications for Palliative Sedation?

The most frequent symptoms requiring the administration of palliative sedation were delirium (41%–83%; $n = 11–288$), pain (25%–65%; $n = 13–116$), and dyspnea (16%–59%; $n = 4–239$).[26–28,33,34]

One study showed that refractory symptoms such as psychological and existential distress were copresent in 48% ($n = 13$) of participants.[26] Other articles reported the presence of existential refractory symptoms in 10%–14% of patients ($n = 2–9$)[33,34] and of psychological distress in 24% of the patients ($n = 126$).[27]

Two articles specified the need for sedation in patients because of psychological or existential distress.[27,33] In the first study, 5% ($n = 30$) of the patients presented psychological distress as an indicator for palliative sedation.[27] The second study explains how nine patients (14%) had existential suffering and reports that in one patient it was the only refractory symptom present.[33]

Other symptoms requiring palliative sedation were convulsions (25%; $n = 5$),[34] vomiting (5%–22%; $n = 6–25$),[26,27] malignant obstruction (15%; $n = 3$),[34] confusion (7%; $n = 2$), tachycardia (4%; $n = 1$), facial myoclonuses (4%; $n = 1$), asphyxia (5%; $n = 1$),[34] and, finally, massive bleeding (3%–5%; $n = 1–17$).[27,34] The study by Monreal-Carrillo et al.[34] is the only study reporting the conditions of convulsions and facial myoclonus. It may be that the study objective to characterize level of unresponsiveness in sedated patients using Bispectral Index may have influenced patient selection.

Three articles reported the presence of more than one refractory symptom leading to the administration of palliative sedation (60%–90%; $n = 17–40$),[26,33,34] whereas the study by Caraceni et al.[27] mentioned only one refractory symptom in 54% ($n = 287$) of the patients,[27] two in 38% ($n = 201$), and more in 8% ($n = 43$).

Evaluation and Consultation Procedures

The articles showed that the decision-making process was led by the palliative care team,[27,29–32,34] and in some cases, specifically it was led by the attending palliative physician.[31,32,34] In one study, the general practitioners (GPs) were the ones performing palliative sedation at home. The GPs highlighted the importance of team work with palliative care professionals as most of them had limited experience in palliative sedation.[26]

Most of the articles did not specify how they performed assessment of the refractory symptoms but just mentioned the refractory symptoms for which palliative sedation was administered.[26–28,33,34] Moreover, one study added that it is not clearly established what neither intolerable suffering is nor the refractoriness of symptoms because of their subjectivity.[31]

All the studies recorded, before sedation, patients' demographic data (gender and age) and their diagnosis.[25–34] In addition, some studies also collected data at baseline about 1) functional status with the Karnofsky Performance Status,[31,33] Palliative Performance Scale,[30] or Eastern Cooperative Oncology Group Performance Status;[29] 2) level of consciousness with Glasgow Coma Scale;[30,31] 3) symptoms[25,33] with the Edmonton Symptom Assessment System[31] or its revised version;[30] The Support Team Assessment Schedule,[29] the Delirium Confusion Assessment Method,[25] or rated symptoms between 0 and 10 on a numerical rating scale;[28] 4) administered medication;[30,31,33] 5) patients' preferences about palliative sedation;[27] 6) prognosis;[29] 7) fluid or food administration during palliative sedation;[30] and 8) the presence of comorbidities.[26] There is no information about consultations with psychiatric specialists or other professionals.

Selection of the Sedation Method

Three articles explained that specific protocols or national guidelines were used to justify the considered criteria before sedation of a patient and the selected type and route of administration for sedation.[26,29,30] One study reported that a specific protocol was followed to choose the type of sedation to use,[29] whereas another mentioned that all institutions involved in the study administered continuous deep sedation according to a national clinical guideline. This guideline indicates that continuous deep sedation can be administered in patients with refractory symptoms with an estimated survival of two weeks or less.[30]

In some studies, the palliative sedation process was supervised and modified (if needed) by experts with

Table 6
Medication for Sedation, Dose, Time Sedated, and Additional Medications in Nine Prospective Articles

Author (Reference)	Sedated/ Not Sedated, *n* (%)	Sedatives	Initial Dose (mg/Day)[a]	Maintain Dose (mg/Day)	Time Until Death (Median)	Additional Medications Reported	Additional Information
Claessens et al., 2014[25]	20/226 (7%)	Midazolam	NR	NR	60 hours	NR	—
Monreal-Carrillo et al.,2017[34]	20/254 (8%)	Propofol plus midazolam in combo[b]	230 P plus M 115?[b]	NR	24 hours	Opioids, antipsychotic, other symptom medications allowed	Time to desired sedation level is six hours
Maeda et al., 2015[30]	269/1827 (15%)	Midazolam 84% or phenobarbital 9% or propofol—others	M 20–40; or PH 100–750	NR	NR	NR	—
Caraceni et al., 2018[27]	531/2894 (18%)	Midazolam (88%) alone or in combination of sedatives or propofol or phenobarbital	NR	NR	46 hours	Opioids, neuroleptics, another benzodiazepine, antihistaminic	—
Pype et al., 2018[26]	27/1181 (2%)	Midazolam (85%) Phenobarbital (15%)	NR	M 153 Ph 640	25 hours (15 minutes–seven days)	Morphine maintained, dexamethasone retired	11/27 suboptimal sedation (awaking or long time to sedation)
Mercadante et al., 2014[28]	24/219 (11%)	Midazolam	20–60	27–53	42 ± 30 hours	Other sedatives or symptomatic medications allowed	Level of satisfaction fair in 1/24
Imai et al., 2018[29]	50/398 (13%)	Midazolam	M 12–50 vs. M 100–250 until deep sedation, then decrease	26–34 vs. 38–48	75 hours (10–444) vs. 42 hours (1–169)	NR	Apneas 4% vs. 22%
Parra Palacio et al., 2018[33]	66/2890 (2%)	Midazolam	50	100	45 hours (1–21)	Opioids	—
van Deijck et al., 2016[31,32]	130/467 (28%)	Midazolam (85%) vs. phenobarbital (15%)	NR	NR	25 hours (2–161)	NR	—

[a]NR = nonreported; M = midazolam; P = propofol; Ph = phenobarbital.
[b]MIDAS (Intensive Management of Pain, Anxiety and Distress) palliative sedation protocol: Initial propofol doses of 0.16 mg/kg/hour and midazolam 0.08 mg/kg were adjusted according to the individual patient response. The continuous infusion rate ranged between 0.16 and 1.3 mg/kg/hour for propofol and between 0.08 and 0.5 mg/kg/hour for midazolam. The calculation of initial dose is based on 60 kg and is offered for the comparison with other articles.

knowledge of guidelines and the correct use of palliative sedation.[25,27,30] One study indicated that during the process of palliative sedation, certified palliative care specialists directly ordered dose and titration of sedatives.[30]

Articles use different terms to refer to the sedation conducted in practice. Some articles reported the use of continuous palliative sedation referring to a gradual introduction of sedation depending on patient needs for symptom control.[26,27,31,32,34] Mercadante et al.[28] used the generic term of palliative sedation throughout their article, but the information provided within it is comparable with the term continuous palliative sedation as used in the other articles and explains titration steps and reports that sedation was maintained until death. Maeda et al.[30] used the term continuous deep sedation, which was explained as the continuous use of sedatives to relieve intolerable and refractory symptoms by the total loss of a patient's consciousness until death and recommends a titration approach.

A Japanese study investigated the effect of two approaches to palliative sedation: proportional sedation by increasing the depth of unresponsiveness, if necessary, and deep sedation right from the start.[29] They used different starting doses of midazolam (0.5−2 mg/hour vs. 5−10 mg/hour until deep sedation was achieved and then the dose was reduced to 0.5−3 mg/hour). The authors set different primary endpoints for the so-called two types of sedation, determined at 4 hours: in the proportional sedation, this was the achievement of symptom relief and the absence of agitation, whereas, in the protocol of deep sedation, achievement of deep sedation was the endpoint. For proportional sedation, symptom relief as a treatment goal was achieved in 68.8% of the cases, in this group; in 31.3% of cases, deep sedation was needed. In deep sedation, deep sedation as a goal was achieved in 83.3% of cases. Authors report survival data for both approaches. On the proportional sedation group, survival from the beginning of sedation to death was 75.5 hours (range 10−444); and on the deep sedation group was 42.5 hours (range 1−269). They do not provide a statistical comparison on survival among the two approaches; they suggest that it was due to patients been close to death.

In another study, two types of sedation were considered: midazolam was administered intermittently (using it scheduled at four-hour to eight-hour interval) or as a continuous infusion, depending on whether the refractory symptom was continuously present causing significant suffering or not. In both types, medications were titrated until symptom control was achieved.[33]

Claessens et al.[25] mentioned that no definition of palliative sedation was given; ensuring that all possible cases of palliative sedation were included in the study including the following levels of sedation: mild-intermittent, mild-continuous, deep-intermittent in nonacute situations, deep-intermittent in acute situations, deep-continuous in nonacute situations, and deep-continuous in acute situations. Their study entails a combination of all the aspects mentioned in previous articles regarding continuous or intermittent sedation and levels of sedation.

Dose Titration, Patient Monitoring, and Care

Medication used for sedation, dose titration, time frame, and concomitant medication used are reported in Table 6. Midazolam is used in all articles, mainly as the first-line medication, and usually indicated as the single medication for sedation.

Midazolam is usually administered via continuous intravenous or subcutaneous infusion.[26,27,30,33] Subcutaneous infusion is more often used for palliative sedation at home.[27] Other methods of administrating medications are using pro re nata (as-needed) doses or on an hourly basis.[27,33] Initial doses of midazolam were usually less than 50 mg/day via intravenous or subcutaneous routes (except for the study using midazolam in combination with propofol with an initial dose of around 115 mg/day.[34] Alternative medications for palliative sedation were phenobarbital[26,27,30] and propofol.[27,30]

In one article, propofol in combination with midazolam was reported as the protocol of palliative sedation established in a palliative care service in Mexico.[34] The article aimed to characterize the level of consciousness in patients undergoing palliative sedation by monitoring cerebral electrical activity using electroencephalogram.

Caraceni et al.[27] reported the use of a range of sedative medications at the time of performing the sedation: only one medication was used in 69% of cases (usually midazolam), but the remaining 30% received a combination of several sedatives.

Articles reported the use of adjuvant medications for symptom control according to the patient's needs during palliative sedation.[34,33] In one study, morphine is described as the most commonly used additional medication as it was maintained if previously given for other reasons (e.g., pain or dyspnea).[33] Other articles reported the use of antipsychotics, such as levomepromazine, chlorpromazine, and haloperidol, in some cases for the specific management of delirium.[27,28]

Administration of hydration and nutrition during palliative sedation is mentioned in half of the studies. One Belgium study specifically described the decline on oral and artificial food and fluid intake in Flemish palliative care unit patients and the possible effect of palliative sedation.[25] In these cases, there was a

tendency to reduce the volume of fluid administered to about 500 cc/day.[25] An additional comment regarding the Belgian study is that in 10% of the cases, parenteral nutrition is also maintained during sedation.[25] In a Dutch study,[32] in most of the cases (97%) in the hospice or palliative care unit, they did not administer hydration or withdrew it during palliative sedation. The studies in Japan, Belgium, Mexico, and Colombia mainly maintained hydration during sedation.[25,30,33,34]

Duration of sedation varied between articles from a median duration of approximately 25 hours[26,32,34] to mean durations of 40–70 hours.[25,27–29,33] However, there are sedated patients with longer survival, for example, 12 of 531 patients lived longer than seven days in the study of Caraceni et al.[27]

One study compared survival between sedated and nonsedated patients with no significant differences on survival between these two groups.[30] The unweighted median survival was 27 days (95% CI 22–30) in the continuous deep sedation group and 26 days[24–27] in the no sedation group (median difference −1 day [95% CI −5 to 4]; hazard ratio 0.92 [95% CI 0.81–1.05]; log rank test, $P = 0.20$). van Deijck et al.[31] did not find statistically significant differences in survival between sedated and nonsedated patients from admission until death (mean 33.1 days, SD 43.3 and mean 34.8 days, SD 41.2).

The level of sedation was assessed with the Richmond Agitation Sedation Scale (RASS),[26,29] Ramsay Sedation Scale,[33,34] Glasgow Coma Scale,[30] modified version of the Wilson Sedation Scale,[27] or Bispectral Index monitoring.[34]

One study focused on patient discomfort as an outcome by evaluating patients with the Discomfort Scale for Dementia of the Alzheimer's type,[32] before and after palliative sedation. A significant reduction of patients' discomfort was found within eight hours of starting continuous palliative sedation, and the scores remained relatively stable until death.[32] Patient intake of a small amount of fluid or food the previous day to sedation and having refractory vomiting and multiple refractory symptoms emerged as statistically significant factors influencing discomfort in the last eight hours of life. Gender, age, and the presence of malignant neoplasms were not significantly associated with discomfort in the last eight hours of life (Appendix Table 1).[32]

Some of the articles that estimated the efficacy of palliative sedation also considered health professionals' and relatives' opinions about this. For instance, Pype et al.[26] studied the presence of suboptimal palliative sedation by asking experienced and unexperienced GPs' opinions. The authors stated that palliative sedation is the administration of sedatives in doses and combinations that diminish the patient's consciousness to control one or more refractory symptoms. But later when justifying the guidelines they set for suboptimal sedation, they say that continuous deep sedation until death is the most frequently used procedure and that its purpose is to bring the patient into a deep sleep without further awakenings; and not the previously mentioned symptom control. The authors described palliative sedation as suboptimal when the time needed until deep sleep was more than one and a half hours, and/or there were three or more awakenings after deep sleep was reached. With this definition in mind, GPs considered that 41% of the sedations in which they were involved had been suboptimal.[26] van Deijck et al.[32] measured on a four-point scale the effect of palliative sedation on symptom control as rated by the physician and reported complete symptom relief in 80% of the sample vs. 20% with no to partial symptom relief. Another study estimated symptom control as complete (89%), partially achieved (5%), not achieved (1%), and missing data (5%).[27] The statistical analysis of these scores compared with the discomfort scores registered by an independent nurse researcher on the Discomfort Scale—dementia of Alzheimer type showed statistical significance, supporting an association that showed patient symptom relief. One study studied the level of satisfaction of the relatives about palliative sedation and its correspondence to the level reported by the health professionals, being optimal in 63% of patients, good in 33%, and fair in 4% (compared with 75%, 20%, and 5%, respectively).[28]

Discussion

This systematic review shows that the number of prospective articles in the last five years about palliative sedation is scarce and focused mainly on patients with cancer. Articles show the presence of more than one refractory symptom, and some considered psychological and/or existential intolerable distress as refractory. There has been some improvement in the use of tools to assess refractory symptoms, but information on the tools used is still limited just as the expertise of clinicians assessing them. It shows that in general the EAPC framework guideline of midazolam as the most commonly used medication for palliative sedation is being applied. The review shows that palliative sedation aims to relieve refractory symptoms, but there is limited evidence of having achieved improvement on patients' discomfort.

Terms, Definitions, and Clinical Practice

Different terms are used to refer to the sedation conducted in practice, which adds confusion and hampers the comparison of the results. Our review

on prospective clinical articles shows that most of them transmitted the underlying and sometimes explicit idea that palliative sedation needs to be proportional to the need for refractory symptom relief of the patient. It reflects the concept of proportionality implicitly present in the original definition.[35] It said palliative sedation was the intentional administration of sedative medications in dosages, and combinations required reducing the consciousness of a terminal patient as much as necessary to adequately relieve one or more refractory symptoms.[35] According to Twycross,[14] proportionality is a fundamental aspect where the aim of palliative sedation is symptom relief and not termination of life. However, it is surprising that only one article reported on the different levels of sedation that patients had in the last eight hours of their lives[27] reported on the different levels of sedation before death. A more systematic way of investigating the level of sedation can contribute to the proportionality conducted in clinical practice. Besides, this review shows that except for Parra Palacio et al.[33] who also reported on intermittent sedation, the other clinical prospective articles only report on continuous sedation. This despite having taken a more inclusive approach on the search strategy and not used the MeSH term palliative sedation as circumscribed to continuous deep sedation.

Besides, in the literature, there is some concern about the importance of being aware that having an unresponsive sedated patient does not necessarily mean that is unaware.[14] This concern has showed that the exploration of consciousness is in its infancy[36] outside operating theater or intensive care contexts.

What Refractory Symptoms Indicate a Need for Palliative Sedation?

All the articles reported the presence of refractory symptoms at the end of life as an essential requirement before palliative sedation. Mostly physical symptoms are reported as refractory symptoms. However, it is difficult to assess which are the predominant symptoms that require palliative sedation as in some articles more than one refractory symptom was present or it was not specified.[26,33,34] In any case, physicians should be aware that delirium, pain, and dyspnea are usually reported as involved in the indication for palliative sedation.

Often it is not clear if the presence of existential or psychological distress was explored, with the risk of underidentifying these. These data contrast with recommendations of conducting a holistic assessment before deciding about palliative sedation.[8] There is a discussion in the literature about the acceptability of existential or psychological distress as a refractory symptom. However, grouping of symptoms as either physical or not physical has been criticized as being an overly simplistic view of human suffering.[8,37] This review shows that articles that explored these areas identified combinations of physical and existential or psychological suffering as refractory symptoms.[27,33] A few articles included patients who only presented with existential or psychological refractory symptoms,[27,33] but these lacked a clear definition[5,9,17,33] or guidelines to assess them,[8,27] which may hamper its identification. This issue requires specific ethical,[27] psychological, and clinical assessments and would benefit from a multidisciplinary approach.

This review shows that most of the articles did not specify how assessment of the refractory symptoms was performed,[26–28,33,34] which limits comparison. Compared with a previous review,[18] our findings suggest some improvements on the use of standardized tools to assess symptoms. In both reviews, there is almost no reference to specific assessment tools for existential or emotional distress, except for general tools as the Support Team Assessment Schedule or the Edmonton Symptom Assessment System that include some items in this regard. There is either reference to an interdisciplinary approach to assess these, for example, through interviews with experienced palliative care professionals who assess the subjective experience of the patient. The limited information provided by articles about the preparation and training of health care professionals, who assess these symptoms, generates questions about the symptom burden assessment and the decision-making process. Many articles were conducted within palliative care services, and it could be argued that staff is used to deal with very complex situations. This is underlined in a study conducted with GPs, where anxiety and fear of failure because of their limited experience was reported. They explained how they valued the additional support from palliative care professionals.[26] This supports the importance of working in teams and encouraging appropriate training and consultation with colleagues to deal with refractory symptoms as is included in some guidelines. Interdisciplinary evaluation together with evaluation by clinicians with sufficient experience and expertise in palliative care and palliative sedation should be encouraged.[8]

Future clinical articles should investigate how the different areas (physical, psychological, or existential) have been assessed before deciding to opt for palliative sedation and the expertise and training of the health professionals who conducted the holistic assessment. It would be interesting also to compare practices and outcomes among treatment settings.

Medication Used for Palliative Sedation

Midazolam was used in all articles, predominantly as a single medication by intravenous or subcutaneous

continuous infusion. This finding was also reported in a previous review.[17] The reported initial and maintenance doses of midazolam seem clearly aligned with the suggestions in the EAPC framework.[8] Propofol and phenobarbital are sometimes used as an alternative to midazolam.[26,27,30] In general, no neuroleptics were used for palliative sedation. Chlorpromazine and haloperidol were used more for the specific management of delirium,[27] continuing with it if the patient was receiving it before starting palliative sedation with midazolam[28,34] or in combination with midazolam as third step when introducing other sedative drugs.[28] Likewise, no opioids were used for sedation; although a number of articles described the continuation of previously initiated opioid medications.

There were two articles using different palliative sedation strategies than recommended by the EAPC framework.[8] One article used propofol as first line (in combination with midazolam),[34] mentioned in the EAPC framework as general anesthetic that has a quick onset of sedation.[8] It may be related to the central goal of proving the Bispectral Index monitoring. The other article proposed high dose of midazolam with the set goal of deep sedation as the only option for definitive symptom relief.[29] However, the EAPC framework describes that the aim of palliative sedation is to relieve the burden of intractable suffering in a manner that is ethically acceptable, whereas a decreased level of consciousness per se is not the only aim in the palliative sedation setting.[8]

The decision to administer artificial hydration during end-of-life care is another ethical debate.[30,38,39] The available data do not provide a clear pattern and do not allow an interpretation of cultural differences in the use of hydration in sedated patients. More detailed reports on this issue would facilitate further comparisons.

Assessment Procedures Applied for Palliative Sedation

Our systematic review shows that palliative sedation effects were measured by focusing on level of consciousness,[37] health professionals and relatives opinions,[27,33] or survival.[31] Although it could be argued that analyzing survival is required to contribute to the ethical discussion about the side effects of sedation (life shortening and safety), it should be emphasized that the main aim of palliative sedation is symptom control and relief of suffering. In this regard, the prospective study from van Deijck et al.[32] is interesting because they systematically measured and compared the level of discomfort before and during the administration of continuous palliative sedation. This can be contrasted to studies that measure time to deep sedation as an indirect parameter of symptom control; the sooner deep sedation is reached, the sooner there is symptom relief.[26]

It is obviously challenging to assess symptoms in a patient that, to some degree, has a decreased level of consciousness and responsiveness. The EAPC framework only mentions two assessment tools, namely the Critical-Care Pain Observation Tool and the RASS. Future updates of the framework or clinical studies should include tools such as the RASS RASS-PAL[40] or others to assess comfort or symptom relief. For example, tools that evaluate the degree of (dis)comfort in sedated patients. These are the Discomfort Scale—dementia of Alzheimer type,[32] based on observing different behavioral indicators; and the Patient Comfort Score,[41] which considers pain and level of consciousness. Technical approaches are starting to be used to assess level of sedation, adapting to assess physiological response assessments coming from anesthesiology to end-of-life context.[42,43] Bispectral Index Score[34,43,44] or Neurosense monitor are some examples.[33] These try to assess level of consciousness exploring beyond a patient's ability to respond. The reliability of these methods outside the controlled setting of an operating theater requires further testing.[43] Not only the technical equipment but also the wide range of Bispectral Index Score values in deeply sedated patients makes its use in routine clinical practice unlikely.[45]

Here assessment in dialogue with proxies can also be an important source of information as they usually are present during the process and are very aware of indirect indications of patient discomfort (i.e., grimaces). It would be important to include assessment of possible side effects or complications. Clinicians have in mind these as they were mostly missing in the reviewed articles.

The included articles do not make any reference to the patient care provided, highlighted as an important topic in the EAPC framework.[8] This is understandable as articles have a very specific focus, but it may be pertinent for future studies to mention, even briefly, the care provided to the sedated patient (beyond the sedation itself) to emphasize the importance of maintaining the same level of dignified personal care (i.e., washing, talking to the patient, and comfort care measures).

Assessing if the objective of palliative sedation is achieved relates to its quality. There is no clarity on what can be considered the overall quality/effectiveness of palliative sedation. Some articles have tried to address this by asking health professionals for their views.[26,27,32] There is an urgent need to identify some parameters to assess the quality of palliative sedation including family and patient perspectives.

Study Strengths and Limitations

In general, the quality of the included articles is good, and the review provides a recent view on the

topic. The selected articles were published in English, which is one of the main publication languages, but we may have missed relevant articles published in other languages. Guidelines are often published in local languages; patient studies are probably more often published in peer-reviewed English journals. In addition, these articles had very specific objectives (i.e., describing characteristics of patient-related determinants and administration of sedation, sedation at home, comparing artificial hydration use on sedated patients), so provided limited/partial information about current practice on palliative sedation in itself.

The variability of the data and the definitions provided in the articles hamper the possibility of analyzing and comparing the results (i.e., meta-analysis). Most of the studies were conducted in patients with cancer; therefore, the results may not be transferable to those with other diagnoses.

Conclusion

Delirium, pain, and dyspnea are the main refractory symptoms requiring palliative sedation together with existential or psychological distress, although only in a few occasions are they the sole refractory symptom identified. Assessment of refractory symptoms should include physical evaluation with standardized tools applied and interviews for psychological and existential evaluation by expert clinicians working in teams.

Clinical prospective studies on palliative sedation show an underlying commonality, the need for proportional sedation. There is variability regarding continuity and level of sedation being used.

Future research needs to evaluate the effectiveness of palliative sedation considering the relief of refractory symptom burden and related suffering as its main objective. There is a need to advance our understanding and specifying what is considered good quality of palliative sedation, effective palliative sedation, including family and caregiver views.

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References

1. de Graeff A, Dean M. Palliative sedation therapy in the last weeks of life: a literature review and recommendations for standards. J Palliat Med 2007;10:67–85.

2. Bishop MF, Stephens L, Goodrich M, Byock I. Medication kits for managing symptomatic emergencies in the home: a survey of common hospice practice. J Palliat Med 2009;12:37–44.

3. Calvo-Espinos C, Ruiz de Gaona E, Gonzalez C, Ruiz de Galarreta L, Lopez C. Palliative sedation for cancer patients included in a home care program: a retrospective study. Palliat Support Care 2015;13:619–624.

4. Rousseau P. Existential suffering and palliative sedation: a brief commentary with a proposal for clinical guidelines. Am J Hosp Palliat Care 2001;18:151–153.

5. Morita T, Tsunoda J, Inoue S, Chihara S. Terminal sedation for existential distress. Am J Hosp Palliat Care 2000;17:189–195.

6. Rousseau P. Existential distress and palliative sedation. Anesth Analg 2005;101:611–612.

7. Taylor BR, McCann RM. Controlled sedation for physical and existential suffering? J Palliat Med 2005;8:144–147.

8. Cherny NI, Radbruch L. European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care. Palliat Med 2009;23:581–593.

9. Maltoni M, Miccinesi G, Morino P, et al. Prospective observational Italian study on palliative sedation in two hospice settings: differences in casemixes and clinical care. Support Care Cancer 2012;20:2829–2836.

10. Caraceni A. Palliative sedation: more data and fewer opinions. Lancet Oncol 2016;17:15–17.

11. Miccinesi G, Rietjens JAC, Deliens L, et al. Continuous deep sedation: physicians' experiences in six European countries. J Pain Symptom Manage 2006;31:122–129.

12. Deschepper R, Laureys S, Hachimi-Idrissi S, Poelaert J, Distelmans W, Bilsen J. Palliative sedation: why we should be more concerned about the risks that patients experience an uncomfortable death. Pain 2013;154:1505–1508.

13. Seymour J, Rietjens J, Bruinsma S, et al. Using continuous sedation until death for cancer patients: a qualitative interview study of physicians' and nurses' practice in three European countries. Palliat Med 2015;29:48–59.

14. Twycross R. Reflections on palliative sedation. Palliat Care Res Treat 2019;12:117822421882351.

15. Rys S, Mortier F, Deliens L, Deschepper R, Battin MP, Bilsen J. Continuous sedation until death: moral justifications of physicians and nurses—a content analysis of opinion pieces. Med Heal Care Philos 2013;16:533–542.

16. Blondeau D, Roy L, Dumont S, Godin G, Martineau I. Physicians' and pharmacists' attitudes toward the use of sedation at the end of life: influence of prognosis and type of suffering. J Palliat Care 2005;21:238–245.

17. Beller EM, van Driel ML, McGregor L, Truong S, Mitchell G. Palliative pharmacological sedation for terminally ill adults. Cochrane Database Syst Rev 2015;1:CD010206.

18. Brinkkemper T, van Norel AM, Szadek KM, Loer SA, Zuurmond WWA, Perez RSGM. The use of observational scales to monitor symptom control and depth of sedation

in patients requiring palliative sedation: a systematic review. Palliat Med 2013;27:54–67.

19. Payne SA, Hasselaar J. European palliative sedation project. J Palliat Med 2020;23:154–155.

20. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.

21. Arantzamendi M, Belar A, Centeno C. Palliative sedation: a systematic review of clinical prospective studies. PROSPERO 2019 CRD42019136326. Available at: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019136326. Accessed October 15, 2020.

22. Dunleavy L, Walshe C, Oriani A, Preston N. Using the "Social Marketing Mix Framework" to explore recruitment barriers and facilitators in palliative care randomised controlled trials? A narrative synthesis review. Palliat Med 2018;32:990–1009.

23. Critical Appraisal Skills Programme (CASP). CASP checklists. Oxford: CASP. Critical appraisal Skills Programme (CASP). CASP checklists, 2014. Available at: https://casp-uk.net/casp-tools-checklists/. Accessed October 15, 2020.

24. Noyes J, Booth A, Flemming K, et al. Cochrane Qualitative and Implementation Methods Group Guidance series paper 3: methods for assessing methodological limitations, data extraction and synthesis, and confidence in synthesized qualitative findings. J Clin Epidemiol 2018;97:49–88.

25. Claessens P, Menten J, Schotsmans P, Broeckaert B. Food and fluid intake and palliative sedation in palliative care units: A longitudinalprospective study. *Prog Palliat Care* 2014;42:1–8.

26. Pype P, Teuwen I, Mertens F, Sercu M, De Sutter A. Suboptimal palliative sedation in primary care: an exploration. Acta Clin Belg 2018;73:21–28.

27. Caraceni A, Speranza R, Spoldi E, et al. Palliative sedation in terminal cancer patients admitted to hospice or home care programs: does the setting matter? Results from a national multicenter observational study. J Pain Symptom Manage 2018;56:33–43.

28. Mercadante S, Porzio G, Valle A, Aielli F, Casuccio A. Palliative sedation in patients with advanced cancer followed at home: a prospective study. J Pain Symptom Manage 2014;47:860–866.

29. Imai K, Morita T, Yokomichi N, et al. Efficacy of two types of palliative sedation therapy defined using intervention protocols: proportional vs. deep sedation. Support Care Cancer 2018;26:1763–1771.

30. Maeda I, Morita T, Yamaguchi T, et al. Effect of continuous deep sedation on survival in patients with advanced cancer (J-Proval): a propensity score-weighted analysis of a prospective cohort study. Lancet Oncol 2015;17:115–122.

31. van Deijck R, Hasselaar J, Verhagen S, Vissers K, Koopmans R. Patient-related determinants of the administration of continuous palliative sedation in hospices and palliative care units: a prospective, multicenter, observational study. J Pain Symptom Manage 2016;51:882–889.

32. van Deijck R, Hasselaar J, Verhagen S, Vissers K, Koopmans R. Level of discomfort decreases after the administration of continuous palliative sedation: a prospective multicenter study in hospices and palliative care units. J Pain Symptom Manage 2016;52:361–369.

33. Parra Palacio S, Giraldo Hoyos CE, Arias Rodríguez C, Mejía Arrieta D, Vargas Gómez JJ, Krikorian A. Palliative sedation in advanced cancer patients hospitalized in a specialized palliative care unit. Support Care Cancer 2018;26:3173–3180.

34. Monreal-Carrillo E, Allende-Perez S, Hui D, Garcia-Salamanca M-F, Bruera E, Verastegui E. Bispectral Index monitoring in cancer patients undergoing palliative sedation: a preliminary report. Support Care Cancer 2017;25:3143–3149.

35. Broeckaert B, Nuñez Olarte J. Sedation in palliative care: facts and concepts. In: ten Have H, Clarke D, eds. The ethics of palliative care: European perspectives. Buckingham: Open University Press, 2002:166–180.

36. Rohaut B, Eliseyev A, Claassen J. Uncovering consciousness in unresponsive ICU patients: technical, medical and ethical considerations. Crit Care 2019;23:78.

37. Rodrigues P, Crokaert J, Gastmans C. Palliative sedation for existential suffering: a systematic review of argument-based ethics literature. J Pain Symptom Manage 2018;55:1577–1590.

38. Papavasiliou E, Payne S, Brearley S. Current debates on end-of-life sedation: an international expert elicitation study. Support Care Cancer 2014;22:2141–2149.

39. Good P, Richard R, Syrmis W, Jenkins-Marsh S, Stephens J. Medically assisted hydration for adult palliative care patients. Cochrane Database Syst Rev 2014:CD006273.

40. Bush SH, Grassau PA, Yarmo MN, Zhang T, Zinkie SJ, Pereira JL. The Richmond Agitation-Sedation Scale modified for palliative care inpatients (RASS-PAL): a pilot study exploring validity and feasibility in clinical practice. BMC Palliat Care 2014;13:17.

41. Bruera E, Sweeney C, Willey J, Palmer JL, Strasser F, Strauch E. Perception of discomfort by relatives and nurses in unresponsive terminally ill patients with cancer: a prospective study. J Pain Symptom Manage 2003;26:818–826.

42. Benitez-Rosario MA, Castillo-Padrós M, Garrido-Bernet B, Ascanio-León B. Quality of care in palliative sedation: audit and compliance monitoring of a clinical protocol. J Pain Symptom Manage 2012;44:532–541.

43. Barbato M, Barclay G, Potter J, Yeo W, Chung J. Correlation between observational scales of sedation and comfort and bispectral index scores. J Pain Symptom Manage 2017;54:186–193.

44. Six S, Laureys S, Poelaert J, Bilsen J, Theuns P, Deschepper R. Comfort in palliative sedation (Compas): a transdisciplinary mixed method study protocol for linking objective assessments to subjective experiences. BMC Palliat Care 2018;17:62.

45. Masman AD, van Dijk M, van Rosmalen J, et al. Bispectral Index monitoring in terminally ill patients: a validation study. J Pain Symptom Manage 2016;52:212–220.e3.

Appendix Table 1
Data Extraction Sheet

Author, Year, (Reference), Country, Study Design	Objectives (Primary and Secondary Objectives)	Setting, Patients, Sample	Refractory Symptoms	Sedation Results (Quality)	Monitoring and Documenting
Caraceni et al., 2018[27] Italy Longitudinal observational study	Comparing HC and HS settings for PS rate, patient clinical characteristics before and during PS, decision-making process, and clinical aspects of PS	• Setting: 38 HC and HS PC services in Italy from January 2010 to December 2011 • Patients: Adult patients with cancer followed till death • Sample: Among 4276 patients cared, 2894 were followed till death and 531 (18%) underwent PS. About 55% males, mean age of 70 yrs, and an average KPS of 22.3. Most common primary tumors are gastrointestinal tract (32.2%) and lung (27.5%)	Most patients had only one intolerable symptom, and 38% had two intolerable symptoms Frequent refractory symptoms to indicate sedation were delirium (54%) and dyspnea (45%). Sedation was applied also just for pain (83%) and psychological distress (5%) in cases	Prevalence different in the participating centers: median 17% and IQR 8%−29% No statistically significant differences between duration by setting, 40 vs. 48 hours Hydration during PS was less frequent in the HC setting (27% vs. 49%; $P < 0.001$). In the last eight hours of life Symptom control was judged by the health care provider as complete in 472 patients (89%), partial in 28 patients (5%), and not achieved in three patients (1%) (missing data in 28 cases; 5%)	• Patient basic demographic and clinical data • Refractory symptoms as indication to PS (pain, dyspnea, delirium, vomiting, hemorrhage, psychological distress, and other symptom). Registered by nurses every eight hours • Disease and prognosis awareness of patient and family members • Patient preference about PS • Informed consent to PS obtained from patient and/or family members • Medications used for PS • PS duration • Use of hydration during PS • MWSS: Consciousness. Registered by nurses every eight hours Treatment strategies: First lines: Different medication combinations but preference for benzodiazepines • Initial dose: More than one sedative medication was used in 31% of patients • Midazolam was the most frequently used medication (88%) • Chlorpromazine and haloperidol were used in about 12% of patients. Promethazine and morphine (20.9%) were also used • Titration: Medication dosages were titrated to obtain a reduction of the

(*Continued*)

Appendix Table 1
Continued

Author, Year, (Reference), Country, Study Design	Objectives (Primary and Secondary Objectives)	Setting, Patients, Sample	Refractory Symptoms	Sedation Results (Quality)	Monitoring and Documenting
					level of consciousness, safe and adequate to relieve suffering
Claessens et al., 2014[25] Belgium Prospective, longitudinal, and descriptive design	To describe the evolution of oral and artificial food and fluid intake of patients residing in Flemish PCUs	• Setting: Eight units geographically spread over Flanders • Patients: Older than 18 yrs, incurable cancer, life expectancy less than three months, and gave formal written informed consent • Sample: 20 of 266 patients received PS. 54% male, median age of 72 yrs (Q1 = 65; Q3 = 81). Primary diagnoses: lung cancer (24%), bowel cancer (15.4%), and breast cancer (12.4%) Median Palliative Performance Scale score 40 (Q1: 30; Q3: 50) Glasgow Coma Score at admission: 15 (Q1 = 14; Q3 = 15)	• No data	• PS started on average 2.5 days before death	• Midazolam was the medication of choice to induce PS • Data assessment: On admission and every Monday, Wednesday, and Friday. Registration of variables between the nurses and the researcher (one every two weeks) • Functional assessment (Palliative Performance Scale) • Symptom occurrence (Modified Edmonton Symptom Assessment Scale) • Symptom distress (Modified Edmonton Symptom Assessment Scale) • Level of consciousness (Glasgow Coma Scale) • Demographics • Oral food and fluid intake (five-point Likert scale) • Artificial food and fluid intake • Medication (name, dose/24 hours)
Imai et al., 2018[29] Japan Cohort study prospectively collected	Investigate the effects of two intervention protocols; proportional sedation and deep sedation	• Setting: PCU of a 934-bed-designated cancer hospital • Patients: Terminally ill patients with cancer who received the continuous infusion of midazolam according to intervention protocols for refractory symptoms in PCU • Sample: 50 patients of 398 terminally ill patients who died during the	None Hypothesis: Each protocol would closely reflect the treatment intention of each practice, i.e., the proportional sedation protocol would achieve acceptable symptom relief while maintaining some patients' consciousness, and the deep sedation protocol would achieve more	*N*: 50 Thirty-two patients received proportional sedation, and 18 patients received deep sedation • Parental hydration: 87.5% (28 of 32) in PPS and 100% (18 of 18) in PSU • Survival at four hours: 100% (32 of 32) in PPS and 94.4% (17 of 18) in PSU	• Baseline data: age, sex, primary tumor, general condition (the Eastern Cooperative Oncology Group performance status), refractory symptoms, admission periods, clinically estimated prognosis, the presence or the absence of respite sedation, length of sedation, midazolam dose,

	study period received continuous infusion of midazolam (12.6%). About 32 patients received proportional sedation and 18 deep sedation	definite symptom relief although most patients would lose consciousness	• Survival at 24 hours: 71.9% (23 of 32) in PPS and 61.1% (11 of 19) in PSU • Median survival time from beginning of sedation to death: 75.5 hours (range 10−444) in PPS and 42.5 hours (range 1−269) in PSU • Goal achievement at four hours after sedation: 68.8 (22 of 32; 95% CI 52.7−84.9) in the PPS and 83.3% (15 of 18; 95% CI 66.1−100) in PSU • Mean score of STAS in PPS decreased from 3.8 before sedation to 0.8 at four hours and 0.8 at 24 hours • Mean score of STAS in PSU decreased from 3.7 before sedation to 0.3 at four hours and 0.3 at 24 hours • Mean score of RASS in PPS decreased from +1.2 before sedation to −1.7 at four hours and −2 at 24 hours • Mean score of RASS in PSU decreased from +1.4 before sedation to −3.7 at four hours and −4.5 at 24 hours • Deep sedation (RASS ≤−4): at four hours: 31.3% in PPS and 83.3% in PSU • Adverse events: Apnea: 3.8% of PPS (1/32) and 22.2 of PSU (4/18) • Mean respiratory rates (times/minute): 11.9 (SD: 4.2 at initiation), 13.3 (5.4) at four hours and 13.0 (5.8) at 24 hours in PPS; 15.9 (SD: 6.8 at initiation), 16.6 (6.7) at four hours and 14.6 (8.2) at 24 hours in PSU No cardiac arrest or agitation reported	medication route, and the amount of parenteral hydration recorded • Maximum plasma concentrations for midazolam after intravenous and subcutaneous bolus injection Assessments: • STAS • Severity of agitation and sedation with the RASS STAS and RASS scores were recorded before sedation and four and 24 hours after sedation Proportional sedation protocol: • First lines: midazolam • Initial dose: midazolam 0.5−2 mg/hour with bolus dose of midazolam 0.5−2 mg • Titration: Measure STAS and RASS every 15/30 minutes (intravenous/subcutaneous). Treatment goal: symptoms relief (STAS 1) and no agitation (RASS ≤0). If no: bolus dose of midazolam 0.5−2 mg followed by dose-up at two-hour intervals Deep sedation protocol: • First lines: midazolam • Initial dose: start midazolam 5−10 mg/hour with bolus dose of midazolam 0.5−2 mg • Titration: Measure RASS every 15/30 minutes Goal: deep sedation (RASS ≤−4). If no: bolus dose of midazolam 0.5−2 mg followed by dose up. If yes: maintenance phase: dose down to 0.5−3 mg/hour • Hydration: This and nutrition decided separately to continue or withheld along with continuous sedation

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Appendix Table 1
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Author, Year, (Reference), Country, Study Design	Objectives (Primary and Secondary Objectives)	Setting, Patients, Sample	Refractory Symptoms	Sedation Results (Quality)	Monitoring and Documenting
Maeda et al., 2015[30] Japan Prospective cohort study	• To examine whether CDS shortens patient survival • To explore whether artificial hydration benefits or harms patient survival	• Setting: Participants between September 3, 2012 and April 30, 2014, from 58 palliative care institutions across Japan (19 hospital palliative care teams, 16 inpatient PCUs, and 23 home-based palliative care services) • Patients: Eligible for the secondary analysis if they were adult patients (aged 20 yrs and older), diagnosis of locally advanced or metastatic cancer. Excluded: patients who lived longer than 180 days and missing data for outcome variables • Sample: After applying exclusion criteria, the population for analysis consisted of 1827 patients	None	• 269 (15%) received CDS before death • Unweighted median survival was 27 days (95% CI 22−30) in the CDS group and 26 days[24−27] in the no sedation group (median difference −one day [95% CI −5 to 4]; HR 0.92 [95% CI 0.81−1.05]; log-rank test, $P = 0.20$) • The two survival curves of sedated and nonsedated patients were nearly identical before and after propensity score weighting	Demographic and clinical characteristics were measured three times: at enrollment (patient characteristics, disease status, and symptom burden); three weeks after enrollment (symptom occurrence: fever, delirium with confusion assessment method, dyspnea, and appetite loss); and at the date of either death, final observation, or 180 days after enrollment (life or death; date, place, and cause of death and medical treatment before death Treatment strategies: First lines recommended sedative midazolam (used 84%) with 0.2−1 mg/hour starting dose and 5−120 mg/day (usually 20−40 mg/day) maintenance dose. Alternative sedatives are phenobarbital used in 9% (4−30 mg/hour continuous subcutaneous infusion [starting dose]) and propofol
Mercadante et al., 2014[28] Italy Prospective study	To assess the efficacy of a PS protocol, established by the HOCAI group in a preliminary investigator meeting, in a prospective study of patients with advanced cancer followed at home. Secondary aims include analysis of the	• Setting: Two home PCUs of the HOCAI group All the patients admitted to the care units from July 2012 to December 2012 were assessed Sample: About 219 patients were surveyed; 117 and 102 in L'Aquila and Turin, respectively. Mean	The principal reasons to begin PS were agitated delirium ($n = 20$) and dyspnea ($n = 4$)	• PS continued until death; none of the patients' relatives asked to discontinue • Mean duration of PS was 42.2 ± 30.4 hours • Level of satisfaction for the home care team was optimal, good, and fair in 18, five, and one case(s),	• It was recorded: characteristics of this group, the indication to start PS, information about decision making, internal conflicts, and reasons for discontinuation sedation • Pain, dyspnea, agitated delirium, and

characteristics of these patients between two centers, problems encountered, and level of satisfaction of the team and relatives	age was 73.6 yrs, and 112 (51.1%) were males. Mean KPS score at admission was 57.5 ± 18.7. Primary cancer diagnoses: gastrointestinal 47, urogenital 42, and lung 36. Survival from diagnosis was 810–1128 days The PS was performed in 24 of 176 patients who died at home (13.6%). The mean age of these 24 patients was 67 ± 19 yrs, and 10 (41.7%) were males	respectively. Satisfaction for relatives was optimal, good, and fair in 15, eight, and one case(s), respectively The PS occurred more frequently in younger patients ($P = 012$; analysis of variance test), whereas no differences in gender were found ($P = 0.325$; Chi-squared test)	psychological distress data, rated on a 0–10 numerical scale were collected at the beginning of sedation (T0) and then at one-day intervals • In most cases, after starting PS, pain was no longer evaluated because of deep sedation or altered consciousness. Other symptoms were based on the judgment of proxies Information about medications and doses used during PS was recorded at the same time until death • Relatives were asked about symptom intensity when the patients were unable to provide this information • The Communication Capacity Scale • Agitation Distress Scale • Level of satisfaction regarding the efficacy of PS for home physicians and relatives was recorded after the patient's death Treatment: • Intravenous or subcutaneous midazolam was started in doses of 20–30 mg/day, independent from the previous use of sedative or neuroleptic medications. Opioids were maintained if needed If the physician judged it appropriate, the second step was started, increasing the dose of midazolam up to 30–60 mg/day. The third step was to use doses higher than 60 mg/day.

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Appendix Table 1
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					Other sedative medications, including neuroleptics, were allowed with the third step, or continued if used before, and dosages were used flexibly according to the patients' needs
Monreal-Carrillo et al., 2017[34] México Prospective observational study	To characterize the level of consciousness in patients undergoing PS using BIS monitoring	• Setting: PC unit • Patients: Advanced cancer with no further disease-modifying treatment options, required admission, had refractory symptoms requiring the MIDAS PS protocol, had do-not-resuscitate orders in place • Sample: 254 hospitalized patients for eligibility between April and November 2015. Twenty-seven (13%) were fully eligible. Among these, we obtained surrogate consent in 20 (74%) patients. The median age was 46 yrs, and 12 (60%) were females	Reasons for PS were delirium ($n = 15$; 75%), pain ($n = 13$; 65%), dyspnea ($n = 6$; 30%), seizures ($n = 5$; 25%), malignant obstruction ($n = 3$; 15%), existential distress ($n = 2$; 10%), asphyxia ($n = 1$; 5%), and massive bleeding ($n = 1$; 5%) • Ninety percent of the patients had two or more symptoms, with the combination of delirium and pain in 9 of 20 patients	• During PS, significant decrease in the level of consciousness over time. At baseline, 14 (70%) patients were considered to be awake according to RSS (i.e., 1–3) and 19 (95%) were awake according to BIS (i.e., >60%) This proportion decreased to 31.2% and 56.2% at four hours, 26.7% and 53.3% at six hours, and 22.2% and 33.3% at 24 hours (data not shown). A tendency toward the increase of RSS was observed as the BIS values decreased • The median time of sedation was 24.5 hours (IQR 6–46), and the median survival was 19 hours	• BIS monitor. Performed continuously from initiation of PS until death at the same time of RSS assessments • RSS was documented at 0, 2, 4, 6, 12, and 24 hours after initiation of PS Treatment strategies: First lines: MIDAS PS protocol: continuous IV infusion that combines the hypnotic effect of propofol with the anxiolytic action of midazolam • Opioids, antipsychotics, and any other medications required for symptom control were continued if needed • Initial dose: Initial propofol doses of 0.16 mg/kg/hour and midazolam 0.08 mg/kg were adjusted according to the individual patient response. We increased these medications if either RSS remained at 1–3 or BIS >60 • Titration: Propofol and midazolam titrations were adjusted based on both RSS and BIS. The continuous infusion rate ranged between 0.16 and

Parra Palacio et al., 2018[33] Colombia Descriptive prospective study	To describe the sociodemographic and clinical characteristics of a group of patients with cancer as well as prevalence, indications, time, and medications used for PS at a specialized PC unit at a cancer institution in Medellin, Colombia	• Setting: Specialized PCU in Colombia • Patients: over 18 hospitalized, cancer • Sample: January and July of 2015 Sixty-six patients requiring PS were included. About 46 patients (70%) were women; the average age was 61 yrs (SD 14.2; range 24–87), and 52 patients (74%) had a KI of 50% or less. The most frequent diagnosis was breast cancer (22%), and 51 of the patients (81.8%) had metastatic cancer	• Main refractory symptoms were dyspnea (59.1%), delirium (45.5%), and pain (31.8%). More than half had more than one refractory symptom (60.1%) Nine patients (13.6%) presented with existential suffering	• Prevalence of PS was 2.2%. Causes that led to complete PS were death in 64 patients (97%) and the control of symptoms in two patients (3%) • Survival time after the start of PS was 44.9 hours (SD 41.1; range 1.3–215) • An inverse and significant relationship between the Karnofsky and the total hours under PS ($P < 0.01$) • Significant correlation between the initial and final doses of midazolam ($P < 0.01$) and between the final Ramsay score and final dose of midazolam ($P < 0.05$)	1.3 mg/kg/hour for propofol and between 0.08 and 0.5 mg/kg/hour for midazolam Only four (20%) patients had RSS 4–6 and BIS below 60 the first 24 hours and did not require dose escalation The remaining 16 (80%) patients required an increase in their propofol and/or midazolam doses • Data instrument was designed. It included demographic data, clinical info (Karnofsky) symptoms for which medical care was requested and information on the implementation of PS—indication, medications used prior PS, medications and dosages used, sedation according to Ramsay, type of sedation (intermittent or continuous), start and end times of sedation Treatment strategies: The medication used was midazolam Initial dose: Mean initial dose of 48.4 mg/day (SD 54.8 mg/day; range 8–384 mg/day) and a final average dose of 100.4 mg/day (SD 97.42 mg/day; range 0–480 mg/day) Ninety-one percent of the patients required adjuvant medications with morphine as the most commonly used medication (75.8% patients) at a dose of 64 mg/day average (12–240 mg/day) at the

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Appendix Table 1
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					start of PS and 113 mg/day (20–480 mg/day) at the end of PS. The second opioid used was hydromorphone with a frequency of 7.6% (five patients). No other opioids were used
Pype et al., 2018[26] Belgium Mixed method prospective study	1. To describe the occurrence and characteristics of suboptimal sedation in primary care 2. To explore the way GPs experience suboptimal PS in their practice	Setting: Seven of 15 palliative home care teams agreed to participate. These teams consist of specialized palliative care nurses visiting patients at home and specialized palliative care physician supporting the nurses Quantitative: The participating PHCTs registered 1181 deaths. In 63 (5.3%) cases, continuous PS was administered. In 27 (43%) cases, registration forms have been completed • Sample: Sedation was administered to 23 men and women, 21 of them were oncological patients, mean age 71 (range 7–91) Qualitative: Of the registered PS cases, all suboptimal cases were identified according to GP, and they were invited to participate. Of the 11 GPs who performed one of the identified cases of suboptimal sedation, seven agreed to be interviewed	• Most frequent refractory symptoms: anxiety ($n = 18$), pain ($n = 17$), and psychological or existential symptoms ($n = 13$), delirium ($n = 11$), dyspnea ($n = 11$), vomiting ($n = 6$), confusion ($n = 2$), tachycardia ($n = 1$), and facial myoclonus ($n = 1$) • In most of the cases ($n = 18$), more than one refractory symptom was mentioned as a reason to initiate PS	• Time until deep sleep varied from three minutes to 14 hours (median 60 minutes) • One patient died without having reached full sedation • The mean number of awakenings was 2 (range 0–12) • Time until death after starting the procedure ranged from 15 minutes to 17 days and 17 hours (median 25 hours and 34 minutes) with 16 patients having died in the first 48 hours • Eleven sedations were suboptimal according to study criteria • These unmet expectations gave GPs a sense of failure • Some GPs reported pressure and even reproach from family members to hasten the procedure • The anticipatory fear for failure became reality while experiencing the suboptimal PS But after the death of the patient, for most GPs, the feeling of failure changed rapidly	Patient's age, diagnosis, comorbidity, refractory symptoms, concomitant medication use, the starting dose of sedatives, the time span between the successive dose adjustments, the level of dose adjustments, time until death, the number of awakenings, and the use of adjuvant sedatives • RASS Treatment strategies: Subcutaneous administration • Midazolam (23 sedations) and phenobarbital (4 sedations) • Mean maintenance dose: 153 mg/24 hours (range 50–250) for midazolam and 640 mg/24 hours for all patients receiving phenobarbital Continuation of previously administered medication. In nine patients, oral morphine was switched to subcutaneous morphine. Ten patients received oral corticosteroids before the sedation; in only one case, this was continued subcutaneously
van Deijck et al., 2016[31] The Netherlands	To identify patient-related determinants of the		Statistically significant differences in patients	March 2011–2013, data collection ended when	

Prospective multicenter observational study	administration of CPS at admission to a hospice or nursing home-based PCU	• Setting: Six Dutch hospices, three nursing home-based PCUs • Patients: Estimated life expectancy at admission to less than three months, according to referring physician. About 803 patients admitted in total during study period, and 503 gave written consent • Sample: Of 467 patients who died, 130 received CPS. Patients aged 76 yrs and older, having cancer, with a KPS score of 40 or less, and a GCS score of 13 or more. The distribution of men and women was similar. Half of the patients (50.2%) used one or more opioids, and 42.2% of the patients used psycholeptics. The mean number of medications used was 5.7	with younger age ($P = 0.009$), malignancy as a diagnosis ($P = 0.05$), higher KPS score ($P = 0.03$), the use of opioids ($P < 0.001$), or the use of psycholeptics ($P = 0.03$) No significant differences Between nonsedated (mean 33.1 days [SD 43.3]) and sedated patients (mean 34.8 days [SD 41.2]) were observed ($P = 0.70$) until death time • The use of opioids at admission was significantly associated with the administration of CPS (OR 1.90; 95% CI 1.18−3.05; $P = 0.008$)	the patient died, was discharged, or at end of study period A total of 467 patients died and were included for further analysis; 130 of these patients (27.8%) received CPS (range varied from 13.5% to 48.1% associated with location [$P < 0.001$]) The mean duration from admission until death for the 467 patients was 33.5 days (SD 42.7) with a median duration of 19 days (range 0−305)	Data collection within the first five days after admission • Gender and age • Functional status: KPS • Level of consciousness: Glasgow Coma Scale • Symptom: ESAS • Diagnosis: *International Statistical Classification of Diseases and Related Health Problems* • Attending physician determined the indication for CPS and the doses, combinations, and duration of the medications administered
van Deijck et al., 2016[32] The Netherlands Prospective observational multicenter study	To identify course of discomfort using the DS-DAT in patients receiving CPS, who were admitted to a hospice or nursing home-based PCU	• Setting: Six hospices and three nursing home PCUs • Patients: Estimated life expectancy at admission to less than three months, according to referring physician. About 503 of 803 admitted patients during study period gave written consent • Sample: Total of 467 patients died; 130 of these patients (27.8%) received CPS. Most of the sedated patients were women of advanced age, and most patients had cancer		Median sedation duration: 25.5 hours (range 2−161), with a mean duration of 34.2 hours (SD 31.4) • Adjusted mean score of the DS-DAT in the phase before sedation was 12.16 (95% CI 9.83−14.50), and this decreased significantly to 8.06 (95% CI 5.53−10.58) in the titration phase of sedation and remained relatively stable until the moment of death • Mean DS-DAT 7.82; final phase of sedation (mean DS-DAT: 7.42) • Significant reduction in discomfort compared with the phase before sedation was found for all three of the following phases of CPS	Data collection: March 2011−December 2012 with a follow-up of three months Attending physician recorded: • Diagnosis (*International Classification of Diseases and Related Health Problems*) • If indication for CPS: 1. Patient's intake the day before the start of CPS 2. Refractory symptom for CPS 3. Hydration 4. Date and time of the start and end of CPS • DS-DAT for monitoring patient discomfort during CPS. Assessment conducted independently just before CPS and two daily thereafter by nurses not

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				($P < 0.001$). CPS mean duration was 36.86 hours (SD 30.17), with no significant association between duration of CPS and discomfort level in the last eight hours of life ($P = 0.427$) • Higher mean discomfort score during the last eight hours if: patient intake of a small amount of fluid and none/minimal amount of food or more the day before the start of sedation ($P = 0.045$), the presence of the refractory symptom vomiting ($P = 0.014$), and the presence of multiple refractory symptoms ($P = 0.049$) • Physician's opinion: CPS provided complete symptom relief ($n = 46$), mean score of the DS-DAT was 4.61 (SD 3.41) Physician's opinion: CPS provided no to partial symptom relief ($n = 11$), the mean score of the DS-DAT was significantly higher (7.09 [SD 3.56]; $P = 0.026$) • Gender, age, the presence of malignant neoplasm, not significantly associated with discomfort level during sedation in last eight hours of life ($P = 0.911$, $P = 0.299$, and $P = 0.737$)	involved in the daily care of the patient. Nurses were trained on the tool use • After patient death: Effect of CPS on symptom relief according to physician (four-point scale: no, hardly, partially, and completely) Treatment strategies: • First lines: midazolam after subcutaneous injection, the medication of choice for inducing CPS • Titration: done but not specified

HC = home Care; HS = hospice; PS = palliative sedation; PC = palliative care; MWSS = modified version of the Wilson Sedation Scale; PCU = palliative care unit; PPS = proportionate palliative sedation; PSU = palliative sedation to unconsciousness; RASS = Richmond Agitation Sedation Scale; STAS = Support Team Assessment Schedule; CDS = continuous deep sedation; HR = hazard ratio; HOCAI = Home Care-talyI; BIS = Bispectral Index; MIDAS = Management of Pain, Anxiety and Distress program; IQR = interquartile range; RSS = Ramsay Sedation Scale; IV = intravenous; GPs = general practitioners; PHCTs = palliative home care teams; KPS = Karnofsky Performance Status; GCS = Glasgow Coma Scale; OR = odds ratio; ESAS = Edmonton Symptom Assessment System; CPS = continuous palliative sedation; DS-DAT = Discomfort Scale—dementia of Alzheimer type.