

CHAPTER 6

The use of observational scales to monitor symptom control and depth of sedation in patients requiring palliative sedation: A systematic review

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ABSTRACT

Introduction Palliative sedation is the intentional lowering of consciousness of a patient in the last phase of life to relieve suffering from refractory symptoms such as pain, delirium and dyspnoea. In this systematic review, we evaluated the use of monitoring instruments in a palliative setting to assess the degree of symptom control and/or the depth of the sedation.

Methods A database search of PubMed and Embase was performed using central search terms “palliative sedation” OR “terminal sedation”. All articles written in the English, German or Dutch language up till January 2010 were included. Relevant articles consisted of retro- or prospective studies as well as reviews or guidelines containing information on monitoring palliative sedation.

Results The search yielded 264 articles of which 30 were considered relevant. Most studies focused on monitoring refractory symptoms (such as pain, fatigue or delirium) or the level of awareness to control the level of sedation. Five studies (4 prospective and 1 retrospective) used scales validated in other settings; the Numeric Pain Rating Scale, the Visual Analogue Scale, the Memorial Delirium Assessment Scale, the Communication Capacity Scale and Agitation Distress Scale. Only the Community Capacity scale was partially validated for use in a palliative sedation setting. One out of 14 reviews/guidelines described the use of scale validated in another setting.

Conclusion A minority of studies reported the use of observational scales to monitor the effect of palliative sedation. Based on the results found in this review, we are of the opinion that research in each of the modalities discussed in this review should be performed. Future studies should be focused on establishing proper instruments, most adequate frequency and timing of assessment, and interdisciplinary evaluation of sedation depth and symptom control for palliative sedation.

6.1 Introduction

Palliative care is an approach aimed at improving the quality of life of patients and their families facing the problems associated with life-threatening illness.¹ When symptom suppression becomes insufficiently effective for terminal patients, the option of palliative sedation can be considered.² Palliative or terminal sedation,³ is the intentional lowering of consciousness of a patient in the last phase of life, to relieve suffering that is caused by refractory symptoms such as pain, delirium and dyspnoea.^{2,4,5} Palliative sedation should be used in a proportional manner, whereby the depth of sedation is adjusted to the required degree of symptom control.²

Palliative sedation can be applied continuously or intermittently. Continuous sedation is the most far-reaching subtype of palliative sedation, and aims to reduce the consciousness of the patient until the moment of death. The aim of intermittent or short-term sedation is to reduce the consciousness temporarily, creating rest for a severe dyspnoeic or anxious patient. In addition it will provide the possibility of monitoring the refractory symptoms on its permanent presence¹.

A Dutch study revealed that palliative sedation is a frequently used practice, showing that 8.2% of all deaths in 2005 were preceded by continuous palliative sedation⁶ whereby 52% of all respondents indicated to have applied palliative sedation at one time during their career.^{6,7} Also, a study on the use of palliative sedation held amongst palliative care specialists in the United States and the United Kingdom, showed that 77% out of 61 respondents had applied palliative sedation in the 12 months prior to the investigation.⁸

In recent years, studies have been focused on the implementation of palliative sedation. Most frequently, this concerned constructing an adequate definition of palliative sedation,^{3,9-16} defining the appropriate clinical indication to start palliative sedation,^{3,10-12,14-17} decision-making during palliative sedation^{10-12,18} and medication policy.^{3,4,11,12,14,15,17,18} The monitoring of the effect of palliative sedation, however, has received little attention.^{11,14,15,19}

In other settings where sedation is used, such as the intensive care unit (ICU), more attention has been given to the monitoring of sedation.^{20,21} In a systematic review, Devlin et al.²¹ described different measurement instruments which are used to optimize the administration of sedation. Although they pointed out that some instruments needed additional validation, several benefits (e.g. decreased ICU stay, decreased drug costs and increased diagnostic evaluations of unexpected alteration in patient status) of using standardized tools were described. Three years later, Watson et al.²⁰ underlined the results of Devlin et al. in their review and described additional tools used to evaluate the level of sedation and could help to reduce oversedation or undersedation in ICU patients. In addition to these scales, the bispectral index (BIS) monitor has been proposed as a tool to monitor sedation. The use of this tool is still debated.^{22,23} Nevertheless, Arbour et al.²⁴ concluded that BIS monitoring may have a supporting role in sedation assessment.

Even though not all benefits reported for the ICU setting are relevant in a palliative care setting, use of standardized tools for monitoring palliative sedation may improve the quality of care provided by this intervention.^{2,11,25} More accurate assessment of the effect of sedation, may lead to targeted use of medication, a more predictable sedation, and provide caretakers with standardized information for professional communication. Taking the latter into consideration, the fact that patients are cared for by a team of nurses, doctors and in some case relatives, measurement instruments should be usable for a variety of persons with different knowledge backgrounds. Furthermore, since palliative sedation is also performed outside the clinical setting²⁶ high-tech instruments used in a clinical setting (such as the BIS monitor) may not always be feasible. In addition, considering the proportionality requirement of palliative sedation, evaluation of targeted symptoms (for instance pain, dyspnoea, or delirium) should be monitored alongside sedation depth.

Therefore, the objective of this article is to provide a systematic review evaluating ways in which the effect of palliative sedation is monitored in current literature, thereby focusing on the depth of sedation as well as on the level of symptom control. Besides evaluating the manner in which sedation efficacy is monitored, clinimetric properties in terms of validity and reliability of proposed instruments will be addressed.

6.2 Methods

6.2.1 Selection and description of included studies

Taking the first published article on palliative sedation as a starting point, a comprehensive search was conducted of the following databases for research articles published from 1989 to January 2010: PubMed, and Embase using the search strategy ‘palliative sedation’ OR ‘terminal sedation’. Additionally, references from relevant articles were crosschecked to identify relevant articles as well. Results from different databases were screened for possible overlap. The language of the included articles was limited to English, German, and Dutch. Prospective and retrospective patient oriented studies were included describing the effect of palliative sedation or/and the monitoring of this effect. In addition, guidelines or reviews were included containing information on judging the effect of sedation. Case studies or studies providing no information about sample size, studies describing non-adult patients, and studies for which it was unclear that palliative sedation was investigated were excluded from the evaluation.

6.2.2 Data extraction

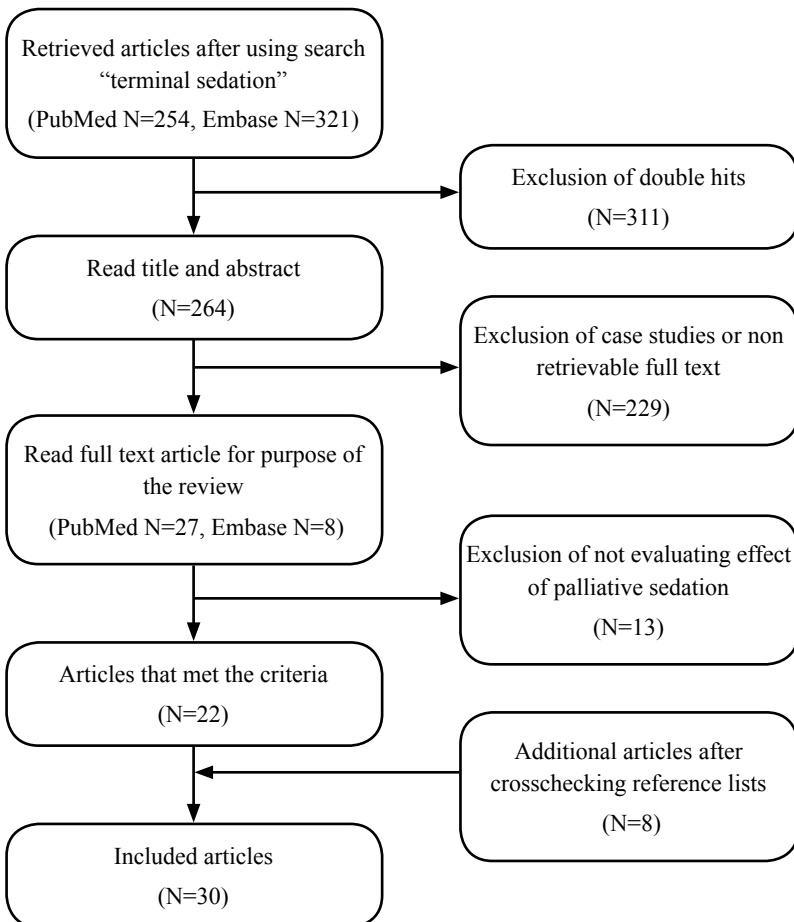
From the selected articles that met these criteria, data on the outcome of the sedation was extracted focusing on the measured effect of the sedation. In addition, we extracted information on the instruments used to measure the sedation and the assessors using the instruments. Furthermore, general characteristics such as author, year of publication, country in which the study took place, language, study design and setting, patient population (number, age, sex) and the practice of sedation (duration, indication and most commonly used sedatives) were extracted.

6.3 Results

The search yielded a total of 575 articles (**Figure 1**), after removing double entries, 264 articles were left. Two reviewers read the title and abstract, 35 articles were considered to be relevant for our review and were read in full. From these 35 articles, 13 did not meet our inclusion criteria. References in the 22 remaining articles were crosschecked to screen for relevant articles, which resulted in 8 additional articles. Consequently, 30 articles were included for the purpose of this review.

In the patient based pro- and retrospective studies (n=12), the practice of sedation in a patient population was described by prospectively monitoring the patients (n=8) or by retrospective data extraction of monitored features from their medical records (n=4). In four studies, retrograde experiences of experts with regard to their last patient receiving palliative sedation were described (3 questionnaire studies and one interview study). In all but one review or guidelines (n=14), recommendations for measuring the effect of palliative sedation were provided.

Figure 1. Flowchart selecting relevant articles



6.3.1 Characteristics of included studies

The setting of the patient based pro- and retrospective studies was predominantly a palliative care unit or a hospital (n=9)^{25,27-34} (**table 1a and table 1b**). In four studies, (also) patients living at home were evaluated,^{29,34,35} and in one study hospice based patients were studied.³¹ All prospective studies had an open follow up design.

In general, the central age tendency for evaluated patients was over 50 years old, and the maximum length of sedation for all studies did not exceed 13 days. In all studies, one or more refractory symptoms were named as reasons to start palliative sedation. Most commonly, these were pain,^{27,29,30} delirium,^{28,31,35} and dyspnoea.^{31,32} In one study, the indication for sedation was existential suffering.³¹ The most frequently reported sedative used was midazolam (n=7). In two studies the use of morphine was reported as an additional option to sedate patients.^{28,31}

For the studies containing physicians' perspectives (**see table 2**), experiences with (teaching) hospital based, nursing home based and home based patients were described.^{8,36-38} Two questionnaire based studies provided no information with regard to the patients' age.^{36,37} None of these four studies reported about the duration of sedation. Multiple indications for starting sedation were described in these studies, whereby pain, anxiety/anguish and dyspnoea/respiratory distress were reported most commonly.

Table 1a. Retrospective studies (patient based)‡

Study; Country	Design (D); Setting (S)	Characteristics #	Indication for palliative sedation ^a	Medication used for sedation	Monitoring sedation effect	Scale†
Porzio (2009); Italy	D: Retrospective study S: Home care unit	N=16 A: 74.5 (27-91)** G: 38 % S: 3.6 (1.6)*	Delirium; Dyspnoea	Midazolam	Symptom-control; Level of awareness	S: Edmonton Symptoms Assessment System, NRS and Ramsay sedation scale A: Patient, nurse or physician R: Twice a day
Rosengarten (2009); Israel	D: Retrospective study S: Home care unit	N=36 A: 65 (33-92)** G: 53 % S: 72 (4-312)**	Agitation; Delirium; Existential suffering; Nausea/Vomiting; Pain	Haloperidol; Midazolam	Symptom-control	S: Symptom control (symptom free-mild/moderate symptomatic-severely symptomatic) Ad hoc assessment of satisfaction (no improvement-slight improvement-good improvement-marked improvement) A: Nursing and medical staff R: 'Each' visit prior and throughout treatment
Kohara (2005); Japan	D: Retrospective study S: Palliative Care Unit	N=124 (n=63) A: 64 (35-87)** G: 33 % S: 3.4*	Dyspnoea; Malaise/unrest; Pain	Haloperidol; Hydrobromide; Midazolam; Scopolamine	Level of consciousness	S: Item 1 of the Communication Capacity Scale (0 awake – 5 unarousable); A: Not reported R: Retrospective assessment using medical file
Fainsinger (1991); Canada	D: Retrospective study S: Palliative Care Unit	N=100 (n=16) A: 62 (12)* G: 49 % S: Not reported	Delirium; Pain	Not reported	Symptom-control; Level of awareness	S: VAS score for pain, nausea, drowsiness, level of awareness, overall symptom control, dyspnoea, delirium; retrospective assessment of medical file A: Patient, trained nurse R: Twice a day
Greene (1991); USA	D: Retrospective study S: Not reported	N=17 A: 69** G: Not reported S: 23* ^b	Not reported	Amobarbital sodium; Thiopental sodium	Comfort; Vital functions	S: Based on observation, no scales used A: Nurses and family/relatives R: Continuous

* Mean (SD); ** Median (range); # (N; n (no. Patients sedated); age patients (years) (A); gender (% female) (G); duration of sedation (days) (S))

† Used scales (S); Assessors (A); Rating frequency (R) ‡ Validity (V); Reliability (R); ^a Most common refractory symptom ^b Did report duration palliative sedation (hours); ‡ None of these studies reported information on clinimetric properties in terms of validity or reliability

Table 1b. Prospective studies (patient based)

Study; Country	Design (D); Setting (S)	Characteristics #	Indication for palliative sedation ^a	Medication used for sedation	Monitoring sedation effect	Scale [†]
Aretha (2009); Greece	D: Prospective, case series S: Hospital (Internal or pulmonary medicine)	N=8 A: 60 (24-73)** G: 38 % S: 5 (4.5-6)**	Distressing intractable symptoms (dyspnoea, anxiety and agitation); Pain	Midazolam	Symptom control; Respiratory rate	S: Sedation scale (1 awake-4 unarousable), Richmond Agitation Sedation Scale, NRS for dyspnoea, VAS score for pain A: Doctor R: 4 times daily
Cowan (2006); USA	D: Prospective, follow-up S: Inpatient and at home	N=1200 (n=28) A: 74** G: 50 % S: 5.0 *	Dyspnoea; Pain; Pain and dyspnoea	Chlorpromazine Midazolam	Symptom control	S: 'Controlled', 'improved', 'not controlled' A: Advanced Illness Assistance (AIA)-team, medical staff or relatives of the patient R: Not reported
Lundstrom (2005); Sweden	D: Prospective, follow-up S: Palliative Care Unit	N=35 (n=22) A: 54 (28-84)** G: 55 % S: 4.9*, 3.5**	Anxiety; Pain; Restlessness	Propofol	Symptom control and level of awareness; Overall effect after sedation; Not necessary to monitor blood pressure, heart rate or respiratory frequency	S: Scale for symptoms (score 0-10), overall effect (poor-inadequate-good-excellent) A: Nurse and/or doctor R: Frequent control in first hour after start of sedation, after 2, 6 and 12 hours
Morita (2005); Japan	D: Multicenter, prospective follow-up S: 21 Palliative Care Units	N=102 A: 63 (113)* 62 (23-89)** G: 40 % S: 64 (71)*, 48 (1-460)** ^b	Delirium; Dyspnoea; Fatigue	Haloperidol Midazolam Phenobarbital	Symptom control; Safety by monitoring Respiratory frequency; Blood pressure; Complications of sedation; Time it took before patient was sedated for a uninterrupted hour	S: Agitation Distress Scale, Memorial Delirium Assessment Scale, Communication Capacity Scale, bronchial secretion (score 0-3), pain intensity, dyspnoea, fatigue and nausea (score 0-5 (no-intolerable)) A: Doctor R: Just before the start of sedation, 4 hours and 24 hours after sedation

Table 1b - [Continuation]

Chiu (2001); Taiwan	D: Prospective, follow-up S: Palliative Care Unit	N= 276 (n=70) A: Most common age >65 G: 46 % S: 12,6 (19.6)*, 5**	Delirium; Dyspnoea; Pain	Haloperidol Midazolam Morphine	Symptom control	S: Scale for pain and dyspnoea (score 0-10), scale for delirium and other symptoms (score 0-3) A: Treatment team R: Daily
Fainsinger (2000); Canada	D: Multicenter, Prospective, follow-up S: Hospice Israel S: Hospice Durban	N= 100 (n=15) A: 67 (14)* G: 52 % S: 3.2*, 3 (1-6)** N= 100 (n=27) A: 59 (19)* G: 57 % S: 1.9*, 1 (1-6)**	Delirium; Pain; Bleeding Delirium; Dyspnoea; Nausea	Haloperidol Midazolam Diazepam Lorazepam Midazolam Morphine	Symptom control Level of awareness	S: Level of awareness (alert - sleepy /drowsy - not responding - missing), symptom control (good - average - poor - missing) A: Doctor R: Daily
S: Hospice Capetown	S: Hospice Capetown	N=93 (n=33) A: 61 (14)* G: 59 % S: 2.4*, 2 (1-5)**	Delirium; Dyspnoea; Nausea	Haloperidol Lorazepam Midazolam		
S: Palliative Care Unit, Spain	S: Palliative Care Unit, Spain	N= 100 (n=22) A: 66 (13)* G: 40 % S: 2.4*, 2 (1-4)**	Delirium; Existential suffering; Family/relatives who suffer or experience fatigue	Diazepam Methotrimeprazine Midazolam Phenobarbitone		
Melver (1994); USA	D: (Prospective) follow-up S: Internal (in Palliative Care Service) & External (by Hospice Home Care Service) nursed patients	N=20 A: 66 (16-81)* G: 55 % S: 1(1-5)**	Restlessness; Dyspnoea	Chlorpromazine	Symptom control Level of awareness	S: 'Level of Arousal scale'; Degree of Restlessness; Efficiency sedation for mentioned indication A: Not reported R: Before start of sedation and on a daily basis

* Mean (SD); ** Median (range); # (N); n (no. Patients sedated); age patients (years) (A); gender (% female) (G); duration of sedation (days) (S) † Used scales (S); Assessors (A); Rating frequency (R) ; ^a Most common refractory symptom; ^b Did report duration palliative sedation (hours)

6.3.2 The effect of sedation

Most patient based pro- or retrospective studies described symptom control (n=9) and the level of awareness (n=5) as parameters for monitoring the effect of palliative sedation (**table 1a** and **table 1b**). Four of these studies evaluated both symptom control and the level of awareness simultaneously.^{30,33,35-39}

In six prospective studies and two retrospective study, the symptoms that lead to the decision to sedate the patient were monitored.^{25,28-31,33,34} Four of these studies also examined the effect of sedatives on the consciousness of the patient.^{30,31,33,34} One retrospective study reported monitoring the consciousness of the sedated patient as a sole outcome.³² In three studies, vital signs such as respiratory rate, blood pressure, heart rate or temperature were monitored for safety reasons (i.e. occurrence of possible complications), or to provide indications of patient distress.^{25,39} In contrast, the study of Lundstrom et al.³³ suggested that monitoring of vital signs such as blood pressure and pulse was unnecessary, as this would not provide adequate information about the effect of palliative sedation (e.g. lowering consciousness).

In two studies reporting about physicians' experiences,^{36,38} the level of symptom control or management was reported as a tool to monitor the effect of sedation (**table 2**). In one study the effectiveness of the treatment was described as an outcome measure to monitor the effect of sedation.³⁷ Chater et al.⁸ proposed the process of sedation including the start of the sedation, the level of suffering/anxiety of the patient and the reaction of the family to be monitored in order to evaluate the effect of sedation.

In four reviews and four guidelines (**table 3**), symptom control was suggested as a method to monitor palliative sedation.^{2-4,11,12,14,17,40} In addition, in four of these publications monitoring the consciousness of the patient as a parameter for evaluation of the effect of sedation was proposed. In two other guidelines, monitoring the consciousness of the patient as a sole outcome was suggested.^{11,12,17,41} Monitoring of vital signs during sedation such as heart rate, blood pressure and temperature was advised in one guideline.¹⁴ Authors of three other guidelines argued against monitoring these vital signs, as it did not contribute to the goal of the sedation (e.g. comfort of the patient).^{3,17,41}

Table 2. Retrospective studies (physicians perspectives) / Questionnaire or interviews †

Study; Country	Design (D); Setting (S)	Characteristics #	Indication for palliative sedation ^a	Medication used for sedation	Monitoring sedation effect	Scale †
Hasselaar (2009); Netherlands	D: Retrospective questionnaire cohort S: All physicians most involved in palliative sedation (hospital based, (nursing) home based)	N=341 (n=160) ^b A: Not reported ^c G: 51% (before); 48% (after) S: Not reported	Anxiety; Dyspnoea; Pain	Diazepam; Midazolam	Symptom-management	S: Practice of benzodiazepines A: Not reported R: Not reported
Reuzel (2008); Netherlands	D: Retrospective questionnaire and interview S: All physicians most involved in palliative sedation (hospital based, (nursing) home based)	N=515 (n=312) ^b A: Not reported G: Not reported S: Not reported	Anxiety; Dyspnoea; Exhaustion; Pain	Diazepam; Midazolam	Effectiveness of treatment	S: Not reported A: Not reported R: Not reported
Rietjens (2006); Netherlands	D: Retrospective personal interviews concerning last patient S: Nursing home, home, hospital based deaths	N=410 (n=211) A: 72 (14)* G: 49% S: Not reported	Anxiety; Dyspnoea; Pain	Benzodiazepines	Symptom control	S: Presences of symptoms on a 5 points Likert scale A: Not reported R: Not reported
Chater (1998); Canada	D: Retrospective study; "Survey of experts" S: Teaching hospital performing palliative care or centre where palliative care physicians received training	N=61 (n=96) A: Not reported G: Not reported S: Not reported	Agitation/delirium/ confusion/hallucinations; Anguish; Pain; Respiratory distress	Lorazepam; Methotrimeprazine; Midazolam	Process of sedation: Start sedation Level of suffering and anxiety of patient reaction of family	S: Successful or unsuccessful A: Palliative care specialists R: Not reported

* mean (SD), ** median (range), # (N; n (no. Patients sedated); age patients (years) (A); gender (% female) (G); duration of sedation (days) (S)) † Used scales (S); Assessors (A); Rating frequency (R), ‡ None of these studies reported information on clinimetric properties in terms of validity or reliability,^a most common refractory symptom^b concerns physicians that reported on the sedation of a patient in past 12 months^c Did report a frequency based on 4 categories (< 40 years, 41-60 years, 61-80 years, >81 years).

6.3.3 Instruments used to monitor effect of sedation

In five patient based pro- or retrospective studies (**table 1a** and **table 1b**), monitoring of the effect of palliative sedation was performed using established instruments.^{25,27,30,32,35} For measuring sedation depth, the Richmond Agitation Sedation Scale (RASS)^{27,35} and the Ramsay sedation scale were used.³⁵ The level of consciousness of delirious, terminally ill patients was measured using a single item of the Communication Scale to measure level of awareness in one study.³²

On symptom level, the Visual Analogue Scale (VAS) was used in two studies to measure pain, nausea and drowsiness, whereby data based on patient administered VAS were used for conscious patients, whereas a trained nurse performed the assessments during sedation.^{27,30} The Edmonton Symptoms Assessment System (ESAS) was used in one study.³⁵ In one study single items for measuring hypo- or hyperactivity of the Agitation Distress Scale (Agitation Scale) and the Memorial Delirium Assessment Scale (MDAS) were used.²⁵ In addition to these established instruments, the use of an ad hoc scoring system was reported in six studies.^{27,28,31,33,34,42} Finally, we found one study monitoring the effects of sedation by unspecified observation.³⁹

In studies evaluating physicians' experiences (**table 2**), consumption of benzodiazepines was described as a way to measure symptom management.³⁶ In one retrospective interview study, the respondents could score the presence of symptoms on a 5 points Likert scale.³⁸ In one retrospective expert survey, sedation was categorized as successful or unsuccessful.⁸ One retrospective questionnaire study did not provide a specific tool or method to assess the sedation effect.³⁷

In one guideline it was recommended to monitor the effects of sedation using established instruments (**table 3**). In that light, the authors named the RASS and the Critical-Care Pain Observation Tool (CCPOT).⁴¹ In two guidelines^{2,14} and two reviews,^{4,11} ad hoc literature or expert based scoring systems were proposed. In addition, six guidelines and two reviews advised to monitor the effects of sedation without providing reference to specific tools or methods.^{3,9,10,12,13,17}

6.3.4 Assessors of the scales

In most patient based pro- or retrospective studies (n=10) monitoring was performed by trained personnel (physicians, n=6^{25,27,31,33,35,42}; nurses, n=5^{31,33,35,39,42}; members of a treatment team, n=1²⁸ or palliative care specialist, n=1⁸) (**table 1a** and **table 1b**). In two prospective patient based studies, and three studies in which physicians' experiences were assessed, no information was provided with regard to the assessors.^{32,34,36-38}

In two reviews and one guideline (**table 3**) it was advised to monitor the effect of sedation by trained personnel.¹¹⁻¹³ Four reviews/guidelines specifically stated that monitoring had to be performed by an expert physician^{10,41} (either an expert in pain and symptom control, a skilled physician³ or a palliative care specialist⁹). In contrast, two other reviews suggested

that patients could provide information themselves as long as they were communicative, or to rely on family assessment in cases where patients were unable to communicate.^{11,12} In one review and two guidelines no information was provided about who should monitor the effect of palliative sedation.^{4,17,40}

6.3.5 *Timing and frequency of monitoring*

In ten pro- or retrospective studies information was provided with regard to frequency of monitoring (**table 1a** and **table 1b**. Daily monitoring (n=3),^{28,31,34} twice a day^{30,35} or four times a day.²⁷ In one study, assessments were performed just before the start of sedation, and at 4 and 24 hours after sedation²⁵. In another study, measurements were reported to take place ‘regularly’ in the first hour after the start of sedation, and at 2 and 6 hours following onset of sedation.³³ Another retrospective study reported to monitor ‘each’ visit prior to and during the treatment.⁴² Kohara et al.³² reported that the whole period of sedation was assessed retrospectively. Green et al. reported to monitor continuously and did not report a specific frequency.³⁹ One patient based study and all studies reporting about physician’s experiences did not provide specific information about frequency or timing of monitoring.^{8,29,36-38}

One guideline (**table 3**) provided specific requirements for the frequency of measuring the sedation,⁴¹ whereby it was advised to monitor every 20 minutes until adequate sedation was achieved, subsequently monitoring three times a day was advised. Other guidelines/reviews reported that measurement should take place every hour¹⁴ or day (n=3).^{2,11,12} In addition, one guideline recommended to measure at the start of sedation only.¹⁰ In five reviews/guideline no directions were provided for timing and frequency of monitoring.^{3,4,13,17,40}

6.3.6 *Validity or reliability of scales used to measure sedation*

Morita et al.²⁵ validated the Communication Capacity Scale (CCS) by comparing its mean scores with four corresponding levels of the sedation scale (cooperative (mean score 4.2 (SD 2.0); oversedated (mean score 12 (SD 0.71); very sedated (mean score 15 (SD 0.96); unarousable (mean score 17)). In addition, they reported the reliability of both the MDAS (good, Cronbachs alpha 0.81-0.84) and the CCS (excellent, Cronbachs alpha 0.91-0.92). All other pro- or retrospective studies did not provide data on validity or reliability of the used scales.

One guideline by Cherny et al.⁴¹ did provide a reference in their appendix in which their proposed scales (RASS and CCPOT) are validated in an adult critical care setting. All other reviews/guidelines did not provide data on validity or reliability of the proposed scales.

Table 3. Reviews/guidelines

Study; Country	Design	Monitoring sedation effect	Scale†	Clinimetric properties ‡
KNMG (2009); Netherlands	Guideline	Symptom control	S: Sedation score A: Treating doctor or nurse R: Daily control and evaluation by doctor	V: Not reported R: Not reported
Cherny (2009); Israel/ Germany/ Italy	Guideline	Level of consciousness, severity of suffering Adverse effects of sedation (e.g. delirium, agitation or aspiration), respiratory rate; Not necessary to monitor heart rate, blood pressure and temperature	S: Richmond Agitation Sedation Scale, Critical- Care Pain Observation Tool A: (Senior) physician and nurse R: Every 20 minutes until adequately sedated, subsequently 3 times a day	V: Not reported ^a R: Not reported ^a
Claessens (2008); Belgium	Review	Symptom control	S: Not reported A: Not reported R: Not reported	V: Not reported R: Not reported
Verkerk (2007); Netherlands	Guideline	Relevant data on Symptom control	S: Not reported A: Treating doctor R: Daily control and evaluation by doctor	V: Not reported R: Not reported
Vissers (2007); Netherlands	Review	Comfort of patient	S: Not reported A: Attending nurses and next of kin R: Not reported	V: Not reported R: Not reported
De Graeff (2007); Netherlands/ Canada	Review	Symptom control; depth of sedation; Comfort of patient (monitoring anxiety/ suffering); Side effects of sedation	S: None available, possibly level of awareness in sommolence vs. stupor vs. coma A: Patient (if possible), family or treatment team R: Daily, frequency/ interval determined by treatment team	V: Not reported R: Not reported
National Ethics Committee (2006); USA	Review and guideline	Level of awareness	S: Not reported A: Doctors working in palliative care or having experience with palliative sedation R: Not reported	V: Not reported R: Not reported

† Used scales (S); Assessors (A); rating frequency (R); ‡ Validity (V); Reliability (R);

^a Did provide reference to study providing validity and reliability of RASS scale in ICU patients

Table 3 - [Continuation]

Study; Country	Design	Monitoring sedation effect	Scale†	Clinimetric properties ‡
Muller-Busch (2006); Germany	Review	Symptom control; Course, depth, length and effect of sedation	S: Not reported A: Patient (if possible), family or treatment team. R: Daily/frequent	V: Not reported R: Not reported
Schuman (2005); USA	Guidelines/ Case discussion	Symptom control; Comfort and unfavourable side effects (e.g. tachycardia, involuntary movement)	S: Ad hoc protocol A: Nurse and/or doctor R: Control until desired level is reached (doctor), every hour thereafter (nurses)	V: Not reported R: Not reported
Braun (2003); Canada	Development of guideline	Not reported	S: Not reported A: Experts in pain and symptom management R: Not reported	V: Not reported R: Not reported
Cowan (2002); USA	Review / Guidelines	Symptom control, respiratory frequency and temperature Not necessary to monitor control of pulse - and blood pressure	S: Not reported A: Skilled medici R: Frequent.	V: Not reported R: Not reported
Cowan (2001); USA	Review	Symptom control	S: (In)adequate symptom control A: Not reported R: Not reported	V: Not reported R: Not reported
Quill (2000); USA	Guideline (and case presentation)	Level of awareness	S: Not reported A: Treatment team R: Not reported	V: Not reported R: Not reported
Cherny (1994); USA	Guideline	Symptom control, level of awareness and comfort Not necessary to monitor pulse -, blood pressure and temperature	S: Not reported A: Not reported	V: Not reported R: Not reported

† Used scales (S); Assessors (A); rating frequency (R); ‡ Validity (V); Reliability (R)

6.4 Discussion

In this systematic literature review an overview is given about the manner in which observational monitoring of palliative sedation has been reported in scientific literature. In a minority of studies reporting on palliative sedation, measurement of effect of sedation was described. Within the studies it is generally agreed upon that the quality of palliative sedation will improve when adequate monitoring of the effect is performed,^{2,11,25} however actual assessment of parameters of the effect is limited. Moderate agreement was found with regard to which parameters to monitor between studies evaluating the effect of sedation. Combining information from the articles included in this review, both indices measuring symptom control as well as sedation depth should be evaluated. This is in agreement with the proportionality requirement of palliative sedation, requiring the depth of sedation to be adapted to the level of required level of symptom control therewith limiting under- or oversedation. However, in order to be able to apply palliative sedation in a proportional manner, both symptom control and sedation depth should be monitored simultaneously. This occurred in only four of the included studies.

Parameters found to be evaluated in the included studies for symptom control were in line with the most frequently described indications for palliative sedation (i.e. pain, dyspnoea, delirium and nausea & vomiting).^{43,44} Discussion remains with regard to the value of monitoring vital signs for palliative sedation. Although monitoring vital signs is considered regular practice in cases where patients are sedated outside the scope of palliative sedation,⁴⁵ arguments remain with regard to its contribution to the evaluation of palliative sedation. Although these data may not contribute much to the purpose of sedation,^{17,30} they can contribute in forming a picture of the condition of the patient^{14,25,39} and allow for an advance warning for hypoxic events making it less likely that these complications occur during sedation.

With regard to measurement of sedation depth, studies focused more or less uniformly on the level of awareness and arousability of the patients. However, the value of measuring the depth of sedation has been questioned by some authors who felt that monitoring in a palliative care setting (in general) would cause too much burden for the patient.^{16,46} For both symptom control and sedation depth, there was no uniformity with regard to the manner in which these parameters should be evaluated. Even if differences between evaluated patient populations may require the use of instruments specific to that population, we are of the opinion that some degree of uniformity with regard to the manner in which the effect of palliative sedation is assessed would contribute to study comparability and therefore to comprehensive assessment of palliative sedation literature.

Furthermore, only a fraction of the studies evaluated in this review actually used established observational monitoring instruments. For only one of these instruments, both validity and reliability had been assessed for consciousness of delirious patients receiving palliative sedation.⁴⁷ For one instrument measuring delirium the reliability was also evaluated in the same study. Although other instruments used by researchers in this review can be considered valid and reliable, they have not been validated for sedated patients in a palliative care setting.^{25,48} Also for studies in which single items of compound scales were used, question marks can be placed since clinimetric properties are usually established for measurement

instruments as a whole. In addition, in some cases outcome of instruments was derived retrospectively from patient records instead of prospectively monitored, which may introduce description and interpretation bias. Taken together with the fact that most studies identified in this systematic review used ad hoc instruments without providing information about the clinimetric properties of these scales, this raises serious questions with regard to the interpretability of the results.

This is surprising, since valid and reliable observational instruments have long been developed and used in a clinical setting. Except for the Ramsay sedation scale, the RASS and the Communication Scale for measurement of patient consciousness or sedation depth found in this review, other instruments are available with proven clinimetric properties such as the Vancouver Interaction and Calmness Scale (VICS)⁴⁹ and the Minnesota Sedation Assessment Tool (MSAT).⁵⁰ Likewise, for the observation of symptoms, adequate measurement instruments have been developed for non-communicative patients, such as the ESAS, Agitation Scale, and the MDAS found in this review.⁴⁸ In addition for pain assessment, different instruments (such as the PainAD) have been tested for validity and reliability.^{51,52} For other prominent indications of palliative sedation, such as delirium and dyspnoea, observational scales have recently been established (i.e. Delirium Observation Scale (DOS)⁵³ and Respiratory Distress Observation Scale (RDOS).⁵⁴ As discussed previously, these instruments should be validated specifically for palliative sedation, which implies that the clinimetric process should take into account the specific patient population, the setting (home, hospice or clinic) and the health care workers involved in palliative sedation.

With regard to this latter issue, the assessors proposed in the studies included in this review comprise the broad scope of disciplines involved in the practice of palliative sedation. Nurses, as well as (general) physicians and palliative care specialists have performed measurements in the evaluated studies. Since many disciplines may be involved in the process of performing palliative sedation, no clear recommendations can be given with regard to which specific discipline should perform the measurements. Therefore, one could argue that to improve standardization in interdisciplinary communication with regard to patient monitoring, methods should be used (or trained) that are accessible and available to different disciplines. In cases where this is unfeasible, it seems advisable to make one discipline responsible for (standardized) patient monitoring. As recommended in a few guidelines evaluated in this review, adequate training of personnel in use of monitoring instruments may be required. With regard to the timing of assessments, again no clear recommendations can be provided since different monitoring frequencies have been proposed in the evaluated literature, without a providing an explanation for the used frequency. In general, taking the clinical perspective of palliative sedation into account, it seems logical to start measurements of symptoms prior to the start of sedation and at regular intervals during the administration of sedation in order to evaluate change in symptom burden and monitor if symptom control remains adequate. With respect to consciousness and sedation depth, monitoring should preferably be performed more frequently during the initial phase of the sedation, again followed by regular timing intervals in the course of sedation coinciding with the measurements of symptom control. Optimal timing and frequency should be subjects of future studies.

Some limitations have to be discussed in the context of this review. As with every systematic literature analysis, this review is inclined to selection bias and interpretation bias. A sensitive search was performed, using broadly defined search criteria, it is possible that relevant articles have been missed. The fact that eight additional articles were found evaluating reference lists of these articles may be suggestive for this. Although articles found were crosschecked by two of the authors, judgment of titles and abstracts could have led to false negative results, thereupon missing studies that should have been included.

Another point of discussion is the fact that we did not conduct a methodological assessment of the articles. Since this was an exploratory review, a broad range of study types (with case series as a lower limit) were considered relevant in order to be able to provide a comprehensive overview of the manner in which observational assessment of sedation effect was performed. Considering the designs of the included studies, none of the articles exceeded a level three strength of evidence as defined by Jadad et al.⁵⁵ As no studies of high methodological strength were found in our search, limiting the inclusion to studies of good methodological quality would have provided insufficient information to meet the goal of this study. However, following an opposite approach, expanding the search to include descriptions of individual cases could have yielded additional information with regard to monitoring of palliative sedation.

Notwithstanding these issues, we are of the opinion that this review provides an adequate representation of current literature concerning the observational monitoring of palliative sedation and the use of monitoring instruments, which suggests that there is room for improvement.

A final limitation of this study is the fact that we only focused on observational “non technical” monitoring of palliative sedation. As described in the introduction, more advanced measurement instrument have been developed for measurement of sedation depth. Although information about these instruments has not been included in this review for feasibility reasons in parts of the setting where palliative sedation is applied, instruments such as the BIS monitor may be a worthwhile aid in settings where these instruments are available. However, this still leaves the necessity for adequate monitoring of symptom control as this is considered the primary aim of palliative sedation.^{2,11,41}

Based on the results found in this review, we are of the opinion that research in each of the modalities discussed in this review should be performed. Future studies should be focused on establishing proper instruments, most adequate frequency and timing of assessment, and interdisciplinary evaluation of sedation depth and symptom control for palliative sedation. It is generally agreed upon that adequate validity and reliability of measurement instruments is essential for scientific research as these concepts define the boundaries with regard to the adequacy of measurement and repeatability of results. Specific attention should be given to these issues, as well as practical aspects of user and patient friendliness of the instruments. Finally, in order to improve between-study comparability, it is desirable to establish practical and scientific guidelines on a minimal dataset of measures to monitor palliative sedation.

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