Medication and Monitoring in Palliative Sedation Therapy: A Systematic Review and Quality Assessment of Published Guidelines

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Introduction

Some patients in their last weeks of life experience intolerable suffering from one or more severe symptoms that cannot be controlled by standard palliative care treatment. As a treatment of last resort for "refractory symptoms," palliative sedation therapy (PST) may be considered.[1] A "refractory symptom" has been defined as a "symptom that cannot be adequately controlled despite aggressive efforts to identify a tolerable therapy that does not compromise consciousness. (…) the clinician must perceive that further invasive or non-invasive interventions are either 1) incapable of providing adequate relief, 2) associated with excessive and intolerable acute or chronic morbidity, or 3) unlikely to provide relief within a tolerable time frame."[2] Terminology and definitions for PST, which is, for example, also called palliative sedation or terminal sedation, vary in the literature.[1] Herein, we define PST 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 […]."[3]

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In recent years, international medical associations, national bodies, and local institutions have taken up the task of developing guidelines and policies with the aim of informing practitioners about the appropriate practice of PST in oncology as well as other fields of medicine.[3–5] As reported elsewhere, current guidance on PST varies considerably with regard to definitions of and indications for PST.[6]

In this article, we present the findings of a systematic review of published PST guidelines on recommended drug selection, dosage, and monitoring. The objectives are to inform palliative care professionals about the similarities and differences of these recommendations, and to assess the quality of the available guidelines against established criteria for guideline development. The findings shall inform the debate on good clinical practice of PST in patients at the end of life and may contribute to the improvement of future PST guidelines.

Methods

Data Sources and Searches

As described in the first publication of the results of this systematic review, which focused on recommendations on ethical and communication aspects of indication and decision making,[6] we conducted a systematic literature search in CINAHL, the Cochrane Library, Embase, PsycINFO, and PubMed to identify and collect published guidelines in English and German. The database search covered the period from January 1, 1980 to July 31, 2014. Search terms were "palliative sedation" or "sedation" and "guideline" or "policy" or "framework." Additionally, the reference lists of eligible articles were screened for further published guidelines. For this article, the guideline definition for the Medical Subject Heading "Practice Guideline" in MEDLINE was used.

Study Selection, Data Extraction, and Synthesis

As a first step, the first and second authors independently reviewed all resulting citations according to title and abstract. Disagreements regarding the eligibility of articles were resolved by consensus after reading the full text. Each guideline received a label according to the developers (e.g., "European Association for Palliative Care [EAPC] framework," "Japanese guideline;" Table 1) to facilitate reference to the specific guideline. Data extraction of the guidelines' contents on medication and monitoring relevant to this article was performed independently by the first and the last author. Disagreements were resolved by discussion amog all three authors. For reporting, we followed the criteria as described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist.[7]

Quality Assessment

The quality of published guidelines was assessed independently by the first and the last author using the Appraisal of Guidelines for Research and Evaluation II instrument (AGREE II).[8] Each item was assessed on a seven-point scale from 1 = strongly disagree to 7 = strongly agree. It was decided in advance that if an AGREE II item was not applicable to the particular guideline, it would be rated as 1, as suggested in the AGREE II instructions.[8] Domain scores for each of the six AGREE II domains were calculated using the scores from both assessors as recommended by AGREE II.

Results

Literature Search and Quality of Guidelines

Nine publications on PST guidelines were included in the review.[1,3–5,9–13] Figure 1 provides an overview of the study selection process. The most frequent reason for exclusion of publications after reading the full text was lack of compliance with the definition of "Practice Guideline" as defined in MEDLINE. The quality assessment according to the AGREE II instrument shows that most guidelines received high scores for the domain "Scope and Purpose" (median 69%, range 28–83%), whereas the domain "Applicability" received the lowest scores (median 15%, range 0–25%). The median values for the other four domains were 28% (Stakeholder Involvement), 23% (Rigor of Development), 42% (Clarity of Presentation), and 25% (Editorial Independence). Five guidelines obtained scores higher than 60% in two domains;[1,3,4,10,13] one of these received a score higher than 60% in a third domain.[10] Four guidelines received scores between 40% and 60% for the domain "Rigor of Development."[1,3,4,10] Table 1 summarizes the overall and guideline-specific results of the quality assessment.

Drug Selection, Dosage, and Titration

Seven of the nine guidelines provide recommendations on specific drugs and also, partly, their respective indications in the context of PST.[1,3–5,9–11] One of the two guidelines that do not present any such recommendations states the lack of evidence as a reason.[12] Five of the seven guidelines that provide drug-specific recommendations name midazolam as the primary agent, either generally or in specific situations[1,5,9–11] (Table 2). The other two of the seven guidelines with drug-specific recommendations state that midazolam is the most frequently used drug.[3,4]

Table 1
Assessment of Included Guidelines Using the AGREE II Instrument

	AGREE II Domains					
Guidelines	Scope and Purpose (%)	Stakeholder Involvement (%)	Rigor of Development (%)	Clarity of Presentation (%)	Applicability (%)	Editorial Independence (%)
Health region guideline, Braun et al[12]	58	28	23	28	15	0
Massachusetts protocol, Hospice & Palliative Care Federation[11]	28	28	1	36	8	0
Hospital guideline, Schuman and Abrahm[5]	69	28	13	42	19	33
Japanese guideline, Morita et al[10]	83	92	43	67	25	38
Dutch guideline, Legemaate et al[9]	58	28	15	39	0	0
International guideline, de Graeff and Dean[1]	72	22	49	67	0	13
EAPC Framework, Cherny and Radbruch[3]	67	36	42	64	19	25
NHPCO statement, Kirk and Mahon[13]	75	44	16	39	25	63
Canadian Framework, Dean et al[4]	69	28	45	56	15	63
Median	69	28	23	42	15	25
Range	28–83	22–92	1–49	28–67	0–25	0–63

AGREE II = Appraisal of Guidelines for Research and Evaluation II.

The lack of evidence to recommend one drug over any other is mentioned by two of the seven guidelines with drug-specific recommendations.[1,4] Barbiturates (phenobarbital or pentobarbital) are suggested in six guidelines as alternative medications, mainly if midazolam alone is not effective.[1,3–5,10,11] Five guidelines recommend neuroleptics such as levomepromazine or chlorpromazine, primarily for patients with profound delirium.[1,3,4,10,11]

Propofol is mentioned in three guidelines, mostly as a sedative drug of last resort.[1,3,4] Other rarely named drugs are flunitrazepam[3,10] and lorazepam.[3] Haloperidol is suggested for patients with dementia in the Massachusetts guideline, whereas two guidelines explicitly state that haloperidol should not be used as a primary medication for PST because of its weak sedative effect.[4,10] Haloperidol in combination with midazolam is recommended for patients with delirium in two guidelines.[1,10] A statement about not using opioids for the purpose of sedation is included in five guidelines.[1,4,9–11] Continuation of opioids for the treatment of pain or dyspnea is explicitly recommended by most guidelines.[3–5,9–11]

Five guidelines also include recommendations for dosages.[1,3,5,10,11] Of these, only the international guideline provides references and a table with mean doses and ranges as reported in the literature.[1] Most guidelines recommend that the goal of titration should be adequate control of suffering and the level of consciousness that is necessary to achieve this.[1,3–5,9,10,13] In contrast, the Massachusetts guideline mentions "first stage anesthesia (onset of disorientation to loss of consciousness)" as the "goal of sedation."[11] An additional recommendation not to decrease the dose of the sedative in certain situations, such as gradual deterioration of respiration and approaching death, is mentioned in three guidelines.[3,5,11] Additional details about drug selection and dosages are shown in Table 2.

Monitoring

All guidelines make statements concerning monitoring after initiation of PST, but show large variations regarding the amount and details of those recommendations. The most basic information with regard to monitoring is provided by the health region guideline, which states that a "physician expert in symptom control" will arrange appropriate monitoring, without giving further details.[12]

Outcome Parameters. Regarding the parameters to be monitored, two guidelines provide basic information that the "effect of sedation"[9] should be monitored and that "considerations of effectiveness and safety" should be taken into account.[13] Six guidelines specify parameters to be monitored.[1,3–5,10,11] Adverse effects of PST are regarded as an important monitoring parameter in all of them.[1,3–5,10,11] Five of the six

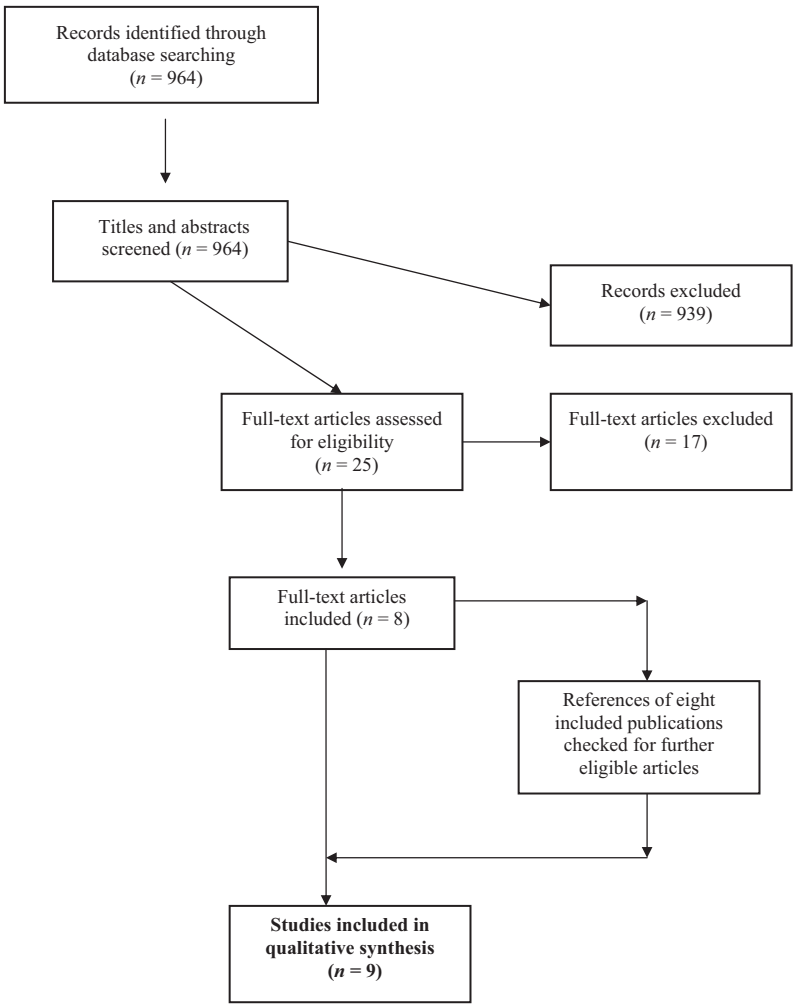

Fig. 1. Flowchart of the literature search.

(not the Massachusetts guideline[11]) include the severity/relief of suffering as one of the main outcome criteria.[1,3–5,10] The Massachusetts and four other guidelines recommend monitoring of the patients' level of consciousness or level of sedation.[1,3,4,10,11] The EAPC guideline states that in short-term, intermittent or light sedation, routine physiological parameters should be monitored.[3] In all other circumstances of sedation, this guideline as well as three others recommend that measurement of vital signs should usually be stopped.[3–5,10] Additionally mentioned parameters to be monitored are the needs of the family,[1] psychological and spiritual distress of family and health care professionals,[4] and potential treatment options for symptom palliation other than sedation.[10] Details on outcome parameters as well as methods of assessment described below are provided in Table 3.

Methods of Assessment. Five guidelines specify how the above-mentioned parameters can be assessed.[1,3,4,10,11] Two suggest measuring relief of suffering by verbal comments of the patient, facial expressions, and body movements.[4,10] Three guidelines recommend assessing the level of consciousness by evaluation of the patient's response to nonpainful stimuli;[3,4,10] two explicitly add that painful stimuli are not acceptable and not necessary in this context.[4,10] The Massachusetts guideline recommends using the eyelash reflex to assess the level of consciousness.[11] The guidelines differ widely regarding assessment tool and scale recommendations: the Canadian guideline states that any scale devised for monitoring of PST should include patient comfort, and that no particular scale can be recommended because the usefulness of existing scales, for example, to assess communication, level of sedation, motor activity, and agitation, has not been proven in PST patients.[4] The international guideline also refers to this lack of evidence but names the Edmonton Symptom Assessment Scale and several monitoring tools that may be used for measurement of communication level, consciousness, motor activity,

Table 2
Recommendations on Drugs for PST

Drug	Indication	Starting Dose	Maintenance Dose	Route	Adverse Effects	Other Aspects
Midazolam	Drug of choice (Legemaate et al[9]) First choice for continuous deep sedation (Morita et al[10]) First-line drug in the absence of delirium; in combination with haloperidol or levomepromazine for refractory delirium (de Graeff and Dean[1]) For respite sedation or if potential reversal of sedation is desired (Hospice & Palliative Care Federation[11], Schuman and Abrahm[5])	0.5–1 mg/hour (Cherny and Radbruch[3]) 0.2–1 mg/hour (Morita et al[10]) 0.01–0.05 mg/kg (i.e., for 70 kg: 0.7–3.5 mg) over two minutes (Schuman and Abrahm[5]) 0.5–1.5 mg/hour after loading dose of 1–5 mg (Hospice & Palliative Care Federation[11])	1–20 mg/hour (24–480 mg/24 hours) (Cherny and Radbruch[3]) 22–70 mg/24 hours (mean dose), range 3–1200 mg/24 hours (de Graeff and Dean[1])[a] 20–40 mg/24 hours (range 5–120 mg/24 hours) (Morita et al[10]) 0.02–0.1 mg/kg/hours (0.7–3.5 mg/hour = 16.8–84 mg/24 hours) or 25% of the loading dose (Schuman and Abrahm[5]) 30–100 mg/24 hours (25–33% of the required loading dose; Hospice & Palliative Care Federation[11])	IV or SC (de Graeff and Dean,[1] Cherny and Radbruch,[3] Hospice & Palliative Care Federation,[11] Morita et al,[10] Schuman and Abrahm[5])	Paradoxical agitation (Dean et al,[4] Cherny and Radbruch,[3] Morita et al,[10] ad Hospice & Palliative Care Federation[11]), respiratory depression (Cherny and Radbruch,[3] Morita et al,[10] Hospice & Palliative Care Federation[11]), withdrawal (Cherny and Radbruch,[3] Morita et al[10]), tolerance (Cherny and Radbruch,[3] Morita et al,[10] de Graeff and Dean[1]), lowering of the root of tongue (Morita et al[10]), hiccups (Hospice & Palliative Care Federation[11]), nausea and vomiting (Hospice & Palliative Care Federation[11])	Reduce anxiety/cause amnesia, synergistic sedative effect with opioids and antipsychotics, anticonvulsant, rapid onset (Cherny and Radbruch[3]) Easy titration owing to short half-life, anxiolytic, anticonvulsant, muscle relaxant (Dean et al[4]) Short half-life, anxiolytic, antiepileptic, and muscle relaxant (de Graeff and Dean[1]) Water soluble, can be mixed with other medications, anticonvulsant, quick onset, presence of antagonist, dose-dependent sedative effect (Morita et al[10]) Short half-life, may be mixed with other medications, CNS depressant, so use cautiously with opiates or other CNS depressants; Diltiazem and verapamil increase midazolam levels (Hospice & Palliative Care Federation[11])
Phenobarbital	As an adjunct to midazolam or an antipsychotic or alone (Dean et al[4]) Severe agitation, sedative drug of last resort (de Graeff and Dean[1]) One of the recommended drugs if midazolam is ineffective (Morita et al[10])	100–800 mg/day, dose reduction after adequate sedation achieved (Morita et al[10]) 60–120 mg PR, PO, SC, loading dose = 200 mg bolus (Hospice & Palliative Care Federation[11]) 1–3 mg/kg SC or IV bolus dose, then 0.5 mg/kg/hour	800–1600 mg/24 hours (median dose), range 200–2500 mg/24 hours (de Graeff and Dean[1])[a] Approximately 50 mg/hour (1200 mg/24 hours) (Hospice & Palliative Care Federation[11])	IV, PO, SC, PR (Hospice & Palliative Care Federation[11]) SC, rectal (Morita et al[10])	Paradoxical excitation in high doses or in the elderly (Dean et al,[4] Hospice & Palliative Care Federation[11]); respiratory depression in high doses (Dean et al[4]); skin irritation, hepatotoxicity (Morita et al[10]); hypotension, nausea, and vomiting; Steven Johnson's Syndrome; angioedema;	Anticonvulsant (Morita et al[10]), accumulation, medication interactions, cannot be mixed with other medications (Morita et al[10]), Long half-life, reversal of sedation difficult (Hospice & Palliative Care Federation[11])

					rash; agranulocytosis; thrombocytopenia	
Levomepromazine	In cases with profound terminal delirium (Dean et al[4]) Particularly for delirium (Cherny and Radbruch[3]) For refractory delirium (de Graeff and Dean[1]) One of the recommended drugs if midazolam is ineffective (Morita et al[10])	12.5–25 mg stat dose and 50–75 mg continuous infusion (Cherny and Radbruch[3]) 5–12.5 mg/day (Morita et al[10])	12.5 or 25 mg q8h or up to 300 mg/day continuous infusion (Cherny and Radbruch[3]) 12.5–50 mg/day (Morita et al[10]) 64 mg/24 hours (mean dose), range 25–250 mg/24 hours (de Graeff and Dean[1])[a]	Orally (Cherny and Radbruch[3]) IV (Cherny and Radbruch[3]) SC (Morita et al,[10] Cherny and Radbruch[3]) IM (Morita et al,[10] Cherny and Radbruch[3])	Orthostatic hypotension, paradoxical agitation, extrapyramidal symptoms, anticholinergic effects (Cherny and Radbruch[3]) Anticholinergic effect, decrease in blood pressure, skin irritation, extrapyramidal symptoms, injection pain (IM; Morita et al[10])	Rapid-onset, antipsychotic effect in cases of delirium, some analgesic effect (Cherny and Radbruch[3]) Often given in conjunction with benzodiazepines (de Graeff and Dean[1])
Propofol	Severe agitation, sedative drug of last resort (de Graeff and Dean[1])	0.5 mg/kg/hour (Cherny and Radbruch[3])	1–4 mg/kg/hour (Cherny and Radbruch[3]) 500 mg/24 hours (mean dose), range 400–9600 mg/24 hours (de Graeff and Dean[1])[a]	IV (Cherny and Radbruch[3])	Respiratory depression, profound hypotension (Dean et al[4]) Hypotension and respiratory depression, pain on infusion into small peripheral veins (Cherny and Radbruch[3])	Rapid onset and short half-life; should be used only by an experienced practitioner (Dean et al[4]) Quick onset of sedation, ability to rapidly titrate, rapid washout, use strict aseptic technique; nonsedative benefits: antiemetic, antipruritic and bronchodilatation (Cherny and Radbruch[3])

PST = palliative sedation therapy; IV = intravenous; SC = subcutaneous; CNS = central nervous system; PR = by rectum; PO = by mouth; IM = intramuscular.
[a]Mean/median and range of sedative doses used in the final 48 hours of life as derived from the literature.

and agitation.[1] The EAPC guideline recommends the Critical-Care Pain Observation Tool and the Richmond Agitation Sedation Scale for assessment of pain and distress.[3]

Recommendations regarding who should carry out the assessment vary as well; in one guideline, it is the physician,[9] in another the nurse,[11] and in a third, both.[5] Two guidelines state it should be an experienced clinician,[12,13] and the international guideline recommends that the patient (if possible), family, and staff should evaluate the above-mentioned parameters.[1] All guidelines except the health region and the National Hospice and Palliative Care Organization (NHPCO) guideline consider adequate time intervals for monitoring.[1,3–5,9–11] Recommended intervals during sedation range from hourly,[5] to more than three times a day,[3,4,10] to once a day.[11] During initiation of PST, until adequate sedation is achieved, closer intervals of 15–30 minutes are demanded by some guidelines.[3–5,10,11] The Canadian guideline states—in addition to suggesting certain general intervals—that the pharmacokinetics of the drug used for sedation should influence the frequency of monitoring,[4] and the international guideline recommends that adequate intervals for monitoring should be determined by the team.[1]

Discussion

This article provides a comparative analysis of PST guidelines. Although a recent analysis of international guidelines and position statements has been published by Gurschick et al,[14] there are differences between our research and theirs with regard to the selected guidelines because of different search strategies and inclusion criteria. Further differences include the focus of this research on details of medication and monitoring of PST and the quality assessment of the identified guidelines according to the AGREE assessment tool.

As acknowledged in some of the evaluated guidelines, the relevant evidence base in the literature is scarce.[1,10] Against this background, our comparative analysis is largely descriptive and may serve as starting point for identifying relevant gaps in the evidence that should be addressed to formulate more robust, evidence-based recommendations.

Quality of PST Guidelines

As shown in Table 1, the quality of the identified PST guidelines in the different domains is very heterogeneous, based on the criteria of the AGREE II instrument. This finding is in line with an analysis of guidelines on ethical aspects at the end of life.[15] The quality of the nine guidelines, as indicated by the median of the respective AGREE domain score, is reasonably good (>60%) in one domain (Scope and Purpose), average (42%) in one other domain (Clarity of Presentation), and low (<30%) in the remaining four domains (Stakeholder Involvement, Rigor of Development, Applicability, and Editorial Independence). The results may, in part, be explained by the difficulties associated with methodologically stringent development in a field in which there is little evidence and considerable controversy on ethical grounds.[1,6,15] Another aspect that should be taken into account when evaluating the quality of guidelines is the difference in target groups. Differences between guidelines may be explained, for example, in that national guidelines are concerned with influencing policy, whereas a local guideline is designed to assist a subset of clinicians in their clinical practice. It is a matter for discussion whether the AGREE criteria fit equally well for guidelines issued for a single hospital and for national or even international guidelines. However, given that at least part of the AGREE criteria can be used for guidelines for different target groups, and in light of the finding that apart from Domain 5 (Applicability), in each domain at least one guideline reached a score of 40% or more, we argue that the positively rated elements in the different guidelines may serve as benchmarks for the further development of high-quality PST guidelines. In the meantime, we suggest that clinicians use those guidelines with higher ratings in most domains, keeping in mind the limitations of their development and the scarcity of evidence on which they are based.

Drug Selection, Dosage, and Titration

Medication for PST is not consistently addressed in detail in the analyzed guidelines, a finding that resonates with the analysis of guidelines and position statements by Gurschick et al.[14] In addition, and as pointed out in the first publication resulting from this systematic review, there is also considerable disagreement with regard to the indications for which a specific drug should be provided for PST.[6] With regard to a specific drug, most guidelines that do provide such recommendations name midazolam as the first option.[1,5,9–11] This is in line with the findings of Gurschick et al,[14] a review by Claessens et al,[16] and the review conducted for the international guideline, which found that one-third[16] to approximately two-thirds[1] of the included studies mentioned midazolam as the main drug for PST. However, it should be pointed out that, to our knowledge, these recommendations are not based on controlled clinical trials comparing midazolam with other drugs. As has been acknowledged in the literature, there is generally a lack of good quality evidence to support any drug recommendation for PST.[1,4,12]

Initial and maintenance doses of midazolam for sedation vary among guidelines, and only the dose recommendations in the international guideline are based on a literature review.[1] However, the results of the international guideline differ from the review of Claessens et al;[16] the international guideline found a range of 3 mg/day up to 1200 mg/day of midazolam,[1] whereas Claessens et al[16] found a range from 1 to 450 mg/day in primary studies.[16] For other drugs, the guidelines include less information regarding indications and dosages (Table 2). These findings again reflect the lack of high-quality studies exploring what can be considered as the "right" dose of the "right" drug in the palliative care patient receiving PST. In addition, drugs such as propofol just recently emerged in the palliative care context.[17] Small observational studies assessing the effect of different drugs have recently been published,[18–20] but these as well as the results from earlier published studies[21–23] need to be confirmed by larger prospective, ideally experimental, studies. This evidence is urgently required to develop recommendations on drugs and dosages for PST, to clarify and possibly diminish differences in recommended doses between guidelines, and thereby reduce uncertainty for clinicians in daily practice. As long as the evidence continues to be scarce, recommendations in guidelines should be clearly labeled as primarily expert opinion-based, and ideally use well-described, valid methods to reach consensus between the involved experts, such as the Delphi method.[10]

Most guidelines identify the goal of titration to be adequate control of suffering and reaching the level of consciousness that is necessary to achieve this.[1,3–5,9,10,13] However, one guideline mentions "first-stage anesthesia" as the "goal of sedation" independent from the degree of suffering.[11] In light of the use of PST as the last resort, and its potential harms, it seems mandatory that guidelines are as clear as possible regarding the aim of PST and the goal of titration to preclude uncertainties for practitioners and unnecessarily deep sedation for patients. The specific recommendation of five guidelines, that opioids should not be used for sedation,[1,4,9–11] seems an important safeguard. A study in The Netherlands found that 43% of the specialists, 19% of the general practitioners, and 22% of the nursing home physicians sometimes used morphine for this purpose.[24]

Monitoring of PST

Monitoring of PST is essential to ensure that the patient is comfortable, does not receive too much or too little sedation, and that adverse effects can be recognized and acted on.[4,13,25] Most guidelines included in the present work outline parameters that must be monitored, such as the severity of suffering, adverse effects or level of consciousness,[1,3–5,10,11] providing more guidance to practitioners, and consequently more safeguards for patients. Although it seems intuitive to monitor level of sedation in a sedated patient, one could argue that, in line with the aim of PST—to relieve the patient's otherwise intolerable suffering, the level of suffering should be the primary parameter to be monitored, and the level of sedation that is required to achieve this goal is only an additional parameter. Other authors have agreed that assessment of symptom burden should be performed together with the assessment of consciousness level.[25,26] Against the background of diverging and sometimes vague recommendations, which may lead to misunderstandings in clinical practice, guidelines should provide clear guidance as to the use of degree of suffering as the primary monitoring parameter and the level of sedation as an additional parameter.

Only five guidelines recommend specific methods of assessment.[1,3,4,10,11] The greatest consensus among those five guidelines is that the level of consciousness should be evaluated by nonpainful stimuli.[3,4,10] Only a few guidelines suggest possible monitoring tools: the EAPC and the international guidelines recommend the use of instruments that thus far have only been validated in other than palliative care settings.[1,3] Additionally, the international guideline[1] suggests the Edmonton Symptom Assessment Scale. Conversely, the Canadian guideline refrains from a recommendation for a particular tool because of the lack of validation in a palliative care context.[4] This lack of agreed-on monitoring tools is reflected in clinical practice; a systematic review of the use of observational scales for the monitoring of symptom control and depth of sedation in PST revealed that only a minority of primary studies on PST described how the effect of sedation was measured.[25] Some of the primary studies used scales validated in settings other than palliative care, and only one instrument that has been partially validated for use in a palliative sedation setting was identified.[25,27] More recently, a study testing the validity and reliability of four existing sedation scales specifically for the palliative sedation population resulted in a preliminary recommendation of two monitoring scales, pending further confirmation of their impact on patient comfort and symptom control through future research.[26] Given the lack of consensus regarding adequate scales to monitor palliative sedation and the importance of information about symptom control as consequence of PST to guide clinical practice, studies that can inform use of valid and reliable tools should be a research priority. The current differences in PST guideline recommendations on this topic are obstacles for applying guidance in clinical

Table 3

Overview of Recommendations Regarding Titration, Opioid Prescription, and Monitoring in PST

Recommendation Regarding	Guideline/Author/Year of Publication			
	Health Region Guideline, Braun et al[12]	Massachusetts Protocol, Hospice & Palliative Care Federation[11]	Hospital Guideline, Schuman and Abrahm[5]	Japanese Guideline, Morita et al[10]
Titration	No statement	Start low, titrate the dose to the desired clinical end point. Increase by approximately 30% every hour until sedation is achieved. "First-stage anesthesia" (onset of disorientation to loss of consciousness) is the goal of sedation. Decrease in sedatives if the patient experiences heavy snoring and abrupt onset of apnea. Gradual deterioration of respiration should not alone constitute a reason to decrease sedation.	In protocol for administration of palliative sedation: titration of the infusion rate "to the desired level of sedation." In other paragraph: "Once the desired level of symptom control is achieved, the infusion should be maintained at the lowest rate that supports this desired level of symptom control" If for some reason vital signs are monitored and the patient exhibits lowered blood pressure, respiratory rate or O_2 saturation, this should not lead to reduction of the infusion rate	Sedation methods with the smallest effects on the consciousness levels or physical functions, as long as the suffering is adequately palliated. Generally, intermittent or mild sedation should be attempted first, and continuous-deep sedation should be adopted when intermittent or mild sedation has been ineffective Start at small doses, increase gradually until symptoms are palliated
Opioids	No statement	Sedation will not be attempted by increasing opioid dosages; however, continuation of opioids at the previous level for pain management and to prevent opioid withdrawal	Continuation of opioids for pain control	Not recommended as primary medications to induce continuous-deep sedation because of the weak consciousness reduction effects and the possibility of neurohypersensitivity as a result of accumulation. Continuation of opioids for symptom control
Monitoring/outcome parameters	Physician expert in symptom control will arrange for appropriate monitoring of the patient No other statement	Level of sedation Any adverse effect	Patient's comfort/effects of therapy Parameters to be evaluated include pain, stridor, tachypnea, and effect on target symptom(s). Adverse effects (tachycardia, agitation, involuntary movements)	Severity of suffering, level of consciousness, undesirable effects, potential treatment options other than sedation
Monitoring/time and evaluator	Someone with experience No other statement	Continuously during initiation of therapy and every one hour until the dose is adjusted to a stable dose Registered nurse	By the nurse: at least every 15 minutes for the first hour, then at least every 30 minutes for the second hour, then at least hourly for the duration of therapy. By the physician: After initiation of therapy assessment for at least the first 15 minutes or until the patient is no longer in apparent distress, Assessment of the efficacy of therapy at least daily	Regular assessments (at least every 20 minutes while adequate sedation has not been achieved, then at least 3 times per day)

Monitoring/methods of assessment	No statement	Eyelash reflex is used to assess level of sedation	No statement		Severity of suffering: assessed by verbal complaints, facial expressions, body movements Level of consciousness: assessed by response to verbal and physical stimulations in ordinal nursing care. Diagnostic pain stimulation is unnecessary for the assessment of the consciousness level

	Guideline/Author/Year of Publication				
Recommendation Regarding	Dutch Guideline, Legemaate et al[9]	International Guideline, De Graeff and Dean[1]	EAPC Framework, Cherny and Radbruch[3]	NHPCO Statement, Kirk and Mahon[13]	Canadian Framework, Dean et al[4]
Titration	Degree of symptom control, not level of consciousness, determines dose and combinations of sedatives and duration of treatment	Individual titration of the dose of the sedative to the relief of the symptom and the distress it causes (proportionality) The initial dose of sedatives should usually be small enough to maintain the patients' ability to communicate periodically. Subsequent dose titration proportionate to the patients' needs.	Gradual increase or reduction of doses of medications to a level at which suffering is palliated with a minimum suppression of the consciousness levels and undesirable effects Because downward titration of drug doses places the patient at risk for recurrent distress, in most instances it is not recommended even as the patient approaches death.	Titration to the minimum level of consciousness reduction necessary to render symptoms tolerable	Careful titration to adequate relief of suffering. Lowering of the level of consciousness only as far as necessary to relieve the suffering.
Opioids	Use of morphine to achieve loss of consciousness is bad practice. Morphine should only be given or continued to relieve pain and/or dyspnea	Opioids should not be used for the purpose of sedation	In most cases opioids should be continued, possibly with dose modification, unless adverse effects or signs of overdose are observed	No statement	Opioids are a poor choice for PST because deep sedation will occur only when toxic doses are used, risking neuroexcitatory effects and respiratory depression leading to hastened death. When appropriate opioids may continue to be administered to a patient receiving PST.
Monitoring/outcome parameters	Assessment of effect of sedation must be recorded in the file.	Effect of PST on the patients' comfort should be assessed: Distress and sedation levels, adverse effects of sedation and needs of the family	Severity of suffering, level of consciousness and adverse effects related to sedation When sedation is intended to be short term, intermittent or light: level of sedation and routine physiological parameters such as heart rate, blood pressure and oxygen saturation	Considerations of effectiveness and safety (…) are essential	1. Patient should be monitored for: a. Relief of suffering b. Level of consciousness (depth of sedation) c. Potential adverse effects of sedation 2. Family and health care professionals should be monitored for: a. Psychological distress b. Spiritual distress
Monitoring/time and evaluator	No statement other than: The treating physician should visit the patient at least once a day	Daily/health care team should determine the appropriate intervals for assessment: Outcomes should be evaluated by the patient (if possible), the family and the staff involved	Initially, assessment at least once every 20 minutes until adequate sedation is achieved, then at least three times a day	No statement	Little consensus in the literature, suggested every 20 minutes until adequate sedation has been achieved, then at least three times a day. The pharmacokinetics of the drug used for sedation should

(*Continued*)

Table 3
Continued

Recommendation Regarding	Guideline/Author/Year of Publication				
	Dutch Guideline, Legemaate et al[9]	International Guideline, De Graeff and Dean[1]	EAPC Framework, Cherny and Radbruch[3]	NHPCO Statement, Kirk and Mahon[13]	Canadian Framework, Dean et al[4]
					influence the frequency of monitoring. Frequency of monitoring will also vary based on the location of care, for example, home or institution.
Monitoring/methods of assessment	No statement	Examples of monitoring tools given: Edmonton Symptom Assessment Scale For communication level: Communication Capacity Scale For consciousness, motor activity and/or agitation: Ramsay Sedation Scale, Glasgow Coma Scale, Richmond Agitation-Sedation Scale, Sedation-Agitation Scale, Agitation Distress Scale, Motor Activity Assessment Scale These scales may be used, although their usefulness and appropriateness in palliatively sedated patients has not been proven For measuring consciousness: clinical assessment (somnolence vs. stupor vs. coma) sufficient in most cases	Consciousness: patient's response to stimuli, agitation or motor activity, and facial expression Pain and distress: e.g., critical-care pain observation tool, Richmond agitation sedation scale	Ongoing monitoring by clinicians who are experienced with these medications and palliative sedation	Presently, no particular scale can be recommended for monitoring. Monitoring should include patient comfort, so any scale devised for this patient population should have this orientation. To date no scales with proven usefulness in PST patients exist. Scales involving administration of painful stimuli are not acceptable within the palliative care context. Assessment of: a. Relief of suffering: verbal comments of the patient, facial expressions, body movements or posture b. Level of consciousness (depth of sedation): responses to verbal or nonpainful physical stimuli

PST = palliative sedation therapy.

practice and create uncertainty in this complex area of palliative care.

Limitations

One general limitation of this systematic review and comparative analysis is the inclusion of guidelines published only in journals listed in the indicated databases, leading to publication bias. Using this approach, we may have missed guidelines that have been explicitly developed within professional or regulatory organizations and rely on the Internet, membership, or white paper publication for dissemination and thus are not listed in the searched databases. Also, because of limited resources, we only evaluated published guidelines in English or German. We assume that other national guidelines have been published in other languages in national journals, which often are not included in the searched databases, and that many regional or local guidelines have not been published at all. However, we assume that guidelines not identified through our search strategy share relevant characteristics and problems with the identified guidelines, all of which have been developed by experienced clinicians and researchers and which, by the virtue of journal publication, can be expected to have an impact on clinical practice. A second limitation of this analysis is that we only used the version of the guidelines published in the identified articles. In some cases, there may be a more detailed version published elsewhere. To our knowledge, this is the case for the national "Dutch guideline," for which there is a more detailed and updated version (http://knmg.artsennet.nl/Publicaties/KNMGpublicatie-levenseinde/66978/Guideline-for-palliative-sedation-2009.htm). However, it was decided to analyze and compare only these published versions of the guidelines as these are widely accessible to practitioners and, therefore, are assumed to have a relevant impact on current practice. As another limitation, it should be mentioned that the presented information is based on the analyzed available guidance but not on original clinical studies. Finally, the analysis based on the findings remains largely descriptive, without providing judgments on appropriate PST in clinical practice. However, given the considerable lack of evidence regarding most aspects of the guidelines, as well as country-specific and cultural differences possibly relevant to PST, we believe that our approach can serve as a good starting point for identifying research priorities relevant to high-quality recommendations on PST.

Conclusion

The published guidelines on PST identified in this systematic review are of limited quality, measured against established criteria for guideline development. Moreover, the analyzed guidelines vary considerably with regard to aspects of drug dosing and monitoring, including the level of clarity of the provided recommendations. Given these findings and in light of the strengths and weaknesses of the individual guidelines, the comparative analysis provided here may serve as one starting point for the development of improved guidance on PST. As a result of the scarcity of evidence relevant to numerous recommendations of the PST guidelines, we suggest that clinical research on PST, including the assessment of effects of PST, should be a priority.

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