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Palliative Sedation Therapy in the Last Weeks of Life: A Literature Review and Recommendations for Standards

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ABSTRACT

Purpose: **Palliative sedation therapy (PST) is a controversial issue. There is a need for internationally accepted definitions and standards.**

Methods: **A systematic review of the literature was performed by an international panel of 29 palliative care experts. Draft papers were written on various topics concerning PST. This paper is a summary of the individual papers, written after two meetings and extensive e-mail discussions.**

Results: **PST is defined as the use of specific sedative medications to relieve intolerable suffering from refractory symptoms by a reduction in patient consciousness, using appropriate drugs carefully titrated to the cessation of symptoms. The initial dose of sedatives should usually be small enough to maintain the patients' ability to communicate periodically. The team looking after the patient should have enough expertise and experience to judge the symptom as refractory. Advice from palliative care specialists is strongly recommended before initiating PST. In the case of continuous and deep PST, the disease should be irreversible and advanced, with death expected within hours to days. Midazolam should be considered first-line choice. The decision whether or not to withhold or withdraw hydration should be discussed separately. Hydration should be offered only if it is considered likely that the benefit will outweigh the harm. PST is distinct from euthanasia because (1) it has the intent to provide symptom relief, (2) it is a proportionate intervention, and (3) the death of the patient is not a criterion for success. PST and its outcome should be carefully monitored and documented.**

Conclusion: **When other treatments fail to relieve suffering in the imminently dying patient, PST is a valid palliative care option.**

INTRODUCTION

SOME PATIENTS in their last weeks of life may experience severe uncontrolled symptoms despite optimal palliative care. In these circumstances, no effort should be spared to relieve unbearable suffering that may invade and dominate consciousness and leave no space for other things.[1] As a treatment of last resort, sedation of the patient may then be considered.[2] The available literature suggests that there are large differences between centers and countries with regard to the reported frequency of and indications for sedation.[3–14] Its use varies between countries[15,16] and may be increasing.[10]

As with all end-of-life decisions, the initiation

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of sedation may give rise to emotions and ethical dilemmas.[17–23] When sedation in the imminently dying is used inappropriately, it may even be labeled "slow euthanasia."[24–26] Clearly, there is a need for internationally accepted standards for sedation at the end of life.

There is a lack of systematic research on the use of sedation in the last phase of life. Scientifically sound research (in particular randomized studies) in patients receiving palliative sedation therapy is almost impossible as a result of methodological, practical, and ethical reasons. Therefore, guidelines on this topic will never be rigorously evidence-based.

There are a limited number of guidelines or recommendations for clinical practice.[22,27–37] Two of these were recently published as a national guideline,[32,35] some were developed at institution level by a specific task force[27,31,36] and others reflect the opinion and experience of the authors.[22,28–30,33,34,37]

The proposal to develop recommendations for sedation in the last phase of life was raised in 2002 during an Internet discussion on palliative medicine. An international group of palliative care clinicians from Europe (United Kingdom, The Netherlands, Belgium, France, Germany, Switzerland, Finland), Canada, the United States, Argentina, South Africa, Israel, Japan, Australia, and New Zealand, came together, led by the second author of this paper (M.D.). The aim was to develop internationally accepted definitions and recommendations based on the published literature.

These recommendations apply to patients with progressive and terminal disease with a life expectancy of days to maximally a few weeks. As the majority of the patients described in the literature and in clinical practice have cancer, the recommendations apply primarily to patients with cancer; however, many may be valid for patients with other terminal diseases as well.

METHODS

Procedure

The 29 members of the expert panel identified themselves on the basis of their clinical experience in palliative medicine and their interest in the topic of sedation. (A list of the additional panel members can be found in the Appendix at the end of this paper.) Working groups were formed to address the following issues: terminology and definitions, aims, indications and conditions, decision making and informed consent, cultural issues, drug selection/dosing/titration, types of sedation, nutrition/hydration, ethical issues and outcome/monitoring.

Each group of authors wrote a separate paper, based on a systematic literature review using databases such as MEDLINE, EMBASE, CINAHL, PsychINFO etc. Drafts were distributed to all members of the panel. The papers were revised, based on the comments returned, until everybody agreed with their content. The finalized papers are presently posted on the European Association for Palliative Care (EAPC) website and discussions are in progress for them to be expanded and published.

Members of the group convened at the meetings of the EAPC in The Hague in 2003 to plan the project and in Aachen in 2005 to discuss the papers and the dissemination of the resulting work.

This paper is a summary of the individual papers, written after extensive e-mail discussions among all panel members.

Grading the recommendations

The evidence for each recommendation was graded, based on the level of evidence of the published literature, using a system modified from the Center for Evidence Based Medicine Website (Table 1).[38,39]

RESULTS

Terminology and definitions

Recommendations:

1. Palliative sedation therapy (PST) is the use of specific sedative medications to relieve intolerable suffering from refractory symptoms by a reduction in patient consciousness (grade D).
2. Intolerable suffering is determined by a patient as a symptom or state that he or she does not wish to endure. If the patient cannot communicate, proxy judgment from family and/or caregivers is sought (grade D).
3. Refractory symptoms are symptoms for which all possible treatment has failed, or

Table 1. Classification of the Level of Evidence and Grading of the Strength of the Recommendations[a]

Levels of evidence
- I. Impact studies with low risk of bias or homogeneous meta-analyses
- II. Heterogeneous meta-analyses or confirmatory studies with a low risk of bias
- III. Exploratory studies with a low risk of bias
- IV. Any type of study with a high risk of bias, or investigative studies or nonanalytic studies
- V. Experts' opinion

Grading of the strength of the recommendations
- A. Consistent level I or II studies
- B. Consistent level III studies or one level II study
- C. One level III study or consistent level IV studies
- D. Level V evidence or inconsistent or inconclusive studies of any level

[a]Center for Evidence Based Medicine, Maltoni 2005.[38]

> it is estimated that no methods are available for palliation within the time frame and the risk-benefit ratio that the patient can tolerate (grade D).

A recent review found that of 13 studies on sedation for terminally ill patients only 6 clearly defined sedation.[40] The prevalence of patients requiring sedation varied widely among the studies because of different definitions. Sedation in palliative care has been named in various ways, for example, "sedation,"[12] "terminal sedation,"[22,41,42] "sedation for intractable distress in the imminently dying,"[43] "end-of-life sedation,"[44] "total sedation,"[11,45] "sedation in the terminal or final stages of life,"[10] "controlled sedation,"[46,47] "palliative sedation,"[27,48] and "palliative sedation therapy."[49–51]

Although the term terminal sedation is most often used in the literature,[22] this does not convey the important aim of the treatment, i.e. symptom palliation, and it risks being interpreted as an intention to terminate the patient's life. Sedation is an option for symptom control, and is not euthanasia.[52]

The panel found only five major articles addressing the definitions of sedation in palliative care.[32,41,49–51] The panel prefers the term palliative sedation therapy (PST), because this describes the sedation procedure as a therapy. The term is also compatible with the present MeSH subject headings concerning palliative care. For the purpose of this paper, it is defined as "the use of sedative medications to relieve intolerable suffering from refractory symptoms by a reduction in patient consciousness." This definition makes the aim of the treatment (relief of intolerable suffering resulting from refractory symptoms) and the nature of the procedure (use of specific sedative medications to reduce consciousness) explicit. The degree of sedation necessary to relieve suffering may vary from superficial to deep.

Suffering and distress are subjective criteria, so only the patients can determine the suffering to be intolerable.[26,28] Therefore, the panel believes that it is reasonable that when patients express a certain degree of symptom distress, they themselves should indicate whether the suffering is severe enough for treatment by sedation to be considered. If the patient is unable to express his or her degree of discomfort and/or suffering, a proxy judgment by family members and/or caregivers should be sought. The health care team should be confident that the proxy expresses the (presumed) wishes of the patient and not his or her own.

Refractory symptoms have been defined in various ways, for example, as symptoms for which "all other possible treatments have failed"[41] or for which "palliative care is available but can not adequately relieve suffering."[22] However, the panel recommends Cherny's definition of refractory symptoms as "symptoms for which all possible treatment has failed, or it is estimated that no methods are available for palliation within the time frame and the risk-benefit ratio that the patient can tolerate"[28] as this definition can readily be used in clinical practice.

Many of the drugs used in palliative care for the relief of symptoms may result in sedation as a secondary or side effect. A reduction in the patient's level of consciousness may be a temporary phenomenon and, in most cases, not intended, although it may be beneficial in a restless patient. For the purpose of this paper, we do not regard this as PST.

Aim of PST

Recommendation:

4. The aim of PST is to adequately relieve refractory symptoms, unbearable to the patient, by means of appropriate sedative drugs carefully titrated to the cessation of symptoms. The physician should regularly review the patient's condition and continue to search for non-sedating alternatives (grade D).

The aim of PST is the relief of suffering and not the shortening of life.[5,22,23,37,41,42,48,49,51,53–56] Lack of clarity and consensus regarding the intent of PST is a cause for concern and highlights the need for further research.[16,49,51,54,57] The intention of PST can be assessed by the proportionality or adequacy of the action.[48] In PST the combination and amount of drugs used will be sufficient, but not more than is needed, to alleviate distress by reducing the level of consciousness. Intent may be judged by looking at the drug record. Repeated doses, titrated to ease an individual's distress, are the mark of proportionate sedation. Single large doses are the mark of ignorance or intentional harm.

Viewing sedation (rather than the relief of symptoms) as the desired outcome may discourage regular review and consideration of alternatives. Good palliative care requires regular review of each patient, and this is especially true when a patient is sedated. Other problems may arise that could require a different approach. The physician should continue to search for nonsedating alternatives.

Indications and conditions

Recommendations:

5. PST may be considered for refractory symptoms. This implies that the team looking after the patient has enough expertise and experience to judge the symptom as refractory and that there is consensus on this subject. Advice from specialists in palliative care or, if not available, more experienced colleagues is strongly recommended (grade D).
6. In the case of continuous deep PST, the disease should be irreversible and advanced, with death expected within hours to days (grade D).

Without exception, all papers dealing with PST specify the existence of refractory physical and/or psychological symptoms as a prerequisite for PST. A symptom is regarded as being refractory (as opposed to difficult to treat) when the clinician perceives that further invasive or noninvasive interventions are (1) incapable of providing adequate relief, (2) associated with excessive and intolerable acute or chronic morbidity, and/or (3) unlikely to provide relief within a tolerable time frame.[28] This implies a rigorous diagnostic approach, paying attention to the physical, psychological, social, and emotional dimensions of the symptom.[5,43,58] It also implies that all available symptom-targeted medications, procedures, or interventions attempted have been ineffective or produced unacceptable side effects, or, if considered, were ruled out as too burdensome or risky for the patient, or have been refused by the patient.

Additional factors may influence the determination of refractoriness, such as emotional fatigue of carer and family[12,28] and the values and preferences of professional caregivers[11,59–63] and patients.[64–66]

Several studies indicate widely varying practices of PST among physicians, based on personal factors, for example, philosophy about a good death, beliefs about the effect of PST on survival, medical practice, experience, religious practice, and levels of burnout.[8,11,12,61,67–69]

If a physician is unable to relieve a distressing symptom he/she may feel pressured to use PST, or even disproportionate sedation. There is some evidence that fatigue and burnout of physicians results in increased use of PST.[60,61] The perceived imminence of a patient's death may influence the doctor to prescribe sedation rather than look for alternatives. Other concerns include the wide variation in the reported use of sedation,[49] the proportion of symptoms that are labeled as refractory[70] and the use of PST in a patient who is incapable of making his or her wishes known.[71]

Refractoriness has a temporal component, from both the patient's and the system's perspective. The practice of intermittent or temporary sedation recognizes that either a symptom might respond to continued or future therapy,[7,28,66] or that the patient's ability to tolerate the symptom may be improved following the rest and stress reduction provided by sedation.[19,28] Furthermore, the relative availability

of interventions influences the determination of refractoriness.[19]

Consultation, whether local or distant, may supplement the expertise of the primary carer or team.[72–74] Transfer to a more expert setting, e.g. a palliative care unit, should be considered if deemed appropriate and feasible, and if desired by the patient.

The panel found 22 case series (totaling 936 patients) that described the symptoms occurring in the last days to weeks of life necessitating PST.[3,4–7,10,12,14,55,75–87] In these studies, the most frequent reasons for PST were delirium and/or terminal restlessness not responding to adequate treatment with haloperidol or other drugs (55%). Other reasons were dyspnea (27%), pain (18%), and nausea/vomiting (4%).

Psychological and existential distress as an indication for PST is a controversial issue.[18,19,29,47,55,59,62,64,66,88–92] The panel believes that PST for psychological or existential distress should be initiated only under exceptional circumstances and only after consultations with experts in this area.

Psychological and existential issues may also influence suffering caused by refractory physical symptoms since in the concept of "total" pain (or any other physical symptom) psychological or existential distress may amplify a physical symptom.[93–95] The opinion of the panel is that the patient must have received skilled multidimensional management directed at the physical, psychological and existential dimensions of the symptom before a symptom is considered to be refractory.[27,43,96]

Furthermore, emergency sedation may be considered for catastrophic events such as massive bleeding or asphyxia caused by airway obstruction.

The percentage of patients requiring PST for refractory symptoms varies hugely (from 3% to 68%) as do the indications for PST (e.g., 14 to 91% for delirium, 0% to 63% for dyspnea and 3% to 49% for pain).[3–14,97] These differences may be caused by differences in terminology, selection of patients (in particular with regard to diagnosis and life expectancy), differences in management and/or regional, international or cultural differences.

The panel found 10 guidelines or recommendations for clinical practice for the use of PST.[22,27–37] These used the following indications and conditions:

- The presence of intractable/refractory physical or mental symptoms. [22,27–37]
- Consensus of the (multidisciplinary) palliative care team as to the refractoriness of the symptom based on a state-of-the-art multidimensional assessment[32,35] and, in difficult cases, reached through a case conference.[29,32] If necessary, a palliative care or other expert (e.g. a pain specialist or a psychiatrist) should be consulted.[27,29,31–33,35–37]
- In the case of continuous and deep PST, the disease should be irreversible and far advanced, usually with death expected within hours to days.[27,30,32,35–37]

Decision-making and informed consent

Recommendation:

7. A systematic and inclusive process should be used, actively involving the patient (when possible and appropriate) or the designated surrogate decision maker and/or family as well as all members of the team that is providing care for the patient to determine:
   a) whether the symptoms are truly refractory
   b) whether to use sedation for refractory symptoms
   c) how sedation will be implemented and by whom
   d) how the patient will be monitored
   e) what criteria will be used to assess efficacy, safety and the need to adjust therapy
   f) whether to continue or discontinue concurrent therapies, in particular nutrition, fluids and medication (grade D)

To intentionally reduce patient awareness, even consensually, is a decision requiring careful consideration. Sedation may mean that completing the tasks of life's end are short-circuited or prevented. Initiating PST may lead to strong emotional reactions, not only of the patient and his family, but also of the professional caregivers involved.[98]

The reported degree of involvement of, and information given to patients and families varies considerably[7,9,41,78,99] and the distress of the family members may be high.[65,100]

Several of the published guidelines or recommendations for clinical practice state specifically that PST should be consistent with the patient's wishes and be discussed with the patient (if pos-

sible) and/or his family[22,27,30,32,33,35–37] and that it should be made clear to the patient and/or his family that the aim of PST is to alleviate symptoms and not to hasten death.[29–32,35–37] Such an explanation clearly distinguishes PST from physician assisted death.[16,31,58,65,69]

In emergency situations PST may have to be initiated immediately, without having the opportunity to discuss it with the family or the team. Anticipated emergencies that might necessitate sedation should be managed proactively by discussion with patients, family members and the multidisciplinary team. A management plan should be agreed upon, which may include the use of PST.

Despite a relative lack of com-prehensive discussions of decision-making in PST in the palliative care literature, the following approach can be extrapolated from the literature on sedation for refractory symptoms[7,8,10,20,21,28,41,57,58,78,91,101–104] and from related literature on decision-making in advanced illness or at the end of life.[105–113] A systematic and inclusive process should be used for determining whether to use sedation for refractory symptoms and how sedation is to be used:

1. Actively involve the patient (when possible and appropriate) or the designated surrogate decision maker (where legally recognized) and/or family in the decision-making process:
   a. Elicit the patient's values, beliefs, and goals.
   b. Determine his or her preferences for receiving information and for the degree of direct involvement in making the decision.
   c. If the patient is unable to participate, refer to previous discussions or documentation that suggests the patient's values, wishes, or directives.
   d. Discuss with the patient and/or the family the fact that there is no chance of recovery and life expectancy is very limited.
   e. Discuss the therapeutic options, including potential benefits and risks, and the possibility of intermittent or temporary sedation.
   f. Discuss the issue of (withholding, discontinuing or continuing) nutrition and/or hydration.
   g. Make clear the intent of the interventions (comfort and symptom management, not hastening of death).
   h. Facilitate patient-family discussion.
   i. If appropriate, clarify the difference between decisions based on known wishes, values or goals as previously stated by the patient and acting in the patient's (presumed) best interest if these wishes, values and goals are unknown.
   j. Obtain verbal consent after (if possible) providing some time (if circumstances allow) for the patient and/or the family to process the information provided.
   k. Provide support to family members who are finding it difficult to make critical decisions for a loved one.
2. Involve all members of the team that is providing care for the patient:
   a. Agree on the goals of care and on proportionality of PST.
   b. Actively elicit both practical and ethical/moral concerns of the team about the use of sedation in this case.
   c. Tailor the specific sedating intervention to the patient's (and/or family's) values and clinical needs with regard to clinical goal of care, sedative agent(s) used, depth of sedation intended and type of sedation (continuous versus intermittent).
3. Consider the needs of all by, whenever possible, coordinating the timing of the implementation of sedation with patient, family, and care team.
4. Prospectively determine how to proceed after the initiation of sedation:
   a. Monitoring of the patient with regard to effectiveness and safety of PST.
   b. Adjustment of therapy to ensure that the therapeutic goal is met and maintained.
   c. If sedation is to be intermittent, prospectively determine the schedule for reducing the sedation level, as well as what assessments and interventions are planned during the period of wakefulness.
5. Prospectively determine and decide on concurrent therapies (in particular hydration and concurrent medication).

Cultural issues

Recommendation:

8. Health professionals must have a strong sense of their own cultural identity (including the culture of their professional role and place of work) and be aware that there are many variations in attitudes to sedation at the end of life, which may differ significantly from those of the dominant culture. All staff should develop

the skills to recognize potential variations, to elicit information, to understand and to accept the patient's viewpoint, and to act creatively to meet the needs of the patient and their family (grade D).

Culture is the prism through which we view the world. Cultural perspectives will therefore have a major effect on attitudes to sedation at the end of life—for patients, families and health professionals.

Culture is a "living, dynamic, changing, flexible system of values and world views by which people live, a system by which they define identities and negotiate their lives"[114] and may be applied to an individual, a family, a community, an institution, or any group of people who share a common characteristic such as age, gender, job, disability, place of residence or religious beliefs. It does not necessarily equate with race (which is purely physical) or ethnicity (which includes a psychological sense of belonging). Culture must therefore be viewed in context, as multiple factors may influence the individual or group in a given circumstance.

The use of sedation at the end of life may be influenced by the cultural background of both patient and staff. In a prospective study, large differences in rates of sedation and in indications for PST were found between hospices in Israel, Spain, and South Africa, which may be attributed to cultural differences.[5] There are considerable differences between countries and cultures in the attitudes of physicians with regard to patient involvement in decision making and in preferences of patients and families to be involved in this process.[40,60,115]

There is a paucity of literature about cultural aspects of PST. Purnell[116] has postulated a model of cultural competence that may provide a framework for the determination of patient and family attitudes to palliative sedation. Important aspects of this model include:

- Communication (including discussion of diagnosis and prognosis);
- The role of the family in decision making[117];
- Spiritual beliefs and practices (which may preclude PST)[90];
- Health care practices (preferences for traditional remedies and/or refusal of medication, availability of medications[118];
- Perception by the patient of health care practitioners (determining the role of the physician); and
- Death rituals and preferred place of death.[119]

In order to recognize and acknowledge differences in perspectives toward sedation at the end of life, health professionals must have a strong sense of their own cultural identity, including that of their professional role and place of work. Age, gender, religious or spiritual beliefs, and ethnicity are as significant for health professionals as they are for patients, within the context of the dominant culture. Health care professionals must have a sufficiently broad and open-minded attitude to enable them to forego ethnocentricity—the perception that their own culture, beliefs and values are superior—in order to accept the explanatory models of their patients, and to work within those models.

The interpretation of intolerable physical or emotional distress as an indication for sedation at the end of life might be a perspective specific to some health professionals, and not necessarily shared by patients, families, or other professionals, such as chaplains or others providing spiritual guidance who may have a different view of such distress. This emphasizes the importance of advance communication between health care and other professionals, patients, and families in order to make decisions based on patient preferences rather than the physician's own values.[120]

Types of sedation

Recommendation:

9. If PST is initiated, the initial dose of sedatives should usually be small enough to maintain the patients' ability to communicate periodically. During those periods the indication and efficacy of PST can be (re)assessed, based on judgment by the patient himself. Subsequent dose titration is then proportionate to the patients' needs. Only under exceptional circumstances is deep and continuous sedation required from the initiation of PST (grade D).

Three levels of sedation may be distinguished[32,50,51]:

- Mild (somnolence): the patient is awake, but the level of consciousness is lowered.

- Intermediate (stupor): the patient is asleep but can be woken to communicate briefly.
- Deep (coma): the patient is unconscious and unresponsive.

Regardless of the depth of sedation, sedatives may be administered intermittently (providing some periods when the patient is alert) or continuously (with no intent to discontinue sedation).[50,51]

Discussion about the levels and timing of sedation should consider the following:

- How feasible is mild or intermittent sedation?—In palliative settings, the general state of the patient, the dying process, and the technical training of the carers may make such management difficult to achieve.[28,29] Progression of the disease itself may lead to unconsciousness or even death during attempts at mild or intermittent sedation.
- How deep must the sedation be to relieve suffering?
- How important is it for patients, and their families, to maintain a certain level of consciousness?[7,99,115]
- Will sedation lead to loss of dignity?—Consciousness is a fundamental part of being alive, so its deliberate reduction by intermediate or deep sedation could be difficult to be seen as a positive action and might lead to a perception of loss of dignity.[121,122] PST has been criticized for inducing 'social death' as the patient is no longer able to interact with his environment and family and carers might begin to treat him as if he had already died. However, in two clinical surveys sedation was not considered as altering the patient's[123] or the professional carers'[124] perception of dignity.
- What are the consequences of altering consciousness?—A brief episode of sedation requires a brief therapeutic action and leaves the patient the choice of further sedation. Moreover, reassessment of the indication for PST and of its efficacy remains possible, based on the judgment and preference of the patient himself. In contrast, judgment and preference cannot be obtained from a deeply sedated patient. If prolonged deep sedation is initiated, then the generally proposed option is to wake the patient from time to time (the exact period of time is not specified) in order to verify indication and agreement.[125] Some authors prefer that such "awakenings" should be planned instead of being performed "just to see where we are",[28,37] but other authors mention the risk of disrupting a fragile steady state that could be difficult to achieve again.[29,81,37]

The panel regards the maintenance of communication and thereby the possibility of (re)assessment of the indication and efficacy of PST as an important advantage of mild/intermediate and/or intermittent sedation. However, preferences of the patient should also be considered and attempts at mild and/or intermittent sedation may fail because of progression of the disease leading to irreversible loss of consciousness. Continuous deep sedation is usually only necessary after failure of mild/intermediate and/or intermittent sedation to relieve suffering. Only under exceptional circumstances will continuous deep sedation be required from the initiation of PST.

Drug selection, dosing, and titration

Recommendations:

10. Benzodiazepines (in particular midazolam) should be considered first-line choice in the absence of delirium. They may be administered subcutaneously or intravenously, in single dose or continuous infusion (grade C).
11. Sedation for delirium should only be considered after adequate treatment with haloperidol or other antipsychotics. In refractory cases treatment with midazolam + haloperidol or levomepromazine should be considered. For severe agitation unresponsive to these sedatives phenobarbital and propofol have been used. Prior failure of one sedative does not prevent response to another one (grade C).
12. The dose of sedative should be individually titrated to the relief of the symptom and the distress it causes (proportionality). Only rarely is 'sudden' sedation necessary, e.g. for massive haemorrhage (grade D).

The drugs used for PST can be classified as:

- Anxiolytic sedatives, e.g. midazolam, lorazepam;
- Sedating antipsychotics (neuroleptics), e.g. levomepromazine (North America: methotrimeprazine);

- Barbiturates, e.g. Phenobarbital; or
- General anaesthetics, e.g. propofol.

Fifteen studies provided the broadest information regarding the use of sedatives in the care of patients with cancer in the final stages of life.[4–7,10,12–14,78–80,82,84,124,126] Other studies reporting on the selective use of a particular sedative have been used to gather information on doses used.[41,43,75–77,81,83,127–137] Drugs used vary between settings and countries, but a benzodiazepine, generally midazolam, was the most frequently used sedative, reported in approximately two thirds of all studies.[42–56] There are no studies comparing midazolam to other drugs. However, midazolam has several advantages. It has a short half-life, it may be administered parenterally, it has few undesirable side-effects, and it is not only a sedative, but it also has anxiolytic, antiepileptic and muscle relaxant properties. The most commonly used antipsychotic drug used with the purpose of sedation is levomepromazine, often given in conjunction with benzodiazepines.

Phenobarbital[13,41,42,81,136,137] and propofol[43,131,133,134] are used relatively infrequently, often as sedative drugs of last resort. Opioids rarely feature as sedatives.[78] Many consider opioids inefficient sedatives, with sedation occurring at doses that may be associated with undesirable effects; moreover, even high doses of opioids may fail to induce sedation. The panel strongly feels that opioids should not be used for the purpose of sedation.

Table 2 summarizes doses of the more frequently used sedatives administered in the last 48 hours of life. Tolerance to midazolam, related to younger age and prolonged administration has been described, resulting in the need for increasingly higher dosages.[13,85,132,135,138]

Nutrition and hydration

Recommendations:

13. The ethical aspects of sedation are separate and distinct from the ethical aspects of hydration; thus, the decision whether or not to withhold or withdraw nutrition and/or hydration should be discussed separately from the decision to initiate PST (grade D).
14. Nutrition and fluids should not be offered to imminently dying patients unless it is considered likely that the benefit will outweigh the harm. In a deeply sedated patient who is imminently dying, parenteral fluids are unlikely to influence either symptom control or survival time. If the sedation is intended to be transient or if deep sedation is considered for a patient with a life expectancy of longer than a week, then hydration may be medically indicated (grade D).

Nutritional and fluid requirements change during the course of a terminal illness. The need for nutrition and hydration may change toward the end of life, when the predominant goal of care is to ensure comfort in the period leading to a peaceful death.

While there is an extensive literature about nutrition and fluid management in palliative patients with cancer, none of this relates specifically to sedated, imminently dying patients.

There is no evidence that artificial nutrition prolongs survival in dying patients, and in view of the associated risks, artificial nutrition should not routinely be offered to these patients. When sedation is proposed in patients who are receiving artificial feeding, it may be appropriate to recommend discontinuation.

Table 2. Mean, Median, and Range of Sedative Doses Used in the Final Forty-Eight Hours of Life (all mg/24 hrs)

Drug	*Mean dose*	*Median dose*	*Reported range*	*References*
Midazolam	22–70	30–45	3–1200	4–6, 41, 42, 75–77, 83, 126–130, 132, 135, 136
Levomepromazine	64	100	25–250	41, 42, 12, 13
Phenobarbital	—	800–1600	200–2500	41, 42, 81, 136, 137
Propofol	1100	500	400–9600	43, 131, 133, 134

Note: Mean, median, and range may be derived from different studies.

There is however a diversity of opinion about fluid administration. A systematic review of the literature on fluid status in the dying concluded that there was insufficient evidence to draw firm conclusions about either the beneficial or harmful effect of fluid administration to terminal patients.[139]

For reasons of clarity, the issue of sedation must be distinguished from the distinct and separate issues of hydration.[30,48] The discontinuation of hydration is not a typical or essential element to the administration of sedation in the management of refractory symptoms at the end of life. Ethically, the withdrawal of death deferring treatments in the dying remains, for some, controversial.[140] Opinions and practices vary. This variability reflects the heterogeneity of attitudes of the involved clinicians, ethicists, the patient, family and local norms of good clinical and ethical practice.[41]

Many of the review and opinion papers discuss the perceived pros and/or cons of giving or withholding fluids in terminal patients.[141–151]

Those arguing against the use of fluids in the dying patient who is unable to drink have proposed that fluid depletion in the dying patient may be beneficial as it may result in:

- A reduction in pulmonary, salivary or gastrointestinal secretions with a consequent reduction in certain symptoms (e.g., cough, vomiting) and less need for interventions to manage symptoms (e.g., suctioning).
- A reduction in urinary output, hence less incontinence and less need for indwelling urinary catheters.
- Less peritumor edema with possible consequential pain reduction.
- Less edema and ascites with fewer associated symptoms.

Proponents of withholding artificial fluid therapy suggest that dry mouth and thirst can be adequately managed with sips of fluid and good mouth care. Several studies suggest that thirst correlates poorly with fluid intake.[152–156]

Arguments for fluid therapy include a decreased risk of the following symptoms in hydrated patients:

- Delirium, or opioid toxicity, especially if renal failure develops.[146,157,158] However, two randomized studies did not show an influence of hydration on the occurrence of delirium.[153,159]
- Sedation and myoclonus.[159]
- Constipation, pressure sores, and dry mouth.

The psychological, ethical, cultural and/or legal implications of fluid and nutrition management in palliative patients should also be considered.[160–162]

After weighing the (very limited) evidence and the arguments in the literature, the panel feels that neither nutrition nor hydration is physiologically relevant in the sedated patient if death is imminent. However, account should also be taken of cultural preferences and styles of decision-making. Although the provision of nutrition and fluids may be medically futile, there may be cultural and psychological benefits. If sedation is intended to be transient, hydration may be medically indicated.

One of the most difficult situations is where deep, permanent sedation is given to a patient who is expected to survive for more than one week. Some would argue that, in this situation, dehydration may hasten death. Others would argue that giving fluids would neither prevent death, nor make it more comfortable, but merely prolong the dying process. There is no evidence to support either view.

Ethical aspects

Recommendation:

15. The decision to offer sedation to relieve intolerable suffering during the last weeks of life presents no distinct ethical problem, provided that there is no intention to hasten death. It is distinct from euthanasia because (a) it has the intent to provide symptom relief, (b) it is a proportionate intervention and (c) the death of the patient is not a criterion for the success of the treatment (grade D).

In patients with advanced cancer and other terminal illnesses, a readiness to address pain and other intolerable symptoms is a medical and moral imperative.[163] There is a broad ethical consensus that at the end of life, the provision of adequate relief of symptoms is an overriding goal, which must be pursued even in the setting of a narrow therapeutic index for the necessary palliative treatments.[163–167]

In this clinical context, the decision to offer the use of sedation to relieve intolerable suffering of

terminally ill patients presents no distinct ethical problem.[168,169] Rather, the decision making and application of this therapeutic option represents a continuum of good clinical practice, which is based on a careful patient evaluation that incorporates assessment of current goals of care.

Because all medical treatments involve risks and benefits, each potential option must be evaluated for its potential to achieve the goals of care. Where risks of treatment are involved, the risks must be proportionate to the gravity of the clinical indication. In these deliberations, clinician considerations are guided by an understanding of the goals of care and must be within accepted medical guidelines of beneficence and nonmalficence. The decision to act on these considerations depends on informed consent or an advance directive from the patient.

The use of sedation for the relief of symptoms at the end of life is open to abuse. There are data from several countries indicating that administration of sedating medication, ostensibly to relieve distress, but with the manifest intent of hastening death, is commonplace.[16,170–173] These practices represent a deviation from normative ethical clinical practice and may accurately be described as "slow euthanasia."[24–26] Such practices may be recognized by the use of large and sometimes single doses of sedatives, no attempt at titration (so that regardless of the level of distress the patient is rendered comatose), and infrequent or absent monitoring.

Sedation in the management of refractory symptoms is distinct from euthanasia because: (1) the intent of the intervention is to provide symptom relief; (2) the intervention is proportionate to the symptom, its severity and the prevailing goals of care; and (3) finally and most importantly, the death of the patient is not a criterion for the success of the treatment.[52]

Despite this distinction, some critics of the use of sedation argue that the practice is morally equivalent to euthanasia. The essential core of this argument is that if both sedation for the management of refractory symptoms at the end of life and euthanasia aim to relieve suffering and end with the death of the patient, then they are morally equivalent.[175] Some argue that the discontinuation of nutrition and hydration in association with sedation for the management of refractory symptoms is tantamount to "slow euthanasia" by starvation and dehydration.[142,176–178] This is argued both by opponents to euthanasia, who are concerned about maleficent aspects of the practice of forgoing nutrition and, in particular, hydration,[142,176–179] and also by proponents of elective death who argue that if these acts are morally equivalent, then the more rapid mode of elective death is more humane and dignified.[22,180]

The Principle of Double Effect is sometimes used as an ethical justification for the use of PST. Briefly, this principle states that when a contemplated action (in this case sedation) has a good (relief of suffering) and a bad (possible foreshortening of life) effect it is permissible if (1) the action is either morally good or is morally neutral, (2) the foreseen yet undesired untoward result is not directly intended, (3) the good effect is not a direct result of the foreseen untoward effect, (4) the good effect is "proportionate to" the untoward effect, and (5) there is no other way to achieve the desired ends without the untoward effect. However, this principle does not apply to the use of proportional sedation in the management of refractory symptoms during the last weeks of life because the death of the patient at the end of a long and difficult terminal illness is not necessarily untoward[13,21,180,181] and there is no evidence that proportionally administered sedation shortens life as several retrospective studies show no differences in survival between sedated and non-sedated patients.[6,10,12–14,56,78,97,126,182] The median survival of sedated patients in different case series is 1–4 days.[4–6,10,12–14,40,42,75,77–80,82,84] This is to be expected, because sedation is most often initiated in imminently dying patients. There is no reason to assume that (proportionally dosed) sedatives shorten life in imminently dying patients.

Outcomes and monitoring

Recommendations:

16. The effect of PST on the patients' comfort should be assessed daily. Attention should be paid to distress and sedation levels, adverse effects of sedation and also the needs of the family. PST and support of the family should be modified as deemed necessary (grade D).
17. The indication, aim, type and dose of sedatives and outcomes of PST should be carefully documented (grade D).

Sedation for symptom management at the end of life should, like any other symptom-control

measure, be regularly reviewed to assess symptom control and to adjust treatment. The desired outcome of PST is symptom relief and a peaceful, quiet death by the natural course of the disease. Unexpected and/or undesired outcomes include poor control of symptoms and distress, overdosage of sedatives leading to an unnecessarily low level of consciousness, adverse effects of PST (e.g., pressure effects, respiratory or circulatory depression),[85] prolonged sedation unrelated to the alleviation of symptoms, and hastening of death. The health care team should determine the appropriate intervals for the assessment of the effect of PST.

Monitoring of patients sedated for symptom control at the end of life is an under-researched area. Some studies have been carried out on procedure-related sedation,[183] or sedation in the ICU,[184] but their findings may not be relevant to palliative care.

As the aim of PST is to relieve distress, then comfort, rather than vital signs, should be monitored. Monitoring and care will depend upon the level of consciousness. Attention should be paid to distress and sedation levels, adverse effects of sedation and the needs of the family.[7,65,98] Monitoring tools (e.g., the Edmonton Symptom Assessment Scale[185] and scales measuring communication level (Communication Capacity Scale[85,186]), consciousness, motor activity and/or agitation, such as the Ramsay Sedation Scale,[187] the Glasgow Coma Scale,[188] the Richmond Agitation-Sedation Scale,[189] the Sedation-Agitation Scale,[190] the Agitation Distress Scale[85,186] or the Motor Activity Assessment Scale[191] may be used, although their usefulness and appropriateness in palliatively sedated patients has not been proven. There is a clear need for research in this area. For measuring consciousness, clinical assessment (somnolence versus stupor versus coma) may be sufficient in most cases.

Outcomes should be evaluated by the patient (if possible), the family and the staff involved.

The effectiveness of PST has been poorly studied. A number of studies mention "improvement," "success," or "good relief" in 90%–100% of cases, without specifying how the effect was measured.[41,42,75,76,81,87] Only two prospective studies systematically used outcome measures. The first study reported partial relief in 2 of 20 and complete relief in 18 of 20 patients with terminal restlessness and dyspnea.[82] A recent Japanese study in 102 patients, mostly sedated with midazolam, reported adequate symptom relief in 83% of cases.[85]

The complete process of PST should be carefully documented in terms of indication, aim, types and dosages of drugs used, depth of sedation achieved, type and duration of sedation, relief of distress achieved and satisfaction of patient, family and staff.

DISCUSSION

When other treatments fail to relieve suffering in the imminently dying patient, PST is a valid palliative care option. Unfortunately, its practice is open to misuse or even abuse. There is a clear need for recommendations based on available evidence and/or experience of health care professionals who deal daily with dying patients.

Although a small number of guidelines or recommendations for clinical practice have been published, [22,27–37] this is the first paper offering internationally based recommendations for clinical practice, based on extensive literature reviews, by authors from all over the world.

The issue of PST is a controversial subject and writing this paper provoked extensive and intense discussions between the contributors. Despite this, it has proven to be possible to come to an international consensus.

From the literature reviews, it is apparent that there is a significant lack of research in this area. Most studies are retrospective and descriptive, in selected groups of predominantly hospice-based patients. As a result, almost all of the recommendations are based on level IV or level V evidence. It is unlikely that stronger evidence in this area is going to be available soon; for ethical and practical reasons randomized studies will be nearly impossible to perform.

The indication for PST is intolerable suffering caused by refractory symptoms, often delirium, dyspnea or pain. Determining symptom refractoriness and intolerable suffering requires a full multidimensional assessment of the symptom(s) and expertise of the professional caregivers involved. Consultation with palliative care experts is advisable if not mandatory. PST requires a careful process of decision-making, in which emotions, preferences and wishes, not only of the patients and their families, but also of the members of the health care team are carefully assessed. In some circumstance the ability to communicate may be more im-

portant than complete relief of distress. Cultural factors may play an important role.

The aim of PST is to relieve the distress of the patient; this frequently does not require reduction of consciousness to a level where communication is no longer possible. Thus, the dose of the sedatives is titrated against the relief of suffering (proportionality), emphasizing the importance of adequate monitoring of the effect of PST. Deep and continuous sedation is usually only necessary after failure of mild/intermediate and/or temporary sedation to relieve suffering and should therefore be the exception rather than the rule.

PST is an unusual and extraordinary intervention that requires medical and nursing expertise and communicative skills of the various professional caregivers involved.

Benzodiazepines are the sedatives of first choice. The use of midazolam is widespread and has proven to be safe, but there is little systematic research giving evidence for its efficacy.[85] Levomepromazine is used less often and other sedatives like phenobarbital or propofol are rarely necessary.

The issue of nutrition and hydration should be carefully considered when initiating PST. There is broad agreement that nutrition is ineffective and irrelevant in these patients but hydration is a more controversial issue. Generally, there are few medical arguments for giving parenteral hydration when sedation is initiated in the imminently dying patient who is already unable to take fluids himself, but other (emotional or cultural) considerations may play a role. The ethical aspects of hydration should be considered separately from those of PST itself.

Retrospective studies strongly suggest that appropriately used PST does not shorten life.[6,10,12–14,56,78,97,126,182] The decision to offer the use of sedation to relieve intolerable suffering of terminally ill patients presents no distinct ethical problem and should be regarded as acceptable medical practice.

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APPENDIX

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