

Review Article

Palliative Sedation: A Review of the Research Literature

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Abstract

The overall aim of this paper is to systematically review the following important aspects of palliative sedation: prevalence, indications, survival, medication, food and fluid intake, decision making, attitudes of physicians, family experiences, and efficacy and safety. A thorough search of different databases was conducted for pertinent research articles published from 1966 to June 2007. The following keywords were used: end of life, sedation, terminal sedation, palliative sedation, refractory symptoms, and palliative care. Language of the articles was limited to English, French, German, and Dutch. Papers reporting solely on the sedatives used in palliative care, without explicitly reporting the prevalence or intensity of sedation, and papers not reporting on primary research (such as reviews or theoretical articles) were excluded. Methodological quality was assessed according to the criteria of Hawker et al. (2002). The search yielded 130 articles, 33.8% of which were peer-reviewed empirical research studies. Thirty-three research papers and one thesis were included in this systematic review. This review reveals that there still are many inconsistencies with regard to the prevalence, the effect of sedation, food and fluid intake, the possible life-shortening effect, and the decision-making process. Further research to clarify all of this should be based on multicenter, prospective, longitudinal, and international studies that use a uniform definition of palliative sedation, and valid and reliable instruments. Only through such research will it be possible to resolve some of the important ethical issues related to palliative sedation. J Pain Symptom Manage 2008;36:310–333. © 2008 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words

Palliative sedation, review, terminal sedation, palliative care

This paper was funded by the Fund for Scientific Research, Belgium (G.0092.02).

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Accepted for publication: October 31, 2007.

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Introduction

Patients suffering from a terminal illness, with or without a malignancy, are often confronted with severe symptoms during the last phase of their lives.^{1,2} In the majority of cases, these symptoms can be controlled successfully.^{3–5} However, in some patients, symptoms remain uncontrollable.^{6,7} These refractory symptoms

0885-3924/08/\$—see front matter
doi:10.1016/j.jpainsymman.2007.10.004

may be physical or psychoexistential.^{8–10} Refractory symptoms differ from difficult or “difficult-to-treat” symptoms, because despite multiple efforts of clinical experts, they cannot be adequately treated without compromising the consciousness of the patient.^{8,10} They have a major negative effect on patient functioning and well-being,^{10,11} often increase as the patient approaches the end of life,¹² and interfere with a peaceful dying process. Palliative sedation has been placed in the foreground as one of the options of last resort when patients are confronted with refractory suffering.^{13–15} As such, palliative sedation is increasingly implemented by palliative care programs.^{16,17}

For more than 10 years, palliative sedation has been a much debated and controversial issue within and outside the field of palliative care. Some authors have described it as a form of slow euthanasia or mercy killing in disguise.^{16,18–21} According to these authors, palliative sedation is highly problematic and is associated with many important ethical questions. Despite a very extended theoretical discussion in the medical literature, most of these questions remain unanswered due to the lack of conceptual clarity, clear definitions and guidelines, and the huge number of contradictions in the international empirical literature on the subject.^{21–23}

In this paper, we systematically review the published empirical studies on palliative sedation. Since we introduced the term “palliative sedation” in 2000 to overcome the drawbacks of other terms, we chose to use this term in this article to label the practice of sedation in palliative care.^{24–26} In this review, we give an overview of the available results published in the medical literature with regard to the practice of palliative sedation. These results are critically reviewed in relation to the methodologies used to obtain them and the limitations confronted when doing research in a palliative care population. Suggestions for further research are also advanced.

Methods

Selection and Description of Included Studies

To retrieve the most relevant literature on palliative sedation, we conducted a thorough search of the following databases for pertinent research articles published from 1966 to June

2007: PubMed, Cancerlit, Cinahl, Cochrane, Libis (books), and Invert (Dutch articles). The following key words were used in different combinations: end of life, sedation, terminal sedation, palliative sedation, refractory symptoms, and palliative care. The search yielded a total of 134 articles, 35.8% of which were peer-reviewed empirical research studies and 23.13% of which were peer-reviewed theoretical articles (Table 1). We limited the language of the articles to English, French, German, and Dutch. Papers reporting solely on the sedatives used in palliative care, without explicitly reporting the prevalence or intensity of sedation, and papers not reporting on primary research—such as reviews or theoretical articles—were excluded for the purpose of our review. The methodological quality of the articles was assessed according to the criteria of Hawker et al.²⁷ (Table 2). Each part of the study was appraised as good, fair, poor, or very poor. This decision was taken according to the description of each level given in the paper by Hawker et al.²⁷

Based on the above-mentioned inclusion criteria, 36^{9,12,21,28–59,61} research papers and one doctoral dissertation¹⁰ were included. Of these 37, 19 described 14 separate retrospective studies (Table 3), eight^{28–30,36,38,41–43,58,59} of which were based on the reports of physicians. Eighteen of the 37 papers described prospective studies^{10,12,21,44–57,61} (Table 4).

The majority of the papers focused on a description of the practice of palliative sedation (prevalence, medication used, survival, decision making). Two papers, however, reported on the family’s experience with palliative sedation,^{39,40} six papers gave an overview of the attitudes of physicians toward palliative sedation,^{21,52,53,55–57} one paper evaluated the efficacy and safety of palliative sedation,⁴⁶ one paper evaluated the attitudes of the lay public on palliative sedation,⁵³ one paper compared the attitudes of the physicians with that of the lay public,⁵⁴ and one paper compared palliative sedation with euthanasia³⁰ (Tables 3 and 4).

Samples, Settings, and Definitions Used

Studies on the Practice of Palliative Sedation. The majority of the studies included in this systematic review discussed terminal cancer patients in palliative care units or hospices. Two studies reported on patients in a home care

Table 1
Study Type of the Articles

Study Type	n	%
Empirical study—peer reviewed	48	35.82
Theoretical paper—peer reviewed	31	23.13
Research paper—non-peer reviewed	0	0
Theoretical paper—non-peer reviewed	4	2.99
Professional document	0	0
Case study	14	10.44
Dissertation	1	0.75
Comment/editorial/letter	25	18.66
Review	9	6.72
Other	2	1.49
Total	134	100

Bold faced numbers represent the relative frequency, the percentage of the amount of articles versus the total amount of articles.

program^{12,51} and three studies reported on patients followed up by a palliative support team in acute care settings.^{10,31,45} Only one paper reported on patients in an acute care setting without the palliative support team being involved.⁴⁵ All samples were quite similar with regard to the mean age and the ratio of men to women. Samples differed, however, in the mean duration of stay, with a minimum of eight days and a maximum of 57.7 days. Almost all the studies provided descriptions or definitions of sedation. However, the terminology varied greatly (sedation, continuous deep sedation, total pharmacological sedation, palliative sedation, terminal sedation, controlled sedation [*our translation*]), as did the descriptions of sedation (Tables 3 and 4).

In studies in which physicians gathered information concerning palliative sedation,^{28–30,36,38,41–43} physicians were asked to indicate how many patients were sedated in the past year. Additionally, they had to answer a structured questionnaire so that detailed information could be gathered. In two studies, the questionnaires were sent to palliative care

experts all over the country.^{41,42} One study sent the questionnaire to palliative care experts from different countries,³⁸ and five studies sent their questionnaires to a random sample of physicians, selected by examination of death certificates.^{28–30,36,43} More information on sample size, response rates, countries, and methodology used can be found in Tables 2 and 3.

Studies Exploring the Attitudes of Physicians with Regard to Palliative Sedation. In our literature search, we identified seven papers^{21,52–57} that reported on physicians' attitudes about palliative sedation. Three papers focused on the attitudes of oncologists and palliative care experts in Japan⁵² and compared these, in a secondary analysis, with the opinion of the lay public.^{53,54} A fourth study examined the attitudes of internists in the USA,⁵⁶ a fifth study assessed the attitudes of physicians and pharmacists in Canada,⁵⁷ a sixth study surveyed the attitudes of all physicians that are members of the German Association of Palliative Care,⁵⁵ and a seventh study did a survey among medical ethics experts in Germany.²¹ The mean age of the respondents in these studies varied between 45 and 50 years. In four studies, the majority of the respondents were male, and data collection was based on self-developed questionnaires.^{21,52,55,56} In one study, the sample consisted of 49% male subjects and data collection was based on a critical appraisal of four clinical vignettes.⁵⁷ Five of seven studies^{52–56} defined palliative sedation, albeit in different ways. The sixth study purposefully omitted a formal definition to avoid bias and confusion,⁵⁷ and the seventh study did not report on the definition in the paper.²¹ Three studies had relatively large samples ($n = 697, 457, \text{ and } 677$, respectively).^{52,53,56} Response rates were

Table 2
Methodological Appraisal According to Criteria of Hawker et al., 2002

	Good	Fair	Poor	Very Poor	Comment
1. Abstract and title					
2. Introduction and aims					
3. Method and data					
4. Sampling					
5. Data analysis					
6. Ethics and bias					
7. Findings					
8. Transferability/generalizability					
9. Implications and usefulness					

Table 3
Overview of Prospective Studies

Author(s), Year of Publication, Title	Purpose	Methodology	Results
Menten, 2003, Palliative sedation for refractory symptoms in terminal palliative cancer patients: procedure and results in University Hospitals Leuven	Analyze the indication, procedure and efficacy of palliative sedation for refractory symptoms in terminal palliative cancer patients in the University Hospitals of Leuven	Quantitative, prospective <i>n</i> = 26 palliative, terminal cancer patients, 38% PST, 62% PCU, fully conscious and requested palliative sedation <i>Palliative sedation = those situations where the terminal palliative patient and his physician intend to obtain a deep sleep. Sedation is done without hastening or causing death, just to relieve suffering from one or more intractable symptoms, when all other interventions have failed and the patient is perceived to be close to death</i>	Prevalence: 1.33% sedated by PST and 3.13% sedated on PCU Medication: midazolam in all patients, start with low doses and titrate up based on medical history of patient, individual patient experience, and intensity of refractory symptoms(s) Indications: mainly physical suffering in PST group, mainly psychological suffering in PCU group Effect of sedation: 48 hours after sedation full control of refractory symptoms in 92% of cases Use of sedation: 34% intermittent sedation, three patients evolved to permanent sedation, 61% continuous deep sedation from start Survival: median duration of four days for permanent sedation, median of five days for intermittent
Ventafredda et al., 1990, Symptom prevalence and control during cancer patients' last days of life	To document how long before death symptoms appear that patients term unendurable and that are controllable only with sedation-induced sleep, allowing the patient to respond to external stimuli only if provoked	Quantitative, prospective <i>n</i> = 120 terminal cancer patients, entered home care program, Italy, 61% male, median age 65.5 years <i>Sedation = when symptoms could not be relieved opioids or strong tranquilizers were increased until symptoms were under control and maintained until death</i>	Prevalence: 52.5% CDS Indications: 41% dyspnea, 39% pain, 14% delirium, 6% vomiting Decision making: patient gave consent Survival: no difference in survival between sedated and nonsedated group
Chiu et al., 2001, Sedation for refractory symptoms of terminal cancer patients in Taiwan	To investigate the frequency of sedation in terminal cancer patients, its relationship with intractable symptoms, understand the ethical acceptability and satisfaction of symptom control among patients, family and health care workers	Quantitative, prospective, daily assessment on assessment form <i>n</i> = 251, 54% men, 51% >65 years, 31% survival <7 days, 39.5% between seven and 30 days <i>Sedation = medical procedure to palliate patients' symptoms by intentionally making their consciousness unclear</i>	Prevalence: 27.9% Indications: 57% agitated delirium, 10% severe pain, 22.8% dyspnea, 7.2% insomnia Medication: 50% haloperidol, 24.3% midazolam, 12.9% rapidly increasing doses of morphine Use of sedation: 52.9% intermittently, 37.1% continuously, 10% evolved from intermittent to continuous Decision making: 42.9% consent from patient and family, 50% consent from family (mostly cognitive impairment of patient) Effect of sedation: 71.4% of medical staff satisfied with sedation, 90% of family thought it right to use sedation, 67% of family was satisfied Survival: no difference between sedated and nonsedated, median survival after sedation = five days

Fainsinger et al., 2000, Sedation for delirium and other symptoms in terminally ill patients in Edmonton	To assess the prevalence of difficult symptoms requiring sedation at the end of life	Quantitative, prospective, self-developed data collection form <i>n</i> = 150, consecutive patients who died on acute care, tertiary unit, and hospice unit Mean age, respectively, 71, 62, and 73 years, 60%, 68%, and 46% male <i>Sedation = patients deliberately sedated by increasing doses to control delirium or observed to be reduced to a clearly unresponsive condition by pharmacological management</i>	Prevalence: 6% sedated for delirium in acute care, 10% in tertiary care and 2% in hospice care; 2% sedated for dyspnea in hospice care, overall prevalence of 7% Survival: range, 1–5 days sedated
Morita et al., 2005, Efficacy and safety of palliative sedation therapy: a multicenter, prospective, observational study conducted on specialized palliative care units in Japan	Explore efficacy and safety of palliative sedation therapy and identify factors contributing to inadequate symptom relief and complications	Quantitative, prospective, structured questionnaire in yes/no format 21 palliative care units, Japan, inclusion of all adult patients who received CDS, <i>n</i> = 102, mean age = 63 years, 62% male, mean duration of stay = 42 days	Prevalence CDS: 19% Indications: 44% fatigue, 41% dyspnea, 34% delirium, one patient received sedation for psychoexistential suffering Survival: mean 2.6 days after sedation
Morita et al., 2005, Ethical validity of palliative sedation therapy: a multicenter, prospective, observational study conducted on specialized palliative care units in Japan	To systematically investigate whether empirical evidence supports the ethical validity of sedation	<i>CDS = the continuous use of sedative medications to relieve intolerable and refractory distress by achieving almost or complete unconsciousness until death</i>	Medication: 76% midazolam, 34% phenobarbital AFOFL: before sedation: 47% AH, 11% oral intake; after sedation: 31% of first group and 73% last group no AH and 69% of first group continued and 27% of last group started with AH. Reduction of hydration in 35% of patients due to fluid retention symptoms and/or patient wishes Decision making: 95% of competent patients stated suffering was intolerable, 67% patient explicit wish for sedation, 29% family involved, 4% previously expressed patient wish Use of sedation: 66% of sedated patients received intermittent or mild sedation before CDS Efficacy and safety PS: inadequate symptom relief in 17% of patients, agitation distress scale decreased significantly (<i>P</i> <0.001), delirium remained serious in 4%. Explicit communication decreased from 40% to 7% after sedation and mean communication capacity score ↓ significantly (<i>P</i> <0.001). Respiratory rate did not decrease after sedation and serious complications reported in 22%. Possibility of shortening life: none = 67%, <24 hours in 24%

(Continued)

Table 3
Continued

Author(s), Year of Publication, Title	Purpose	Methodology	Results
Morita et al., 1999, Do hospice physicians sedate patients intending to hasten death?	What is the condition of patients before they are sedated? Is life support care routinely withdrawn after sedation begins? Are there cases where physicians increase the dose of sedatives despite adequate symptom palliation? Are sedatives prescribed in amount that will hasten death?	Quantitative, prospective, data collections sheet <i>n</i> = 71 sedated patients of one PCU, 55% male, mean age = 65 years, median length of stay = 28 days, Japan <i>Sedation = medical procedure to palliate patients' symptoms refractory to standard treatment by intentionally making their consciousness unclear</i>	Prevalence: 45% Survival: median of three days after start of sedation Use of sedation: intermittent = 61%, continuous = 39%, mild = 80%, deep = 20% Indications: 42% physical restlessness, 41% dyspnea, 13% pain, 1.4% nausea, 1.4% multifocal myoclonus, 1.4% psychological distress AFOFL: amount of fluids increased in 7%, maintained in 69% and decreased in 24% of patients Medication: 37% opioids, 31% midazolam, 31% haloperidol
Morita et al., 1999, The decision-making process in sedation for symptom control in Japan	Describe the decision-making process of 87 sedated terminally ill cancer patients	Quantitative, prospective, structured data collection sheet <i>n</i> = 87 sedated terminally ill cancer patients of one PCU, Japan, 61% male, mean age = 63, median length of stay = 30 days	Prevalence: 47% Use of sedation: 67% intermittent, 33% continuous, 41% mild, 49% deep Indications: 67% physical restlessness, 40% dyspnea, 18% pain, 6% nausea, 1% convulsion Survival: median of three days after sedation Decision making: >90% family members informed about risks and benefits
Cameron et al., 2004, Use of sedation to relieve refractory symptoms in dying patients	To document the use of sedation for refractory symptoms in patients admitted to an independent palliative care unit	Quantitative, prospective, <i>n</i> = 20 patients who received sedated drugs, South Africa, mean age = 68 years, cancer, 36% male <i>Sedated patients = all patients receiving sedating drugs apart from sleeping tablets</i>	Prevalence: 20% Indications: 45% delirium, 25% nausea and vomiting, 15% convulsions, 10% dyspnea, 5% pain Survival: three to eight days after start of sedation Medication: mainly midazolam and haloperidol AFOFL: 20% received fluids during sedation, fluids were not started during sedation, always discussed with patients and families Decision making: all patients and/or families fully informed
Peruselli et al., 1999, Home palliative care for terminal cancer patients: a survey on the final week of life	Describe the place, circumstances and "quality" of death of patients admitted to home palliative care units, particularly focusing on symptom control and the patients' situation at death	Quantitative, prospective, weekly assessment until death <i>n</i> = 401 randomly selected patients older than 18 and referred to PCU (home care) for management of terminal stage cancer, median age = 70 years, 57% male, 20% duration of care < 7 days and 71% between seven and 90 days <i>Total pharmacological sedation = the administration of drugs to obtain total loss of consciousness</i>	Prevalence: 25% sedated, high variation between centers

Morita et al., 2002, Practices and attitudes of Japanese oncologists and palliative care physicians concerning terminal sedation: a nationwide survey	To clarify the frequency and practice of sedation therapy for terminally ill cancer patients and to identify physicians' attitudes toward sedation	<p>Sample of eligible physicians (oncologists and palliative care physicians) who met inclusion criteria, $n = 697$, response rate = 49.6%, mean age = 45; 92% male, 80% cancer setting, 13% hospice, PCU, self-developed questionnaire and four cases</p> <p><i>Palliative sedation therapy = the use of sedative medication to relieve intolerable and refractory distress by the reduction of patient consciousness</i></p> <p><i>Distinction between mild-deep and intermittent-continuous</i></p>	<p>Prevalence: mild sedation = 89%, intermittent-deep = 70%, continuous-deep = 66% for physical distress</p> <p>Mild = 64%, intermittent-deep = 46% and continuous-deep = 38% for psychological distress</p> <p>Opinions: 83% agreed that patients had a right to receive palliative sedation, 5.3% PS = unnecessary when conventional palliative therapy was performed, <15% expressed concerns about losing patient trust, being criticized by colleagues or by law, 19% concerns about less efforts made when PS becomes widespread, 19% PS does not sufficiently alleviate patient suffering, 37% PS often associated with risk of shortening patient life, 17% stated that PS is indistinguishable from other acts to hasten death, 48% regarded accurate determination of medical indications for PS as difficult</p> <p>Attitudes: when refractory physical and psychological distress, 14% of respondents chose continuous-deep sedation; when delirium and depression, 35% chose psychiatric treatment without intentional sedation</p> <p>Factors influencing physician's decision: independent determinants for decision to choose continuous-deep sedation were greater preference of symptomatic treatment ($P = 0.021$), higher levels of emotional exhaustion ($P = 0.014$); independent determinants of physician's preference not to opt for psychiatric treatment in cases of delirium and depression were less involvement in end-of-life care ($P < 0.01$) and greater age ($P < 0.01$)</p>
Müller-Busch et al., 2004, Attitudes on euthanasia, physician-assisted suicide and terminal sedation—A survey of the members of the German Association for Palliative Medicine	To evaluate the attitudes toward different end-of-life medical practices, such as euthanasia, physician-assisted suicide, and terminal sedation	<p>Quantitative survey, cross-sectional, Germany, $n = 251$ physicians, response rate = 61%, median age of 46 years, 70% male, median palliative experience = 7.8 years</p> <p>Definitions according to German literature and jurisprudence</p>	<p>Vast majority of physicians opposed to euthanasia 90.4%; 63.3% in favor of withdrawing life-sustaining treatment in futile situations without consent of patient or relatives, 94% in favor of terminal sedation in cases of intolerable or hopeless suffering</p>

(Continued)

Table 3
Continued

Author(s), Year of Publication, Title	Purpose	Methodology	Results
Kaldjian et al., 2004, Internists' attitudes towards terminal sedation in end of life care	Determine the frequency of physician support for terminal sedation in end-of-life care, determine whether physicians who support terminal sedation also support physician assisted suicide and explore characteristics of physicians who support terminal sedation but not assisted suicide	Quantitative, prospective, cross-sectional, survey, USA, $n = 677$ physicians, response rate = 47%, mean age = 51 years, 80% men, 41% only internal medicine, 32% subspecialty, 27% Jewish, 24% Catholic, 26% none, 17% nonCatholic, 65% cared for 1–25 terminal patients in past year <i>Terminal sedation = diminishing consciousness to halt the experience of pain if a terminally ill patient has intractable pain despite aggressive analgesia</i>	78% supported the use of terminal sedation, 23% did not agree with aggressive analgesia or PS, 47% agreed with PS but not with physician-assisted suicide (PAS), 29% agreed with PS and PAS. When more experience with terminally ill people, more likely to agree with PS; three independent variables associated with agreeing with PS: caring for >10 terminally ill patients in past year, Christian religious affiliation, monthly religious service attendance ($P < 0.05$)
Blondeau et al., 2005, Physicians' and pharmacists' attitudes toward the use of sedation at the end of life: influence of prognosis and type of suffering	To measure the effect of prognosis and the nature of suffering on the attitude toward sedation	Quantitative, prospective, four clinical situations/vignettes, Canada, 2*2 experimental design, physicians and pharmacists, nonrandom volunteer sampling technique, $n = 124$, response rate = 42%, 49% men, 80% physicians, 89.3% < 55 years old, Qualitative content analysis of comments <i>Purposefully no definition supplied</i>	Attitude: Attitude was favorable in situation of physical suffering, regardless of prognosis; with regard to existential suffering, attitude was unfavorable; only suffering variable had impact on attitude Existential suffering: if long-term prognosis, favoring spiritual or psychological support; if short-term prognosis, reference was made to interventions by psychologist, social worker, priest Physical suffering: high proportion held that sedation was indicated in case of intractable suffering; majority's main concern was the patient's autonomy, need for free and informed consent
Morita et al. (2003), Similarity and difference among standard medical care, palliative sedation therapy and euthanasia: a multidimensional scaling analysis on physicians' and the general population's opinions	To examine the conceptual validity of the proposed criteria for palliative sedation therapy by investigating similarities and differences among standard medical care, the subcategories of palliative sedation therapy proposed, and medical acts to hasten death using a multidimensional scaling technique on actual survey data	Secondary analysis of two surveys based on Euclidean distance model of stimulus configuration of measures Survey 1: cf. Morita et al., 2002 Survey 2: convenience sample of Japanese people, $n = 457$. Participants had to answer four-point Likert scale. Had to identify the degree to which they would want each treatment for severe physical or psychological distress refractory to optimal care. Options were: care without intentional sedation, mild sedation, intermittent deep sedation, continuous deep sedation and PAS/euthanasia <i>Palliative sedation therapy = the use of sedative medication to relieve intolerable and refractory distress by the reduction of patient consciousness</i> <i>Distinction between mild-deep and intermittent-continuous</i>	Continuous deep sedation was placed closer to mild and intermittent deep sedation in the physician responses, while it was mapped closer to PAS/euthanasia in the general population data
Morita et al. 2002, Preferences in palliative sedation therapy in the Japanese general populations			

Simon et al., 2007, Attitudes towards terminal sedation: an empirical survey among experts in the field of medical ethics	To find out how German-speaking medical ethics experts think about the term and the moral acceptance of terminal sedation	Prospective study based on questionnaires sent to medical ethics experts <i>n</i> = 281 (response rate of 59%)	<p>Previous involvement: 92% knew the term terminal sedation, 32% had dealt with the topic in detail, 8% had never heard of the term</p> <p>Understanding of the term: 73% only speak of terminal sedation when sedation until death is intended; to 45% this meant complete elimination of consciousness, and to 55%, less deeper forms of sedation; persons with medical background preferred broader definition</p> <p>Alternative terms: 49% preferred palliative sedation, since it puts the focus on symptom control and reduction of the suffering</p> <p>Moral evaluation: 98% found terminal sedation morally acceptable. In cases of mental suffering alone, the acceptance was considerably lower</p> <p>Withdrawing food and fluid together with sedation was less acceptable than sedation alone</p>
Morita et al., 2001, Effects of high dose opioids and sedatives on survival in terminally ill cancer patients	Intention to compare the survival of sedated and nonsedated patients receiving inpatient palliative care, with clear definitions on sedative treatment and using multivariate analytic techniques to adjust for prognostic factors	<p>Prospective study design, secondary analysis. Sample of consecutive patients admitted to a palliative care unit in Japan</p> <p>Assessment of patient characteristics, PPS, and clinical symptoms on admission and following six months</p> <p>Additional information about the use of sedatives and opioids was assessed by chart review for last 48 hours of life</p> <p><i>n</i> = 209, 53% male, mean age of 67 years, average survival of 44 days</p>	<p>PPS less than 60% in 85% of patients</p> <p>Opioids prescribed in 82% of patients</p> <p>60% of patients received some form of sedative in last 48 hours, such as haloperidol (43%), midazolam (23%), and hydroxyzine (15%)</p> <p>PPS, oral intake, edema, dyspnea at rest, and delirium independent prognostic value</p> <p>No significant differences in survival between groups</p>

Table 4
Overview of Retrospective Studies

Author(s), Year of Publication, Title	Purpose	Sample	Results
Rietjens et al., 2004, Physician reports of terminal sedation without hydration or nutrition for patients nearing death in the Netherlands Rietjens et al. 2005, The practice of terminal sedation in the Netherlands Rietjens et al. 2006, Terminal sedation and euthanasia	To describe the practice of terminal sedation in the Netherlands Comparison of cases of euthanasia and terminal sedation based on their clinical characteristics	Quantitative, retrospective, face-to-face interviews based on structured questionnaire with regard to cases of sedation in past year, The Netherlands $n = 410$ physicians (51% clinical specialists, 30% general practitioners, and 19% nursing home physicians), 51% men, face-to-face interviews using structured questionnaire, based on case of last patient that received terminal sedation <i>Terminal sedation = the administration of drugs to keep the patient in deep sedation or coma, until death, without giving artificial nutrition or hydration</i>	Prevalence: 52% of physicians ever practiced terminal sedation Terminal sedation was used in 10% of all deaths during 2000–2001 Patient characteristics ($n = 211$): 78% ≥ 65 years, 54% patients with cancer, 47% male Indications: 51% pain, 38% agitation, 38% dyspnea, 11% anxiety Decision making PS: 59% physician discusses with patient, 93% with family, 79% discussed with other caregivers, 17% not discussed with other caregivers Medication: 21% benzodiazepines, 35% combination of benzodiazepines and morphine, and 4% benzodiazepines in combination with other drugs Intention with regard to PS: 36% without intention to hasten death, 47% partly intention to hasten death, 3% explicit intention to hasten death Survival: 40% physicians believed that life was shortened by 24 hours or less, 27% believed by more than one week Comparison PS and euthanasia: PS was mainly done in hospital, euthanasia at home, patients receiving PS were older ($P < 0.001$); fewer patients with PS had cancer (54%); patients with PS suffered more anxiety ($P < 0.001$), confusion ($P < 0.001$), depression ($P = 0.06$), bedsores ($P = 0.002$), loss of appetite ($P = 0.003$), unclear consciousness ($P < 0.001$), inactivity ($P = 0.001$); sedated patients had more pain and dyspnea, and more often very ill
Stone et al., 1997, A comparison of the use of sedatives in a hospital support team and in a hospice	Determine the frequency, indications and doses of sedative drugs used in a hospital support team and in a hospice inpatient unit, determine	Quantitative, retrospective, chart review Hospital support team and hospice inpatient unit, Great Britain, $n = 61$	Prevalence: 43% sedatives for symptom control, 26% sedatives for sedation, 12% sedatives for both

	how long patients survived after being sedated	patients, medical, nursing, and drug charts reviewed. Sedative drugs = benzodiazepines, phenothiazines, butyrophenones, phenobarbitone, used for symptom control or sedation <i>Sedation = the prescription of sedative drugs where reducing the level of consciousness was part of a treatment strategy with the aim of relieving distress</i>	Patient characteristics: mean age 69.5, mean survival of 19 days after admission Indications for PS: 60% agitated delirium, 27% mental anguish, 20% pain, 20% dyspnea, 3% other Medication: 80% midazolam—MDD = 22 mg, 33% methotrimeprazine—MDD = 64 mg, 37% haloperidol—MDD = 5 mg Survival: no differences between sedated and nonsedated patients Prevalence: 48.3% sedated, in 90% of these patients death was expected within days Indications: 49% dyspnea, 39% pain, 38% general malaise, 23% agitation, 10% nausea, 48% suffered more than one symptom Survival: sedated patients survival after sedation = average 3.9 days Use of sedation: intermittent = 44%, intermittent to continuous = 27%; continuous = 14%; intermittent with death after single use = 15% Decision making: Patient and family fully informed 7%, family fully informed and patients partly 45%, neither family nor patients informed 4% Medication: 55% midazolam, 55% morphine, 33% haloperidol, 15% diazepam, 13% scopolamine, 6% bromazepam, 4% chlorpromazine, 4% barbiturates
Morita et al., 1996, Sedation for symptom control in Japan: the importance of intermittent use and communication with family members	Report the present circumstances surrounding the use of sedation for symptom control in Japan	Quantitative, retrospective, chart review, hospice, Japan $n = 143$ patients, 53% male, mean age 62.4, average period of stay = 57.7 <i>Sedation = medical procedure to palliate patients' symptoms by intentionally making their consciousness unclear. It included an increase in morphine dose resulting in secondary somnolence, and the use of sedative drugs</i>	Prevalence: Israel = 15%, Durban = 29%, Cape Town = 36%, Madrid 22% Indications: mainly delirium and dyspnea Length of sedation: range, 1–6 days Medication: 80% midazolam
Fainsinger et al., 2000, A multicenter international study of sedation for uncontrolled symptoms in terminally ill patients	To improve previous reports by data collection that would enable better characterization of the prevalence of this problem, and by using a multicenter international group, to provide a broader understanding of the circumstances leading to the decision to use sedation in terminally ill patients	Quantitative, retrospective, data collection form completed on the day of death or as close to that date as possible, four hospices, Israel ($n = 100$), Cape Town ($n = 93$) and Durban ($n = 94$), Spain ($n = 100$) Median age = 63 year, 48% male <i>Sedation = to decrease the patient to an unresponsive condition</i>	Prevalence: 30% sedated patients Patient characteristics: mean age 60 years, duration of stay = 8 days Indications: mainly delirium and dyspnea
Fainsinger et al., 1998, Sedation for uncontrolled symptoms in a South African Hospice	Develop understanding of end-of-life problems and their management and help develop improved patient management	Quantitative, retrospective, chart review, hospice, Canada, $n = 76$, 46% male <i>No definition</i>	

(Continued)

Table 4
Continued

Author(s), Year of Publication, Title	Purpose	Sample	Results
Fainsinger et al., 1991, Symptom control during the last week of life on a palliative care unit	To assess the prevalence and severity of different symptoms in patients admitted to a palliative care unit and the need to administer treatment resulting in sedation during the last week of life	Quantitative, retrospective, chart review, $n = 100$, 41% male, mean age = 62, mean duration of stay = 40	Use of sedation: 61% continuous subcutaneous infusion of midazolam, 30% intermittent doses of benzodiazepines, 9% chlorpromazine and lorazepam Medication: Mean dose midazolam = 29 mg Prevalence: 16% sedated Indications: 6% pain, 39% delirium
Miccinesi et al., 2006, Continuous deep sedation: physicians' experiences in six European countries	To estimate the frequency and characteristics of continuous deep sedation in six European countries	Quantitative, retrospective, questionnaire about medical decision making Random sample (stratified) of death certificates of people \geq one year in six European countries Response rate: Belgium = 59%, Denmark = 62%, Italy = 44%, The Netherlands = 75%, Sweden = 61%, Switzerland = 67% <i>Sedation: Continuous deep sedation (CDS) with or without artificial nutrition or hydration (ANH)</i>	Prevalence CDS: Belgium = 8.2%, Italy = 8.5%, Denmark = 2.5%, Sweden = 3.2%, Switzerland = 4.2%; CDS with ANH: 0.9%–5.5%; CDS without ANH: 1.6%–3.7% Patient characteristics: mainly cancer patients, more frequent in hospitals, less frequent patient \geq 80 years, probability of receiving sedation increases by 17% for males, 15% for cancer patients, 91% if between 65 and 79 years, 134% if \leq 65 years, 63% dying in hospital
Kohara et al., 2005, Sedation for terminally ill patients with cancer with uncontrollable physical distress	Investigating the influence on consciousness of sedative drugs on the consciousness of the patient	Quantitative, retrospective, chart review, patients admitted to palliative care unit, Japan, $n = 124$ <i>Sedation = a medical procedure to palliate patient symptoms refractory to standard treatment by intentionally dimming consciousness</i>	Prevalence: 51% sedation Patient characteristics: mean duration of stay = 29 days, median age = 64, 67% male, low PPS score before sedation Indications: 63% dyspnea, 40% general malaise/restlessness, 25% pain, 21% agitation, 6% nausea and vomiting, 54% > one symptom Survival: sedated patients died after 3.4 days Medication: 98% midazolam, MDD during last four days ranges 26.0–32.5 mg Use of sedation: 69% continuous sedation, 30% intermittent of which 80% evolved to continuous Prevalence: 14.6% sedated patients in last 48 hours

Müller-Busch et al., 2003, Sedation in palliative care—a critical analysis of 7 years experience	Provide a critical analysis of seven years experience with the application of sedation in the final phase of life	Quantitative, retrospective, chart review, patients who died on PCU, Germany, $n = 548$ <i>Sedation during last 48 hours</i>	Patient characteristics: sedated patients significantly younger Indications: tendency to shift to more psychological distress Survival: mean survival after sedation = 2.6 days Decision making: ↑ in request for sedation by patients over time Medication: slowly increasing doses of midazolam Use of sedation: 60% continuous sedation, 40% intermittent Nutrition and hydration: 33.8% no oral intake, all patients receive infusions
Chater et al., 1998, Sedation for intractable distress in the dying—a survey of experts	To better understand the use of deliberate sedation to treat intractable symptoms in the dying	Quantitative, retrospective, self-developed questionnaire Palliative care experts from different countries, $n = 61$, response rate = 87% <i>Terminal sedation = the intention of deliberately inducing and maintaining deep sleep, but not deliberately causing death in very specific circumstances:</i> 1) <i>for the relief of one or more intractable symptoms when all other interventions have failed and the patient is perceived to be close to death, or</i> 2) <i>for the relief of profound anguish (possibly spiritual) that is not amenable to spiritual, psychological, or other interventions, and [patient] is perceived to be close to death</i>	Prevalence: 77% reported using PS in last 12 months Indications: 20% pain, 14% anguish, 12% respiratory distress, 12% agitation, delirium Medication: 37% one drug, 30% two drugs, 28% three drugs, mainly midazolam Decision making: 50% patients major involvement, 27% patients minor involvement, 22% no involvement. 96% families major involvement, 27% minor involvement, 4% no involvement Success of sedation: successful in 90%
Morita et al., 2004, Concerns of family members of patients receiving palliative sedation therapy	To gather vivid family descriptions about their experiences in palliative sedation therapy	Quantitative, prospective, cross-sectional, multicenter survey and content analysis 48 statements, bereaved family of patients receiving palliative sedation, median age = 57, 64% female, 55% spouse, 25% child	69% patients considerably or very distressed before sedation, 88% reduction of symptom frequency, 55% patients explicit wish for sedation, others could not express wishes, 89% of families received a clear explanation about sedation, 79% prior discussion about end-of-life treatment between patient and family, 78% family expresses some level of satisfaction with sedation, 77% evaluated time of start as appropriate, 25% of family expressed high levels of distress, 50% concerns about not being able to communicate with patient, 33%
Morita et al., 2004, Family experience with palliative sedation therapy for terminally ill cancer patients	To clarify the family experience during palliative sedation therapy, including their satisfaction and distress levels, and the determinants of family dissatisfaction and high-level distress		

(Continued)

Table 4
Continued

Author(s), Year of Publication, Title	Purpose	Sample	Results
Morita, 2004, Differences in physician-reported practice in palliative sedation therapy	To clarify the physician-reported practices and the factors influencing sedation rates	Quantitative, retrospective, questionnaire regarding use of PS in past year	perceived the decision making as a burden, 85% believed that sedation was dignified
Morita, 2004, Palliative sedation to relieve psychoexistential suffering of terminally ill cancer patients	To clarify the prevalence and characteristics of patients receiving sedation for relief from psychoexistential suffering	Palliative care physicians, Japan, response rate = 80% <i>Continuous deep sedation (CDS) is the continuous use of sedative medications to relieve intolerable and refractory distress by achieving almost or complete unconsciousness until death</i>	Prevalence: CDS for physical symptoms: <10% in 44% of institutions; between 10% and 50% in 53%, >50% in 6.2% of institutions, CDS for psychoexistential symptoms: 64% institutions nonexistent, 32% institutions 0.5–5%, 3.6% institutions >10%. 1% of total population deceased patients psychoexistential problems Indications: >80% pain and dyspnea in patients with limited survival = strong indication and psychoexistential suffering exceptional indication Decision making process: 75% consent from patient, family and nurses; large variation in consent by multiple physicians, 49% of institutions physicians greater role than nurses, 15% nurses greater role and 36% equivalent role. 100% of competent patients, 100% of family, 98% of nurses Survival: predicted survival ≤3 weeks in 94% Opinions of physicians on sedation: ≥70% sedation does not damage patients' or families trust, sedation not criticized by colleagues, sedation has no legal problems, distress not adequately palliated without sedation, patients have right to choose sedation
Van der Heide et al., 2007, End-of-life practices in the Netherlands under the Euthanasia Act	To assess the effects of the 2002 Dutch law and changes in end-of-life care. To assess the reporting rates for euthanasia and PAS and physicians' reasons for nonreporting	Based on death certificates, stratified sample of death cases, $n = 6,860$ (response rate 77.8%), mailed questionnaire statistical analysis based on weighting procedure, statistical significance $P < 0.05$	Prevalence: 8.2% continuous deep sedation; in 7.1% in conjunction with decision that possibly hastened death (e.g., withholding hydration or nutrition); 1.1% sedation without conjunction of other decisions

Sykes and Thorns, 2001, Sedative use in the last week of life and the implications for end-of-life decision making

This study aimed to determine how sedation doses change at the end of life and how often the doctrine of double effect might be relevant

Quantitative, retrospective study based on chart reviews. $n = 237$ hospice inpatient unit, 54% female mean age of 69.7

Four groups of patients: little or no sedation, significant levels of sedation for all seven days, significant amounts of sedatives during last 48 hours and those undergoing a marked increase of sedative drugs during last 48 hours
Sedation = significant sedation based on a judgment of the dose threshold for each drug

Sedation in conjunction with other decisions most often used in patients aged 64 years or younger, in men and in patients with cancer

Prevalence: 48% of patients' sedative drugs were used in doses above the sedative threshold. 52% received no sedation during last week of life.

13% received sedation for at least seven days and 56% received sedation during last 48 hours

Use of sedation: 56% of sedated patients received it during last 24 hours, 54% received intermittent sedation between 48 hours and seven days

Effect of sedation: Number of peaceful deaths similar in all groups

Survival: No difference in survival between patients that received no sedation in last week of life and those that received sedation during last 48 hours. Patients receiving sedation during there last week of life had a significantly longer survival than the other two groups ($P < 0.001$)

Medication: mainly midazolam, median dose of 50 mg/24 hours

68% of patients received regular sedation, two out of three of patients started regular sedation on admission or within seven days

No difference in survival between patient that did receive regular sedation and those that did not

Mean duration of admission: 26 days

Sedation doses increased modestly toward end of life but were not associated with reduction in survival

Vitetta et al., 2005, Sedation and analgesia-prescribing patterns in terminally ill patients at the end of life

This study attempted to identify overall prescribing factors and variation in the use of sedation and analgesia in an inpatient hospice setting at the end of life

Retrospective case review, $n = 102$
Special attention to sedation and analgesia in the last week of life

very similar, but rather low in all studies ($\pm 50\%$) (Tables 2 and 3).

Studies Exploring Family Experiences. We included two studies that discussed the experience families had when a family member underwent palliative sedation. Both studies^{39,40} were based on the same sample and study design. One of the studies gave an overview of the results⁴⁰ and the other highlighted the concerns of family members of patients receiving palliative sedation.³⁹ In this cross-sectional multicenter survey, 185 family members of sedated patients answered a questionnaire. The mean age of family members was 57 years, 35% were male, and 55% were spouses.⁴⁰ The mean interval between patient time of death and return of the questionnaire was approximately two years.

Results

Prevalence of Palliative Sedation

Our review revealed that the prevalence of palliative sedation varied considerably (Tables 3 and 4), especially in terms of setting, definition, and methodology used. Most of the studies were carried out in palliative care units or hospices. The prevalence in these settings ranged between 3.1%¹⁰ and 51%.³⁷ In two Italian studies^{12,51} performed in home care environments almost 10 years apart, one study reported a prevalence of 52.5% and the other reported a prevalence of 25%. We also found a large difference in prevalence among hospital-based palliative support teams. Stone et al.,³¹ for example, reported a prevalence of 26%, whereas Menten¹⁰ reported a prevalence of only 1.33%.

Prevalence of palliative sedation also varied across countries. Two studies reported palliative sedation prevalence as a proportion of all deaths in one of six European countries.^{28,36} For the Netherlands,^{28,43} Belgium,³⁶ and Italy,³⁶ the prevalence was 10%, 8.2%, and 8.5%, respectively. In Denmark, Switzerland, and Sweden, a much lower prevalence of 2.5%, 4.8, and 3%, respectively, was reported.³⁶

Forty-one percent of the studies distinguished between intermittent and continuous palliative sedation. Intermittent sedation was reported in 30%–67% of cases, whereas continuous sedation was reported in 14%–69%

of cases. Morita et al.⁴⁹ reported that 51% of patients received mild sedation and 49% deep sedation. In a second study,⁴⁸ they reported that 80% of patients received mild sedation, whereas 20% received deep sedation. In several studies, intermittent sedation sometimes resulted in continuous sedation at the end of life. This was the case in between 10% and 27% of the patients that had started with intermittent sedation.^{10,32,37,44}

An interesting finding about the beliefs of the lay public and professionals was reported in the study of Morita et al.⁵⁴ While examining the conceptual validity of the proposed criteria for palliative sedation, they found that both physicians and the general population differentiate mild sedation and intermittent deep sedation from standard medical care. Moreover, they reported that physicians consider continuous deep sedation to be close in practice to both mild and intermittent deep sedation. However, the general population considered it to be closer to euthanasia/physician-assisted suicide.

Indications for Sedation

Sixty-eight percent of the reviewed studies listed only physical symptoms as the reason for sedating a patient (Tables 3 and 4), the most important being delirium, dyspnea, and pain. Other physical symptoms listed were fatigue, agitation, physical restlessness, insomnia, and nausea and vomiting.

Twenty-seven percent of the studies mentioned psychoexistential suffering besides physical suffering as a reason for sedating a patient, even though this was only true for a minority of patients.^{9,10,28–31,38,46,47,49} Most frequently mentioned were anxiety, mental anguish, and psychoexistential suffering (without elaboration). In one study,⁴² Morita reported solely on the use of palliative sedation for psychoexistential problems. In this study, physicians indicated that patients received palliative sedation for feeling meaningless (61%), being a burden on others/dependency (48%), death anxiety (33%), wishing to control death (24%), isolation (22%), and economic burden (8.7%). Müller-Busch et al.⁹ and Menten¹⁰ report that palliative sedation is increasingly being administered to patients to treat psychoexistential refractory symptoms rather than physical symptoms.

Survival of Patients After the Initiation of Palliative Sedation

Half of the reviewed studies reported on the survival of patients after palliative sedation.^{9,28–30,32,37,42,44–46,48–50} Based on retrospective reports from physicians, Rietjens et al.^{28,30} found that 38% of patients died within 24 hours, whereas 96% of patients died within one week. According to physicians' estimations, in 40% of patients, it was believed that palliative sedation shortened life by ≤ 24 hours, and in 27% of patients, it was thought to have shortened life by $> one$ week.^{27,29} Morita et al.^{41,42} reported a survival time of less than three weeks in 94% of the patients receiving palliative sedation. Mean survival of patients after the onset of palliative sedation ranged from one to six days.^{9,10,28,30,32,37,44–50}

Other studies compared the survival of sedated and nonsedated patients.^{12,31,37,44,58,61} In accordance with other papers, Vitetta et al.⁵⁹ found no differences in survival time between sedated and nonsedated patients.^{12,31,37,44,58,61} Moreover, no relationship could be found between survival and the individual physician's prescribing pattern.⁵⁹ The paper of Sykes and Thorns,⁵⁸ however, found that the survival time of patients receiving sedation throughout their last week of life was significantly longer ($P < 0.001$) than those who did not receive sedation and those who did receive sedation during the last 48 hours of their life.⁵⁹

Medication and Oral or Artificial Food and Fluid Intake

Thirty-two percent of the studies mentioned midazolam as the main drug used to induce palliative sedation.^{9,10,31–34,37,38,46,47,50,58} Other drugs used either alone or in combination with midazolam were haloperidol, phenobarbital, and opioids. Twenty-four percent of the studies listed the mean daily dose of midazolam, which varied between 18.5 and 40 mg, with a range of 1–450 mg/day.^{10,31,33,34,37,38,47,48,50}

Only eight of 37 papers provided information on artificial food and fluid intake in relation to palliative sedation. Again, figures varied significantly between studies. Miccinesi et al.³⁶ and Menten¹⁰ reported that in 35%–64% of cases, palliative sedation was performed without administering artificial fluids. Others describe the situation before and after palliative

sedation.^{47,48,50} When patients received artificial fluids before sedation, in 20%–69% of patients, fluid intake continued during sedation.^{47,50} In 24%–44% of the patients, administered fluid was reduced.^{47,48} One study³⁴ reported that no sedated patients received artificial fluid. Some studies reported that mildly sedated patients were able to take in fluids and/or food orally.^{9,47,50}

Decision Making

Fifteen papers provided information about the decision-making process related to palliative sedation. All of these reported that consent was obtained from almost all patients who were not cognitively impaired.^{9,10,12,28–30,32,38,41,42,44,46–48,50} The most important reason for not discussing the decision with competent patients was to protect them from anxiety and/or sudden onset of refractory suffering.^{28,32,48} In 50%–99% of the cases, the family was involved in the decision-making process.^{28,32,38,41,42,44,49,52} Seventy-five percent of families felt that the information supplied by health care professionals was sufficient, whereas 22% felt it was insufficient.⁵² Conflicts in opinion between family members, between the patient and family, and between the medical staff and family were observed in 15%, 7.6%, and 9.7%, respectively, of the cases.⁵² In cases of disagreement between the patient and family, 79% of the time physicians would try to find a compromise, and 20% of the time, they would persuade the family to comply.⁴¹ All physicians surveyed indicated that they would not comply with the wishes of the family or the patient if both parties failed to reach an agreement.⁴¹

Overall, 78% of families were satisfied with the decision that was made and with the timing of palliative sedation. Twenty-five percent of the families, however, experienced high levels of emotional distress related to palliative sedation, and 30% of the families perceived the decision-making process as burdensome.⁴⁰ Factors hampering the decision making of families were the presence of delirium, the ambivalence of a patient's wishes, and the absence of objectivity in assessing distress.⁴⁹ The level of family dissatisfaction with palliative sedation seemed to be determined by high levels of persistent distress in patients after sedation, insufficient information, fear of shortening the patient's life, physicians and nurses lacking

sufficient compassion, and lack of discussion with patients.⁴⁰

It is clear from the literature that caregivers play a major role in the decision-making process. When asked how they experience the decision, 15% of physicians found it very easy, 27.5% found it to be somewhat easy, and 57.5% found it to be difficult to very difficult.³⁸ Caregivers were hindered in making decisions by their lack of objectivity in assessing the distress experienced by patients and by conflicts about the sedation (e.g., between patient and family).⁴⁹

Attitudes of Physicians Toward Palliative Sedation

Seven studies described the attitudes of physicians/experts toward using palliative sedation. In two of seven studies, 78%–94% of physicians supported the practice of palliative sedation in cases of intolerable or hopeless distress.^{55,56} Two studies reported that, although physicians advocated palliative sedation, they preferred to administer palliative sedation only in cases of physical suffering rather than in cases of existential suffering.^{21,57} In the study of Morita et al.,⁵² 83% of physicians stated that patients have a right to receive sedation. Only 5.3% reported that palliative sedation was unnecessary. Less than 15% of physicians had concerns about patient trust and being critiqued by colleagues or by law. However, 37% of physicians associated palliative sedation with a risk of shortening life, and 19% believed that sedation does not sufficiently alleviate patient suffering. Important with regard to the practice of palliative sedation is the finding that 49% of physicians thought that it is difficult to accurately identify medical indications necessitating palliative sedation, and 25% believed that there is a high risk of performing palliative sedation inadequately.⁵²

One study⁵² examined the independent determinants underlying physicians' decisions to choose continuous deep sedation in cases of refractory existential and physical distress. When physicians expressed a stronger preference for symptomatic treatment during their own end-of-life care (odds ratio = 1.53; $P=0.021$) and had more emotional exhaustion (odds ratio = 1.02; $P=0.014$), they more frequently chose continuous deep sedation.

Müller-Busch et al.⁵⁵ found that physicians preferred palliative sedation in cases of intolerable or hopeless distress (94%). The vast majority of the physicians that were questioned opposed euthanasia (90.4%). From this, the authors conclude that, according to the physicians involved, palliative sedation and euthanasia are very different and palliative sedation is not (slow) euthanasia.

Family Experience with Palliative Sedation

When families were asked about their experience with palliative sedation, 69% believed that patients were very distressed before sedation. Eighty-eight percent of families felt that palliative sedation helped to considerably decrease symptom distress.⁴⁰ Moreover, 94% of families observed that physicians and nurses visited the patient as much as or more than before. They also noticed that the physician or nurse who knew the patient well was the one who performed palliative sedation. Families clearly disagreed with the idea that palliative sedation was not dignified and with the idea that no meaning could be found in being with the sedated patient.⁴⁰

Research also showed, however, that families expressed concerns about palliative sedation.³⁹ Families reported guilt, helplessness, and physical and emotional exhaustion. Although they believed that palliative sedation was beneficial for symptom relief, they needed to be certain that no other solutions existed. Families also expressed their need for clear explanations about the risks associated with palliative sedation. Moreover, they wanted time to say goodbye to the patient before sedation was initiated. Families also felt it was important that sedated patients receive the same dignified care as do conscious patients.³⁹

Comparison of Patients Receiving Sedation and Patients Receiving Euthanasia

Based on physician reports, Rietjens et al.³⁰ compared the characteristics of patients who received palliative sedation with those of patients who received euthanasia. In hospitals, 49% of palliative sedation was performed by clinical specialists, 25% was performed by general practitioners, and 26% by nursing home physicians. Euthanasia was mainly performed in home-care situations (55%). Patients who received palliative sedation were significantly

older (mean: 72 years; $P < 0.001$) and suffered less from cancer than patients receiving euthanasia. Symptoms such as anxiety, confusion, depression, bedsores, loss of appetite, unclear consciousness, and inactivity were more frequently observed in patients receiving palliative sedation than in patients receiving euthanasia.

Efficacy and Safety of Palliative Sedation

Only four papers examined the observed effect, and the efficacy and safety of palliative sedation for treating refractory suffering. Morita et al. reported that palliative sedation adequately relieved symptoms in 83% of the cases.⁴⁶ Full control of the symptoms was reached 60 minutes to 48 hours after sedation was initiated.^{10,46} Forty-nine percent of patients awakened only once after they entered deep sleep. Time to sedation, however, was significantly shorter when midazolam was used in comparison to when phenobarbital was used ($P = 0.01$).⁴⁶ Serious complications, such as respiratory suppression without arrest, aspiration, and paradoxical reaction, were noted in 22% of the patients.⁴⁶ Also, higher dosages of midazolam were needed in young patients, in patients lacking icterus, in patients pre-exposed to midazolam, and in patients requiring sedation of long duration.⁴⁶ Menten¹⁰ and Chater et al.³⁸ reported a success rate of 90%-92%, and Chiu et al.⁴⁴ reported that in 71% of the cases, physicians were satisfied with the treatment of palliative sedation, 67% of the family was satisfied, though 90% of the families agreed that this treatment was the best option for the patient.

Discussion

Substantial Findings

The Prevalence of Palliative Sedation. This systematic review summarizes all available empirical information published in the medical literature on the practice of palliative sedation. One of our most important findings is the divergence that exists in the literature with regard to the prevalence of palliative sedation. In our view, this is mainly due to the fact that palliative sedation—often for the purpose of the study—is narrowed down to only one form of palliative sedation. For example, Rietjens

et al.²⁸ examined palliative sedation in terms of continuous deep sedation in combination with the withholding of food and fluids. This clearly differs from the papers of Morita et al.,^{54,60} who also included mild and intermittent sedation, and even primary vs. secondary sedation.⁶⁰ Obviously, prevalence figures are expected to be much higher in the latter case. Other factors that might explain the wide variations in the reported results of this review are the unclear concept of “refractory symptom,” accepted indications for sedation (psychoexistential suffering?), the fact that studies are carried out in different settings (home care, palliative care units, hospital support teams), the methodology used to assess the prevalence of palliative sedation (retrospective studies are prone to memory bias), patient characteristics, expertise, and progress in symptom control, the country (is there a law on euthanasia or not?), and the culture in which the study took place.⁶²

Discussing the different definitions that are used and available in the literature is clearly very interesting and important. This article, however, focuses on the empirical results of primary research. The discussion of the definitions is important and extensive enough to warrant another article (submitted). Nevertheless, it is clear that the lack of consensus in defining palliative sedation reflects the broad and varying ways in which palliative sedation is applied.^{21,63}

Narrowing the concept of palliative sedation, as is done in several empirical studies (e.g., Refs. 28–30,36,38), jeopardizes the crucial notion of proportionality, which is really at the heart of the concept of palliative sedation: Palliative sedation implies that the consciousness is reduced just enough to relieve refractory suffering in an adequate way.^{24–26,63} The notion of proportionality is crucial to differentiate palliative sedation from euthanasia.^{24–26}

To be able to give an overall definition that captures all possible forms of palliative sedation occurring in practice, mild and intermittent sedation must be included in the definition of palliative sedation.^{24–26,46,51,63} Because little empirical information about palliative sedation is currently available, an overarching definition is essential if we are to fully understand the practice of palliative

sedation. In order to stress, on the one hand, the common goal and intention of the different types of palliative sedation, and on the other hand, the crucial importance of proportionality in all these types of palliative sedation, we have defined palliative sedation as follows: “*The intentional administration of sedative drugs in dosages and combinations required to reduce the consciousness of a terminal patient as much as necessary to adequately relieve one or more refractory symptoms.*”^{24–26} Starting from this broad definition, further differentiations (mild/deep, continuous/intermittent) can be made.^{24–26,60} Only when clear-cut definitions of palliative sedation are proposed and applied will it be relevant and methodologically correct to compare prevalence figures.

Nature of Refractoriness. Most studies found that palliative sedation was administered primarily to relieve refractory physical suffering; some studies, however, found it was also used to relieve a combination of refractory physical and psychoexistential suffering (Tables 2 and 3). Over the years, researchers have noticed that palliative sedation is increasingly being used solely to control refractory psychoexistential suffering.^{9,10} According to palliative experts, this is due to the enormous progress in managing physical suffering. Successful treatment of physical suffering (e.g., pain) opens the way for patients to focus more on psychoexistential and spiritual issues, or on suffering.¹⁰ Administering palliative sedation to alleviate psychoexistential suffering remains a controversial issue,^{7,52} partly because it is difficult to determine when this type of suffering is refractory.^{7,52}

Does Palliative Sedation Shorten Life? One of the most important controversies that still exist is the presumed life-shortening effect of palliative sedation. Authors that oppose palliative sedation often consider it to be a form of “slow euthanasia,” especially when it is combined with the withholding or withdrawing of life-sustaining treatment, such as artificial food and fluids.¹⁸ Because this is a much-debated issue, one would expect to find much data on this topic. We found, however, only seven papers that discussed food and fluid intake in sedated patients, again with very different conclusions (cf. above).^{9,10,34,36,47,48,50}

We have argued^{24–26} that the decision to use palliative sedation to treat refractory symptoms

must be made independent of the decision to reduce or withhold artificial food or fluids. These decisions must be separated and must be considered individually for each patient, taking into account the patient’s wishes and his situation before palliative sedation is initiated. A similar argument has been developed by Rousseau.²² If a patient shows signs of imminent death (e.g., loss of appetite, decreased food/fluid intake) before sedation, then it seems irresponsible and unethical to hamper the natural dying process by administering artificial food or fluid during sedation. Moreover, to do so is considered to be a futile treatment for patients suffering from cachexia. This, in combination with research findings showing that survival of sedated patients is not shorter than that of nonsedated patients,^{12,31,37,44,58,61} suggests that palliative sedation has no proven life-shortening effects. This refutes the argument that palliative sedation is a form of “slow euthanasia.”^{21,24–26} Although more prospective research on this matter would be needed to corroborate this assertion, it will never give a definite answer. Performing a randomized study is the only way to prove that palliative sedation has no life-shortening effect, but for obvious ethical reasons, this will never be performed.

Another important aspect that relates to a possible life-shortening effect is the safety of palliative sedation. Although palliative sedation has no significant effects on patient survival on a mass level, some patients experience life-threatening complications on an individual level. Morita et al.⁴⁶—the only study that examines systematically the safety of palliative sedation—report a rather high percentage of serious complications. Therefore, it is essential that palliative sedation, though a normal medical practice, is used with the necessary caution.

Midazolam: The Drug of Choice for Palliative Sedation. Midazolam appears to be the drug of choice for initiating palliative sedation. Porta Sales⁶⁴ and Menten¹⁰ strongly defend this choice of drug, because midazolam is easy to titrate, has rapid onset and offset (the latter being very important in cases of intermittent sedation), can be combined with other drugs used in palliative care, and has an antidote (Flumazenil[®] or Anexate[®]). Only one study⁴⁸ reported opioids as the drug of choice for

palliative sedation. This apparently limited use of opioids to induce sedation is probably done in patients who already are receiving opioids before palliative sedation is started. It must be stressed that the use of opioids to induce palliative sedation has not proven to be the most efficient way to treat refractory suffering. Although they might cause drowsiness in patients, opioids usually do not lead to a loss of consciousness.⁶⁵ Three studies reported that barbiturates are still used for palliative sedation,^{32,33,38} albeit in a minority of cases. Barbiturates often result in cardiovascular instability, and, therefore, are less appropriate.⁶⁴ In some studies, haloperidol is listed as a sedative⁶¹ and described as being used to initiate palliative sedation. Haloperidol, however, is not a sedative and, therefore, should not be used to induce sedation. This clearly indicates that there is still much confusion as to what sedation is and again shows that clear definitions and clinical guidelines are necessary to guarantee the quality and safety of palliative sedation as a therapy for refractory suffering.

In many of the papers we reviewed in which midazolam was listed as the drug of choice for inducing palliative sedation, authors reported “mean dosages” used for sedation to give readers an idea of the amount of drug needed for sedation. Sedation status, however, cannot be solely based on mean drug dosages, because the effective dosage range varies largely (sometimes up to a factor of ≥ 10) in different patients. Therefore, it is important that dosages are individually and continuously titrated based on a patient’s medical history, the patient’s reaction to benzodiazepines, and the intensity of the patient’s refractory symptoms (cf. the crucial notion of proportionality).^{10,24–26} Thus, palliative sedation requires that the professionals involved must be competent and must have appropriate clinical experience. In contrast, what should be called slow euthanasia would start at a standard level and be progressively and intentionally titrated up according to a fixed protocol until the patient dies; this practice does not imply expert palliative care or expert clinical experience and betrays a different intention. This is *not* palliative sedation.

Informed Consent of Patient and/or Family. A positive finding of our review is that in the majority of cases, palliative sedation was performed with the explicit consent of the patient

and the family. Health care professionals did not obtain informed consent from the patient only in cases of acute physical refractory suffering (e.g., massive bleeding) or when patients were cognitively impaired. When obtaining informed consent to carry out palliative sedation, researchers noted that caregivers and family found the experience of deciding whether to sedate a patient to be very difficult and emotionally burdensome.^{38,40} This finding confirms that palliative sedation, though part of normal medical practice, is certainly not an ordinary medical act. Indeed, palliative sedation is a serious, well-discussed medical treatment of last resort.^{13,14}

Methodological Issues

Half of the studies included in this literature review were retrospective in nature (Table 3). Obviously, these studies were influenced by recall (memory) bias. Moreover, the quality of data is determined by the limited data available in patients’ charts. Given that retrospective methodology has several limitations, recent studies have shifted to using a prospective, cross-sectional design. Although of better quality, this design does not allow researchers to consider the history of a patient, an aspect that can be extremely interesting when looking at certain issues of palliative sedation, such as food and fluid intake. Moreover, most studies are based on convenience sampling and are carried out in very different settings, making it difficult to compare the results.

Implementing the best possible study design, however, remains a difficult task, because a given population of terminally ill patients has certain characteristics that may influence the choice of a particular study design or may be inextricably linked with bias. Terminally ill patients are very heterogeneous; therefore, it is very difficult to delimit a population of terminally ill patients under study. Additionally, these patients experience many symptoms concurrently, have limited survival, and are confronted with mental and physical exhaustion—all factors that hamper the feasibility and acceptability of performing studies based on patient interviews or patient self-report questionnaires.

Despite the problems we are confronted with in doing research with terminally ill

patients, we believe there is a need for more multicenter, international, prospective, longitudinal studies that use an optimal study design. We must acknowledge, however, that some questions will remain unanswered due to patient characteristics and the ethical issues involved (e.g., life-shortening effect of palliative sedation, effect of hydration).

Another important flaw in the studies we reviewed is that valid and reliable instruments specifically geared to assessing palliative care are lacking. Most of the studies were based on self-developed questionnaires (Tables 3 and 4), which underwent little or no validation process. This threatens the quality and generalizability of the results. Additionally, we found that these studies provided very vague information about informed consent procedures. One could argue that using few or no validated instruments and lacking a clear-cut procedure for consent is very problematic. On the other hand, this may be a special situation, because we are doing research in patients who are terminally ill and extremely vulnerable.

As mentioned above, comparing data from available studies is very difficult, because most of the research was done in different countries having very different cultures. For example, the practice of palliative sedation probably differs in countries with a law on euthanasia compared to countries without a law on euthanasia. Only multicenter studies in different countries will be able to reveal these differences.

Conclusions

This systematic review shows that much work remains to be done within the domain of palliative sedation. Several gaps in our current understanding still exist with regard to the effect of sedation, food and fluid intake in sedated patients, the possible life-shortening effects, and the decision-making process, to list a few. Further research should be based on multicenter, prospective, longitudinal, and international studies that use a uniform definition of palliative sedation, and valid and reliable instruments (such as instruments to assess the refractory symptoms of patients and the level of sedation/consciousness). Only through such research will we be able to resolve some of

the important ethical issues related to palliative sedation.

References

1. Georges J, Onwuteaka BD, van der Heide A, van der Wal G, van der Maas P. Symptoms, treatment and 'dying peacefully' in terminally ill cancer patients: a prospective study. *Support Care Cancer* 2005;13:160–168.
2. Hermann C, Looney S. The effectiveness of symptom management in hospice patients during the last seven days of life. *J Hosp Palliat Nurs* 2001;3:88–96.
3. Vainio A, Auvinen A. Members of the Symptom Prevalence Group. Prevalence of symptoms among patients with advanced cancer: an international collaborative study. *J Pain Symptom Manage* 1996;12:3–10.
4. Zech DFJ, Grond S, Lynch J, Hertel D, Lehman KA. Validation of World Health Organization guidelines for cancer pain relief: a 10-year prospective study. *Pain* 1995;63:65–76.
5. Ahmedzai S. New approaches to pain control in patients with cancer. *Eur J Cancer* 1997;33:S8–S14.
6. Lo B, Rubinfeld G. Palliative sedation in dying patients. *JAMA* 2005;294:1810–1816.
7. National Ethics Committee, veterans Health Administration. The ethics of palliative sedation as a therapy of last resort. *Am J Hosp Palliat Care* 2006;23:483–491.
8. Cherny NI, Portenoy RK. Sedation in the management of refractory symptoms: guidelines for evaluation and treatment. *J Palliat Care* 1994;10:31–38.
9. Müller-Busch HC, Andres I, Jehser T. Sedation in palliative care—a critical analysis of 7 years experience. *BMC Palliat Care* 2003;2(1):2.
10. Menten J. Cancer pain: interdisciplinary and comprehensive management (Dissertation). Acco: Catholic University Leuven, 2003.
11. Coyle N, Adelhardt J, Foley KM, Portenoy RK. Character of terminal illness in the advanced cancer patient: pain and other symptoms during the last four weeks of life. *J Pain Symptom Manage* 1994;5:83–93.
12. Ventafridda V, Ripamonti C, De Conno F, Tamburini M, Cassileth BR. Symptom prevalence and control during cancer patients' last days of life. *J Palliat Care* 1990;6:7–11.
13. Quill TE, Lo B, Brock DW. Palliative options of last resort. A comparison of voluntary stopping eating and drinking, terminal sedation, physician-assisted suicide and voluntary active euthanasia. *JAMA* 1997;278:2099–2104.
14. Quill TE, Byock IR. Responding to intractable terminal suffering: the role of terminal sedation

- and voluntary refusal of food and fluids. *Ann Intern Med* 2000;132:408–414.
15. Cherny NI. Sedation for the care of patients with advanced cancer. *Nat Clin Pract Oncol* 2006;3:492–500.
16. Howland J. Questions about palliative sedation. *Ethics Medics* 2005;30:1–2.
17. Boyle J. Medical ethics and double effect: the case of terminal sedation. *Theor Med* 2004;25:51–60.
18. Billings JA, Block SD. Slow euthanasia. *J Palliat Care*;12:21–30.
19. Craig G. Terminal sedation. *Cathol Med Q* 2002.
20. Taylor RM. Is terminal sedation really euthanasia? *Med Ethics* 2003;10:3–8.
21. Simon A, Kar M, Hinz J, Beck D. Attitudes towards terminal sedation: an empirical survey among experts in the field of medical ethics. *BMC Palliat Care* 2007;6:4.
22. Rousseau P. Palliative sedation and sleeping before death: a need for clinical guidelines? *J Palliat Med* 2003;6:425–427.
23. Claessens P, De Blaeser L, Broeckaert B. [Palliative sedation]. [Dutch] *Acta Hosp* 2003;4:37–47.
24. Broeckaert B. Palliative sedation: ethical aspects. In: Gastmans C, ed. *Between technology and humanity. The impact of technology on health care ethics*, 1st ed. Leuven: University Press, 2002: 239–255.
25. Broeckaert B. Palliative sedation defined or why and when sedation is not euthanasia. *J Pain Symptom Manage* 2000;20(6):S58.
26. Broeckaert B, Nuñez-Olarte JM. Sedation in palliative care: facts and concepts. In: Ten Have H, Clarke D, eds. *The ethics of palliative care. European perspectives. Facing death series*. Buckingham: Open University Press, 2002: 166–180.
27. Hawker S, Payne S, Kerr C, Hardey M, Powell J. Appraising the evidence: reviewing disparate data systematically. *Qual Health Res* 2002;12:1284–1299.
28. Rietjens JAC, van der Heide A, Vrakking AM, et al. Physician reports of terminal sedation without hydration or nutrition for patients nearing death in the Netherlands. *Ann Intern Med* 2004;141:178–185.
29. Rietjens JAC, van der Heide A, Onwuteaka-Philipsen BD, van der Maas PJ, van der Wal G. The practice of terminal sedation in the Netherlands. *Ned Tijdschr Geneesk* 2005;149:467–471.
30. Rietjens JAC, van Delden JM, van der Heide A, et al. Terminal sedation and euthanasia. A comparison of clinical practices. *Arch Intern Med* 2006;166:749–753.
31. Stone P, Phillips C, Spruyt O, Waight C. A comparison of the use of sedatives in a hospital support team and in a hospice. *Palliat Med* 1997;11:140–144.
32. Morita T, Inoue S, Chihara S. Sedation for symptom control in Japan: the importance of intermittent use and communication with family members. *J Pain Symptom Manage* 1996;12:32–38.
33. Fainsinger RL, Waller A, Bercovici M, et al. A multicentre international study of sedation for uncontrolled symptoms in terminally ill patients. *Palliat Med* 2000;14:257–265.
34. Fainsinger RL, Landman W, Hoskings M, Bruera E. Sedation for uncontrolled symptoms in a South African hospice. *J Pain Symptom Manage* 1998;16:145–152.
35. Fainsinger R, Miller MJ, Bruera E, Hanson J, Maceachern T. Symptom control during the last week of life on a palliative care unit. *J Palliat Care* 1991;7:5–11.
36. Miccinesi G, Rietjens JAC, Deliëns L, et al. Continuous deep sedation: physicians' experiences in six European countries. *J Pain Symptom Manage* 2006;31:122–129.
37. Kohara H, Ueoka H, Takeyama H, Murakami T, Morita T. Sedation for terminally ill patients with cancer with uncontrollable physical distress. *J Palliat Med* 2005;8:20–25.
38. Chater S, Viola R, Paterson J, Jarvis V. Sedation for intractable distress in the dying—a survey of experts. *Palliat Med* 1998;12:255–269.
39. Morita T, Ikenaga M, Adachi I, et al. Concerns of family members of patients receiving palliative sedation therapy. *Support Care Cancer* 2004;12:885–889.
40. Morita T, Ikenaga M, Adachi I, et al. Family experience with palliative sedation therapy for terminally ill cancer patients. *J Pain Symptom Manage* 2004;28:557–565.
41. Morita T. Differences in physician-reported practice in palliative sedation therapy. *Support Care Cancer* 2004;12:584–592.
42. Morita T. Palliative sedation to relieve psycho-existential suffering of terminally ill cancer patients. *J Pain Symptom Manage* 2004;28:445–450.
43. Van der Heide A, Onwuteaka-Philipsen B, Rurup ML, et al. End-of life practices in the Netherlands under the euthanasia act. *N Eng J Med* 2007;356:1957–1965.
44. Chiu TY, Hu WY, Lue BH, Cheng SY, Chen CY. Sedation for refractory symptoms of terminal cancer patients in Taiwan. *J Pain Symptom. Manag* 2001;21:467–472.
45. Fainsinger RL, deMoissac D, Mancini I, Oneschuk D. Sedation for delirium and other symptoms in terminally ill patients in Edmonton. *J Palliat Care* 2000;16:5–10.

46. Morita T, Chinone Y, Ikenaga M, et al. Efficacy and safety of palliative sedation therapy: a multicenter, prospective, observational study conducted on specialized palliative care units in Japan. *J Pain Symptom Manage* 2005;30:320–328.
47. Morita T, Chinone Y, Ikenaga M, et al. Ethical validity of palliative sedation therapy: a multicenter, prospective, observational study conducted on specialized care units in Japan. *J Pain Symptom Manage* 2005;30:308–319.
48. Morita T, Tsunoda J, Inoue S, Chihara S. Do hospice clinicians sedate patients intending to hasten Death? *J Palliat Care* 1999;15:20–23.
49. Morita T, Tsunoda J, Inoue S, Chihara S. The decision-making process in sedation for symptom control in Japan. *Palliat Med* 1999;13:262–264.
50. Cameron D, Bridge D, Blitz-Lindeque J. Use of sedation to relieve refractory symptoms in dying patients. *SAMJ* 2004;94:445–449.
51. Peruselli C, Di Giulio P, Toscani F, et al. Home palliative care for terminal cancer patients: a survey on the final week of life. *Palliat Med* 1999;13:233–241.
52. Morita T, Akechi T, Sugawara Y, Chihara S, Uchitomi Y. Practices and attitudes of Japanese oncologists and palliative care physicians concerning terminal sedation: a nationwide survey. *J Clin Oncol* 2002;20:758–764.
53. Morita T, Hirai K, Okazaki Y. Preferences in palliative sedation therapy in the Japanese general population. *J Palliat Med* 2002;5:375–385.
54. Morita T, Hirai K, Akechi T, Uchitomi Y. Similarity and differences among standard medical care, palliative sedation therapy, and euthanasia: a multidimensional scaling analysis on physicians' and the general population's opinion. *J Pain Symptom Manage* 2003;25:357–362.
55. Müller-Busch HC, Oduncu FS, Woskanjan S, Klaschik E. Attitudes on euthanasia, physician-assisted suicide and terminal sedation—survey of the members of the German Association for Palliative Medicine. *Med Health Care Philos* 2004;7:333–339.
56. Kaldjian LC, Jekel JF, Bernene JL, et al. Internists' attitudes towards terminal sedation in end of life care. *J Med Ethics* 2004;30:499–503.
57. Blondeau D, Roy L, Dumont S, Godin G, Martineau I. Physicians' and pharmacists' attitudes toward the use of sedation at the end of life: influence of prognosis and type of suffering. *J Palliat Care* 2005;21:238–245.
58. Sykes N, Thorns A. Sedative use in the last week of life and the implications for end-of-life decision making. *Arch Intern Med* 2003;163:341–344.
59. Vitetta L, Kenner D, Sali A. Sedation and analgesia-prescribing patterns in terminally ill patients at the end of life. *Am J Hosp Pall Care* 2005;22:465–473.
60. Morita T, Tsuneto S, Shima Y. Proposed definitions for terminal sedation. *Lancet* 2001;358:335–336.
61. Morita T, Tsunoda J, Inoue S, Chihara S. Effects of high dose opioids and sedatives on survival of terminally ill cancer patients. *J Pain Symptom Manage* 2001;21:282–289.
62. Nuñez-Olarte JM, Guillén DG. Cultural issues and ethical dilemmas in palliative and end-of-life care in Spain. *Cancer Control* 2001;8:46–54.
63. de Graeff A, Dean M. Palliative sedation therapy in the last weeks of life: a literature review and recommendations for standards. *J Pall Med* 2007;10:67–85.
64. Porta Sales J. Palliative sedation. Clinical aspects. In: Gastmans C, ed. *Between technology and humanity. The impact of technology on health care ethics*, 1st ed. Leuven: University Press Leuven, 2002: 219–237.
65. Verhagen EH, Eliel MR, De Graeff A, Theunissen SCCM. Sedation in the terminal life phase. *Ned Tijdschr Geneeskd* 1999;143:2601–2603.