

# Palliative Sedation in the Management of Refractory Symptoms

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*"I will tell him, the doctor, that he must think of something else. It's impossible, impossible, to go on like this."*

— Leo Tolstoy, *The Death of Ivan Illych*

**T**he process of dying is a ubiquitous milestone that allows patients and family members a time of reconciliation, growth, and spiritual enrichment as life enters its final chapter [1, 2]. Lamentably, it can also be a time of considerable suffering, precipitating physical and emotional anguish and fomenting desperate and unnecessary requests for physician-assisted death.

Even though symptoms can be adequately managed in most dying patients, suffering in all its domains may be refractory to standard palliative measures. When such suffering occurs, the goals of care are often modified so that the relief of symptoms may prevail over all other considerations, including the maintenance of consciousness. For that reason, when palliative therapies have been exhausted and symptoms remain refractory, palliative sedation is a valuable therapeutic adjunct that affords a more comfortable and dignified death [1]. Nevertheless, palliative sedation remains somewhat contentious, due to lack of a consistent and universal definition, disparity in clinical use, ethical and moral apprehensions, confusion regarding sedative medications, and a paucity of well-controlled research.

## Definition and Epidemiology

Palliative sedation has not been universally and definitively defined [3, 4], making interpretation,

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comparison, and extrapolation of many studies and case analyses problematic. Several definitions have been proffered, of which three will be put forward for illustration:

- Broeckaert and Olarte [5] define palliative sedation as 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.

- The Hospice and Palliative Nurses Association [6] defines palliative sedation as the monitored use of medications intended to induce varying degrees of unconsciousness, but not death, for relief of refractory and unendurable symptoms in imminently dying patients.

- The American Academy of Hospice and Palliative Medicine [7] forgoes a formal definition but suggests the use of sedating medications is intended to decrease a patient's level of consciousness to mitigate the experience of suffering, but not to hasten the end of life.

While these definitions are acceptable, many clinicians argue that palliative sedation does not necessarily mandate sedation to total unconsciousness and, instead, suggest there are variable degrees of sedation as well as duration of sedation. Although Morita and associates [8] propose a concise definition of palliative sedation similar to the above-mentioned definitions, they suggest subcategories of palliative sedation based upon degree and duration of sedation. Nevertheless, it may be better to include subcategories in the definition of palliative sedation to preclude confusion and variation in the study and practice of palliative sedation. Consequently, palliative sedation may be more clearly defined and clinically characterized as the primary intention of deliberately inducing a temporary or permanent light-to-deep sleep, but not deliberately causing death, in patients with terminal illness and specific refractory symptoms.

Although palliative sedation is unquestionably a valuable and efficacious palliative intervention and was fundamentally sanctioned by the United

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### Case History

Mr. Jones was a 73-year-old male with extensive metastatic cancer of the pharyngotonsillar region, complicated by significant chronic obstructive pulmonary disease and diabetes mellitus. His symptoms were relatively well controlled with sustained-release morphine (150 mg twice daily); immediate-release morphine sulfate (75 mg,) for breakthrough pain; and, on an “as needed” basis, haloperidol (0.5 mg) for nausea and vomiting, lorazepam (0.5 mg) for anxiety, and inhaled albuterol and ipratropium for dyspnea.

Mr. Jones did quite well on this regimen for several months, but as the disease progressed, his dyspnea worsened secondary to gradual tracheal compression from a large metastatic lesion, culminating in admission to an inpatient hospice unit for symptom control. Upon admission, numerous interventions were attempted in an effort to assuage Mr. Jones’ dyspnea, including conversion from oral morphine to a continuous subcutaneous infusion (4 mg/h); individually scheduled, small-volume nebulizations of albuterol, ipratropium, morphine, and furosemide; lorazepam (0.5 mg every 4 hours); chlorpromazine (25 mg every 6 hours); oxygen via a nasal cannula; and a fan gently blowing on his face.

Unfortunately, none of the treatments alleviated or attenuated his sense of dyspnea, and, in fact, stridor became apparent, aggravating his labored respirations. At this point, endotracheal intubation with mechanical ventilation was discussed with Mr. Jones and his family; however, they elected to forgo artificial respiratory support and chose to continue with symptomatic treatment, invoking the patient’s do-not-resuscitate election in light of the futility of intubation and assisted ventilation.

Since his dyspnea was refractory to all palliative measures, and impending respiratory failure

was clinically evident, palliative sedation was proposed as a humane and compassionate approach to allay his suffering. After explanation of the procedure, both he and his family readily agreed to deep and continuous palliative sedation. An informed consent document was signed, and a note describing the indications and plans for palliative sedation was recorded in the patient’s chart. A 5-mg subcutaneous bolus of midazolam was then administered, followed by a continuous subcutaneous infusion of 1 mg of midazolam per hour. The Ramsay Sedation Scale was utilized to monitor depth of sedation, and the dosage of midazolam was titrated upward to maintain a deep level of sedation (a 5-mg bolus every 30–60 minutes, as needed, was utilized, with the continuous infusion increased by 1 mg/h after each bolus).

Within 5 minutes he was sedated, but after 30 minutes he was still arousable with verbal stimulation, so a second bolus of midazolam was administered and his infusion increased to 2 mg/h. Titration continued over the next few hours until he was deeply sedated, with an eventual dose of 5 mg/h required to maintain deep and continuous sedation. He died 2 days later, sedated, peaceful, and with his family at his bedside.

Midazolam was chosen to provide Mr. Jones’ sedation because of its short half-life. In addition, there is extensive clinical experience with its use as sedative pharmacotherapy at the end of life. Phenobarbital is also a cost-effective and efficacious agent that can be used as a first- or second-line medication and would have been added to Mr. Jones’ regimen had a high-dose (ie, 120–200 mg/d) of midazolam failed to provide adequate sedation. Propofol has also been touted as a valuable agent for palliative sedation; however, its cost and intravenous route of administration limit its use outside of an intensive care unit.

States Supreme Court decision opposing a constitutional right to physician-assisted suicide [9–12], its use remains somewhat nebulous, with a reported incidence ranging from 2% to 52% [13–15]. Such variance in use is likely attributable to the above-mentioned lack of a universal definition, the retrospective nature of many studies, lack of consensus on the definition of a refractory symptom (particularly refractory existential suffering), ethical and moral concerns, and cultural and ethnic diversity [1, 9, 13].

### Early Studies

In 1990, Ventafridda and associates [15] were the first to describe their experience with palliative sedation, when they found that 52.5% of 120 terminally ill homebound patients required sedation to control “unendurable symptoms” during the last week of life. Their study was followed by a review of 17 case studies compiled over a 14-year period by two community-based urologists, who discussed the use of barbiturates to sedate patients

and improve symptom control during the final days and hours of life [16]. In 1991, Fainsinger and associates [17] reported on a retrospective review of 100 patients admitted to a palliative care unit during a 14-month period, noting that 16% of these patients required palliative sedation.

Then, in 1997, Stone and associates [18] retrospectively reviewed the charts of 115 patients dying in a hospital or hospice and observed that 26% received palliative sedation (31% at the hospice, 21% at the hospital). Of note in this review was the lack of difference in total time of survival after admission between sedated and nonsedated patients (18.6 vs 19.1 days, respectively).

Since those initial publications describing palliative sedation, several others have appeared. One of the more recent reviews of palliative sedation utilized an electronic database search between the years 1990 to 1999 that revealed 13 series and 14 case reports involving 342 patients; in this series of studies and case reports, sedative pharmacotherapy was used in 20%–30% of terminally ill patients [19]. Clearly then, the literature on the incidence and use of palliative sedation has been increasing and, as a result, providing more visibility, interest, and data on sedation at the end of life; however, once again, the importance of a universal definition cannot be stressed enough. Indeed, until an accepted definition is adopted by palliative care clinicians, analysis and interpretation of studies, as well as clinical acceptance and use of palliative sedation, will remain wanting by cautious and hesitant clinicians and family members.

### Ethical Framework of Palliative Sedation: The Principle of Double Effect

The ethical rationale for the use of palliative sedation derives from the principles of double effect, informed consent, and autonomy, although double effect is by no means necessary to endorse appropriate and proportionate sedation to alleviate refractory suffering. The doctrine of double effect was developed by the Roman Catholic church [20] and dates back to the Salmanticenses theologians of the 16th and 17th centuries [21]. It is applied to situations in which it is impossible to avoid all harmful actions, helping clinicians decide whether one potentially harmful action is preferable to another. In fact, double effect was utilized by the Attorney General of New York in the *Vacco v Quill* Supreme Court case to support the state's distinction between assisted suicide and what was

then referred to as terminal sedation [11, 22].

The traditional formulation of the doctrine encompasses four basic conditions:

1. The nature of the act must be good or morally neutral and not in a category that is absolutely prohibited or intrinsically wrong.
2. The intent of the healthcare provider must be good, and while the good effect and not the bad effect must be intended, the bad effect can be foreseen, tolerated, and permitted.
3. A distinction between means and effects must be envisioned, in that death must not be the means to the good effect.
4. A proportionality between the good and bad effects must be substantiated by reason, in that the good effect must exceed or balance the bad effect [13, 20].

The principled and ethical use of palliative sedation incorporates the four conditions that constitute the doctrine of double effect, although some argue that at times the beneficial intent of the clinician may be unclear and that whether death is intended or merely foreseen is ambiguous and less clear [18]. Aligned with the perceived ambiguity of intent is the distinct possibility that sedation can also be initiated without explicit consent of the patient or surrogate. Although palliative sedation can be instituted without overt discussion with patients or their surrogates, a possibility that can occur with any medical intervention, such practice is contrary to ethical and moral standards and should be vociferously prosecuted if and when discovered.

In addition, the intent of the patient, like that of the clinician, must also be considered. Ethical and moral dilemmas may arise when a patient furtively desires a quick death by requesting palliative sedation; if the patient's intent is known or suspected, ethical and psychiatric consultations are obligatory [13]. Finally, autonomy and informed consent are closely intertwined with double effect. They allow a reasonable person to make self-directed and personal treatment choices based upon a truthful and understandable presentation of information, and they are unquestionably mandatory prior to initiation of palliative sedation [13]. Both autonomy and informed consent require the patient or surrogate to have decision-making capacity, defined as the ability to receive and understand information, to deliberate and choose between alternatives, and to communicate wishes. However, clinicians should be mindful of the fact

that decision-making capacity may fluctuate and vary from time to time, thus encouraging frequent reassessment. Also, decision-making capacity is different than the legally determined attribute of competency [4], and the two terms should not be used interchangeably.

### Definition of Refractory Symptoms

A refractory symptom may be subjective and, at times, nonspecific. However, as observed by Broeckaert and Olarte [5], it is imperative not to misinterpret refractory symptoms as “difficult” symptoms, since many symptoms considered refractory are at times successfully managed by specialized hospice and palliative care programs. Interestingly, in a study by Braun and associates [23], 50% of patients receiving palliative sedation at the beginning of their study were sedated in response to symptoms that were not considered refractory. Moreover, after the implementation of clinical practice guidelines for palliative sedation, the incidence of palliative sedation was reported to be

significantly reduced. Consequently, the importance of defining a refractory symptom is central in utilizing palliative sedation in a safe, efficacious, and ethical manner.

The malignant tumors most often associated with refractory symptoms include those in the lungs, gastrointestinal tract, head and neck, colon, rectum, and breasts, though certainly any malignancy can cause refractory symptoms. Pain, dyspnea, persistent emesis, and agitated delirium are the symptoms most commonly requiring sedation [1, 23]. In addition, nonmalignant disorders may exhibit refractory symptoms, including congestive heart failure, chronic obstructive pulmonary disease, and debilitating neurological ailments, such as dementia and amyotrophic lateral sclerosis.

Most patients requiring palliative sedation demonstrate more than one refractory symptom [4, 19], and a survey of palliative medicine experts reported that 34% of their patients received sedation for nonphysical symptoms [24]. In patients sedated for nonphysical symptoms, 60% were for neuropsychiatric symptoms, whereas 6% were for “anguish.”

As to defining refractory, Cherny and Portenoy [25] suggest that a refractory symptom is one that cannot be adequately controlled despite aggressive efforts to identify a tolerable therapy that does not compromise consciousness. They also suggest that, in deciding when a symptom is refractory, the clinician must perceive that further invasive and non-invasive interventions are incapable of providing adequate relief, are associated with excessive and intolerable acute or chronic morbidity, or are unlikely to provide relief within a tolerable time frame. Similar to Broeckaert and Olarte [5], Cherny and Portenoy [25] caution that the refractory symptom must be distinguished from the difficult symptom that could potentially respond to aggressive palliative measures within a tolerable time frame without compromising consciousness.

### The Problem of Psychological Suffering

Although the term “symptom” usually connotes a physical malady, such as pain or dyspnea, Cherny and Portenoy [25] do acknowledge psychological suffering and suggest that, in a small proportion of patients, therapeutic approaches, including palliative sedation, may be necessary for such suffering. However, palliative sedation for psychological or existential suffering is ethically and morally more

**Table 1**  
Suggested Guidelines for Palliative Sedation

**Basic criteria for choosing palliative sedation:**

- Presence of a terminal illness with a refractory symptom(s)
- A do-not-resuscitate (DNR) order
- Exhaustion of all palliative treatments, including treatment for depression, anxiety, delirium, and familial discord
- Consideration of ethical and psychiatric consultations
- Consideration of assessment for spiritual issues by a skilled clinician or clergy member
- Discussion regarding the continuance of nutritional support or intravenous or subcutaneous hydration in patients receiving such treatments
- Obtaining informed consent
- Consideration of a trial of respite sedation in selected cases

**Once palliative sedation has been agreed upon:**

- Choose appropriate agent and initiate sedation
- Consider monitoring depth of sedation via Ramsay Sedation Scale or other instrument
- Titrate sedative dose upward as necessary to maintain desired level of sedation
- Administer additional bolus doses or add other agents as necessary to maintain desired level of sedation

Adapted, in part, from Rousseau [26]; used with permission.

problematic for many clinicians than is sedation for physical suffering.

To some extent, the clinical dilemma for palliative sedation in existential suffering is the lack of standardized clinical and psychological assessments for existential distress, particularly during the dying process, when overwhelming and demoralizing losses are exceedingly prevalent. Patients with existential distress may also be awake, alert, and without obvious physical symptoms, further confounding and complicating the decision to utilize palliative sedation. Most certainly, if palliative sedation is considered for existential suffering, untreated depression, delirium, anxiety, and familial discord must be distinguished from tangible refractory existential distress, and ethics and psychiatric consultations should be considered. All the same, clinicians must be cognizant that suffering from existential anguish can be just as significant and distressful as refractory physical symptoms, thus endorsing consideration of palliative sedation in refractory cases [26].

### Clinical and Pharmacological Guidelines for Palliative Sedation

To assist in decision-making regarding the use of palliative sedation, guidelines have been proposed, including the concept of respite sedation, a procedure that involves temporary and time-limited sedation [9]. Although specific criteria for palliative sedation are lacking, basic, but not all-inclusive, criteria include (Table 1) the presence of a terminal illness with a refractory symptom(s); a do-not-resuscitate (DNR) order; exhaustion of all palliative treatments directed at the symptom(s), including treatment for depression, delirium, anxiety, and any other contributing disorders; consideration of ethical and psychiatric consultations; assessment for spiritual issues by a skilled clinician or clergy member; discussion regarding the continuance of nutritional support or intravenous or subcutaneous hydration in patients receiving such treatments; obtaining informed consent; and consideration of a trial of respite sedation in selected cases.

#### RESPITE SEDATION

The concept of respite sedation involves sedating a patient for a predetermined interval, such as 24–48 hours, then downwardly titrating the sedative dose until consciousness reappears [9]. With respite sedation, second-guessing and reassessment

**Table 2**

**Medications and Suggested Doses for Palliative Sedation**

DRUG	SUGGESTED DOSE <sup>a</sup>
Midazolam	0.5–5 mg bolus IV/SC, then CII/CSI at 0.5–1 mg/h; usual maintenance dose, 20–120 mg/d
Lorazepam	0.5–2 mg PO, SL, or SC every 1–2 hours or 1–5 mg bolus IV/SC, then CII/CSI at 0.5–1 mg/h; usual maintenance dose, 4–40 mg/d
Chlorpromazine	10–25 mg PO, IV, or PR every 2–4 hours
Haloperidol	0.5–5 mg PO or SC every 2–4 hours or 1–5 mg bolus IV/SC, then CII/CSI at 5 mg/d; usual maintenance dose, 5–15 mg/d
Pentobarbital	60–200 mg PR every 2–4 hours or 2–3 mg/kg bolus IV, then CII at 1 mg/h; titrate upward to maintain sedation
Phenobarbital	200 mg IV/SC bolus, then CII/CSI at 600 mg/d; usual maintenance dose, 600–1,600 mg/d
Thiopental	5–7 mg/kg bolus IV, then CII at 20 mg/h; usual maintenance dose, 70–180 mg/h
Propofol	10 mg/h as CII; may titrate by 10 mg/h every 15–20 minutes; bolus of 20–50 mg may be used for emergency sedation

<sup>a</sup> Clinicians should consult pharmacy textbooks, pharmacists, and other knowledgeable professionals for further dosing suggestions. PO = oral; PR = per rectum; SL = sublingual; IV = intravenous; SC = subcutaneous; CII = continuous intravenous infusion; CSI = continuous subcutaneous infusion.

Adapted from Rousseau [26]; used with permission.

by clinicians and family members may be feasible [9, 13, 14], but, more importantly, patients may break a cycle of anxiety and insomnia that precipitated the request for palliative sedation, abolishing the need for further sedation.

#### MEDICATIONS OF CHOICE

The medications used for palliative sedation vary, but benzodiazepines and barbiturates are favored agents. Other medications used include the phenothiazine chlorpromazine, the butyrophenone haloperidol, and the anesthetic agent propofol (Table 2). The choice of an agent is dependent, for the most part, upon clinician preference as well as institutional policy and formulary restrictions.

Also, in difficult cases, more than one medication may be needed to sedate a patient adequately. Medications may be administered orally (until the patient is sedated), sublingually, rectally, intravenously, or subcutaneously, with the route usually patient and clinician dependent. In addition, since there is no definitive evidence that unconscious patients do not experience pain, opioid administration is usually continued once palliative sedation is initiated, although the dose is usually not increased [9].

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## Palliative Sedation

With respect to dose escalation of sedative medications, no universally accepted guidelines or protocols exist [26, 27]; however, the dose of a sedative medication should not be increased unless there is evidence of inadequate sedation. Unfortunately, there are no validated scales to assess depth of sedation in terminally ill patients, so many clinicians use direct visual observation to determine depth of sedation. However, the Ramsay Sedation Scale [28], the Intra-Operative Sedation Scale [29], and the Richmond Agitation-Sedation Scale [30] have all been utilized, although their validation and corroboration with depth of sedation in terminal illness are lacking.

## Conclusion

To care for a dying person is an honor and privilege afforded few in our society. As clinicians, our main goal is to reduce suffering while maintaining consciousness, yet refractory symptoms may engender increased suffering and a reduced quality of life. In such cases, palliative sedation offers a compassionate and humane alternative to continued suffering, both for patients and attendant family members. All the same, further studies on the use of palliative sedation are warranted; until such time, however, palliative sedation should be considered a valuable and efficacious intervention for refractory suffering at the end of life [13].

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