Palliative Sedation in Dying Patients

"We Turn to It When Everything Else Hasn't Worked"

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Despite skilled palliative care, some dying patients experience distressing symptoms that cannot be adequately relieved. A patient with metastatic breast cancer, receiving high doses of opioids administered to relieve pain, developed myoclonus. After other approaches proved ineffective, palliative sedation was an option of last resort. The doctrine of double effect, the traditional justification for palliative sedation, permits physicians to provide high doses of opioids and sedatives to relieve suffering, provided that the intention is not to cause the patient's death and that certain other conditions are met. Such high doses are permissible even if the risk of hastening death is foreseen. Because intention plays a key role in this doctrine, clinicians must understand and document which actions are consistent with an intention to relieve symptoms rather than to hasten death. The patient or family should agree with plans for palliative sedation. The attending physician needs to explain to them, as well as to the medical and nursing staff, the details of care and the justification for palliative sedation. Because cases involving palliative sedation are emotionally stressful, the patient, family, and health care workers can all benefit from talking about the complex medical, ethical, and emotional issues they raise.

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The Patient's Story

Mrs B, a 49-year-old woman with widely metastatic breast cancer, was admitted to a university hospital to control pain from bony metastases. She had been hospitalized twice within the previous 3 weeks for severe pain. At the time of last discharge, 2 days prior, she and her husband had decided to pursue hospice care. At home, her pain worsened despite her outpatient regimen of celecoxib, amitriptyline, lorazepam, and very high doses of oxycodone hydrochloride and morphine sulfate, as well as ongoing radiation therapy that did not control the progression of her metastases. She therefore returned to the hospital.

She was admitted to a comfort care suite and began receiving intravenous hydromorphone hydrochloride and lorazepam. By hospital day 2, her pain was well controlled. On hospital day 3, her pain worsened substantially and the hydromorphone infusion was increased, ultimately reaching 40 mg/h with frequent boluses of 5 to 15 mg. Overnight the pain became excruciating, despite further increases in her hydromorphone infusion to 100 mg/h and 100-mg boluses every 15 to 30 minutes.

On the morning of hospital day 4, she began to experience myoclonic jerks in her lower extremities that progressed to involve her entire body. In previous hospitalizations, morphine had caused adverse effects and fentanyl had not controlled her pain. She was given increasing doses of intravenous lorazepam, totaling 64 mg over 90 minutes, with no effect on her myoclonic activity. Throughout, Mrs B remained awake and in severe distress. Together with both Mr and Mrs B, the palliative care attending physician discussed the options available to relieve her pain and discussed her goals of care. After this discussion, the decision was made to initiate palliative sedation to provide her relief. She received a loading dose of phenobarbital and was maintained on a continuous phenobarbital infusion. Because her myoclonus persisted after she became unresponsive, intravenous dantrolene was administered. Within 20

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minutes, her myoclonus subsided. Mrs B died peacefully, with her family near, approximately 4 hours later.

PERSPECTIVES

A Perspectives editor interviewed Mrs B's husband, the intern, her nurse, and the palliative care attending physician between November 2004 and April 2005.

MR B: *My wife and I were saying good-bye to each other when suddenly she began to have spasms, whole, wracking, body spasms. Everything from her waist down would spasm every 3 to 5 seconds. After a couple hours of this, she said, "If anything, just let me sleep. I'm in pain, I can't die, and this is a nightmare."*

INTERN: *Mrs B went from being alert . . . and having her pain fairly well controlled, to having pain . . . out of control, such as I had never seen before in my short career. The issue of sedation came up as her pain became wildly out of control, despite being on huge amounts of narcotics.*

NURSE: *I'm a fairly new nurse, so this was a big surprise to me, in that it was just so hard to watch. So, I thought, "I can't believe I'm actually going to do this." The intern and I talked about how we tell patients, "If you have any pain, we will give you something to get rid of it." Ninety-nine percent of the time, that's right. But, when you get that one patient, it makes you realize that there's not a cure for everything, not all the time.*

Despite receiving skilled palliative care, some patients who are terminally ill or moribund experience distressing symptoms that cannot be adequately relieved. In this case, Mrs B endured severe pain despite large doses of opioids. A previous article in *JAMA* discussed refractory pain in cancer patients.[1] In such cases, physicians should consider options such as switching to another opioid,[2] adding other modalities (such as palliative chemotherapy or radiation therapy), addressing psychosocial and spiritual issues that might exacerbate pain, and consulting a palliative care specialist, a pain specialist, or both.

In this article, we first discuss myoclonus as a complication of high-dose opioid administration and its management. Next, we analyze the concept of palliative sedation, pointing out that broader uses of the practice are more controversial. Then we discuss the doctrine of double effect, the traditional justification for palliative sedation. The concept of intention plays a key role in this doctrine; we discuss what it means for physicians to intend to relieve symptoms rather than to hasten death. Finally, we discuss practical aspects of palliative sedation—including discussions with the patient, family, and health care team—forming a detailed plan, and agents and dosages of medication.

MYOCLONUS AT THE END OF LIFE

PALLIATIVE CARE ATTENDING PHYSICIAN: *With every breath, her body would have these uncontrollable shakes. She described it as being very uncomfortable, and it was very uncomfortable to watch her that way.*

Mrs B developed generalized myoclonus while receiving high doses of opioids for pain control. Severe twitching or jerking, usually in the extremities, is a rare but disturbing adverse effect of opioid treatment of terminal patients. Often it begins in the extremities, but, as in this case, it may become generalized. One probable cause of myoclonus associated with many opioids is the neuroexcitory effects of active glucuronide metabolites, which can also cause delirium, hyperalgesia, and seizures.[3,4] Myoclonus occurs more frequently at higher doses, but the dose-response relationship is unpredictable.[2] It may be more common when haloperidol or phenothiazines are administered concurrently.[3] These drugs were not used in this case. Myoclonus can also be caused by such treatable conditions as electrolyte disturbances, infection, and dehydration. In this case, such reversible conditions were not present. In other cases, difficult decisions arise if a prior decision has been made that palliation is the sole goal and that no further blood tests will be drawn. The physician and patient or family should discuss the option of treating symptomatically vs trying to identify potentially reversible underlying causes of the symptoms.

The treatment of myoclonus in this setting is based only on case reports and case series.[2-5] Reducing the opioid dose and rotating to another opioid may be effective.[3,4] The rationale for opioid rotation is that opioids have different affinities for various subtypes of opioid receptors in different patients. However, in this case the medical team determined that the patient's severe symptoms and her failure to respond to fentanyl and morphine precluded these approaches. Midazolam is commonly reported as an effective treatment for myoclonus in this situation; dantrolene and gabapentin have also been reported effective.[3-8] Treatment failures have been reported with diazepam.[3] In this hospital, midazolam was not permitted on the unit where the patient was receiving care. Instead, the palliative care consultant offered palliative sedation with phenobarbital and subsequently dantrolene.

What Is Palliative Sedation and When Is It Appropriate?

PALLIATIVE CARE ATTENDING PHYSICIAN: *We tried to do everything we could short of terminal sedation. Anything short of that was going to be preferable. It was always an option, but an option that came at the end. We got our pain consult service involved, we tried different medicines, we tried sedation, but not the idea of terminal sedation.*

Patients with terminal illness commonly receive sedatives; however, symptom relief generally is achieved while the patient retains consciousness.[9] The frequency of sedation to induce deep sleep, as occurred in this case, varies by setting. A multisite Canadian study reported ranges from 4% in a hospice to 10% in a tertiary palliative care unit.[9,10] In one review, the most commonly reported refractory symptoms leading to palliative sedation were agitation or restlessness, pain, confusion, respiratory distress, and myoclonus.[11]

When terminally ill, conscious patients experience intolerable symptoms that cannot be relieved even by expert palliative care, administering sedatives to induce unconsciousness may be an acceptable last resort to relieve suffering. The term *palliative sedation* has been advocated instead of *terminal sedation* in this context to avoid any implication that the intention of such treatment is to cause the patient's death.[12-14] This case illustrates 3 characteristics of cases in which palliative sedation may be justified.[9,14,15] First, alternative means of relieving symptoms either are ineffective or have intolerable adverse effects. Before characterizing symptoms as refractory, physicians should consult with an expert in palliative care or pain management, if one is readily available. In a similar case, the consultant might recommend midazolam rather than phenobarbital and might use dantrolene earlier. For the sake of discussion, we will assume that other approaches to controlling pain and reducing the dose of opioids had been considered and had either failed or were judged inappropriate. Second, the goal or intention of sedation is to relieve symptoms, not to shorten life. Otherwise, the physician's action cannot be logically distinguished from active euthanasia,[16,17] which is illegal in the United States and highly controversial ethically.[18,19] Third, the patient is "at the point of death, in a dying state, or close to death." That is, the patient is now moribund. Thus, it is unlikely that survival will be significantly shortened.

Palliative sedation might also be considered for patients who are terminally ill but not moribund, in cases involving the withdrawal of artificial nutrition and hydration, and in cases involving existential distress rather than physical symptoms. In terminal illness, it may be more difficult to conclude that symptoms are intractable, because the more extended time frame allows a wider range of palliative options to be considered and tried. However, the ethical rationale for palliative sedation, discussed below, holds equally for patients with refractory symptoms who are terminally ill as well as those who are moribund. Broader uses of palliative sedation, however, are ethically controversial. Some object when it is combined with withdrawing other life-sustaining interventions (particularly artificial nutrition and hydration).[16,17] In this case, however, withholding of artificial hydration and nutrition is not ethically pertinent. Mrs B had already stopped eating and would have died shortly even had they been administered. Moreover, these interventions would not have promoted the goal of relieving her suffering and might have increased her secretions or caused fluid overload.[20] Palliative sedation is also controversial when the refractory symptom is existential or spiritual suffering rather than physical symptoms.[14,17,21,22(pp27-29)] Critics argue that it is difficult to establish that existential suffering is refractory, and there is a perception that death is hastened because patients may live for years with refractory depression.[23,24] Physicians are often unskilled at responding to such suffering[17] and fail to consider referral to a chaplain or the patient's spiritual or religious advisor.[25,26] Despite controversy over the use of palliative sedation in these wider circumstances,[14,16,17,21,22(pp27-29)27] its rationale in cases like Mrs B's is compelling.

Doctrine of Double Effect

INTERN: *Is this euthanasia? Is this using medicine to purposely end someone's life? To me, as someone who had never heard of sedation as an option, the line seemed very blurred. It was a big ethical question that I had to talk out with the doctors and others on my team, so I felt comfortable with it.*

The traditional justification for palliative sedation is the doctrine of double effect, which draws a moral distinction between what a person intends and what is accepted as a foreseen but unintended side effect.[28-34] Administering opioids and sedatives has both intended therapeutic effects and unintended "side" effects that are not desired, but are accepted. According to this doctrine, intentionally causing death is wrong. However, the physician may order high doses of opioids and sedatives, provided that he or she intends to relieve suffering and does not intend to cause the patient's death, even if the risk of hastening death is foreseen.

The doctrine of double effect requires that several additional conditions be met.[28-30] First, the action itself (in this case administering opioids and sedatives) must not be morally wrong, independent of its consequences. Second, the secondary untoward effect (respiratory depression or death) must not be the means to accomplish the primary beneficial effect (relief of suffering). Third, there must be proportionality between the intended primary effects and the unintended but foreseen secondary effect. With palliative sedation, proportionality is established by the terminal condition of the patient, the urgent need to relieve suffering, and the consent of the patient or proxy.[29] Finally, there must be no less harmful option for achieving the goal of relieving suffering. These additional conditions mean that doctors do not have "carte blanche for causing harmful side effects when their ultimate ends are good."[29] Nor is it ethically "permissible to bring about bad results" simply because they are not intended.[28] Critics note that the doctrine of double effect justifies only sedation and not foregoing artificial hydration and nutrition.[35] If sedation interferes with eating or drinking, the ethics of hydration and nutrition should be considered separately from that of palliative sedation.

As in this case, the physician's intention to relieve severe symptoms rather than to hasten death may be inferred from her actions as well as from her statements.[36,37] First, the dose of sedative should be the lowest dose that achieves the goal of symptom relief: The initial dose should not be expected to suppress respiration to the point of carbon dioxide retention or possible respiratory arrest or to cause hypotension. A lethal dose at the onset, which allows no possibility for symptoms to be relieved without the patient's death, constitutes active euthanasia. Increases in dosage are permissible only if lower doses have been ineffective. Second, criteria for increasing the level of sedative drugs should be stated

explicitly and should seem reasonable to other physicians and nurses. The ethicist's bright line between relieving symptoms and hastening death can become blurred at the bedside. An important way to keep the line clear is to document the specific clinical signs that justify increases in sedative medication.[38] In conscious patients, the dosage may be increased if the patient reports unacceptable symptoms. If patients are unconscious or otherwise unable to report pain, physicians and nurses must assess whether patients are comfortable.[39] The dosage should be increased if the patient appears restless or grimaces, withdraws from painful stimuli, has a furrowed brow, or develops hypertension, tachycardia, tachypnea, or any other findings that could reasonably be interpreted as suffering. These parameters are similar to those anesthesiologists use to increase the level of anesthesia during surgical procedures or that intensive care unit (ICU) nurses use for evaluating discomfort in sedated, intubated, critically ill patients.[40]

Despite the wide acceptance of the doctrine of double effect to justify relieving refractory symptoms in this context, it can be criticized on several grounds.[31,41] First, it relies on a questionable account of intention.[31,42] Physicians may have more than one intention when carrying out an action.[43] In one study, in about a third of cases US physicians who ordered sedatives and analgesics while withholding life-sustaining interventions said they intended both to decrease pain and to hasten death.[44] Second, the doctrine of double effect apparently focuses on how physicians state their intentions rather than on what they do. It seems to imply that physicians are more justified in administering large doses of opioids if they can put out of mind the possibility that death may be hastened. As discussed previously, physicians need to appreciate how intentions can be inferred from actions as well as from statements. Third, people generally are held accountable for consequences they foresee or should have foreseen, not merely for those consequences that they intended.[45] Thus, the doctrine of double effect may be inconsistent with societal norms regarding responsibility for actions. In addition, the doctrine assumes that intentionally causing or hastening a patient's death is morally wrong. Some persons may disagree with this assumption and hence find the double effect analysis unnecessary.

Clinicians may find it helpful to reframe the justification for palliative sedation to focus more on proportionality than on intention.[29,46] When terminally ill patients experience refractory symptoms, the physician faces a dilemma because 2 ethical guidelines conflict: to relieve the patient's suffering and not to cause the patient's death. Both guidelines are prima facie binding; that is, while they may not be absolute, they may be overridden only for compelling reasons. Proportionality helps to balance these conflicting guidelines.[29] The risk of hastening death is warranted if lower doses of opioids or sedatives have failed to relieve the severe symptoms.[45] In this situation, compassion allows the physician to give higher priority to relieving refractory symptoms than to prolonging an existence dominated by severe suffering for a few hours or days, or even, in our opinion, a few months. The perspective of the patient is important in assessing proportionality.[32,47] Patients have different preferences for the appropriate amount of sedation in their last hours or days. Some, like Mrs B, will want relief from intolerable distress even if totally sedated, while others will prefer to have some awareness despite some continued pain or suffering.

Support for palliative sedation in the circumstances Mrs B faced, as a last resort to relieve refractory symptoms in dying patients, transcends disagreements on other bioethics controversies. Opponents of active euthanasia and physician-assisted suicide generally accept the doctrine of double effect.[17] The Supreme Court has signaled its approval of high-dose opioids to relieve refractory pain in patients with terminal illness; this may help relieve physicians' concerns about legal liability for palliative sedation.[36]

Clarifying and Communicating the Reasons for Palliative Sedation

INTERN: *Ethics, personal feelings, and medical issues can be confused and intertwined. It's important to sit down and try to separate them.*

Caregivers naturally have strong emotional reactions when a terminal patient experiences severe distress; they may be uncertain, ambivalent, or confused about the options for care and their ethical acceptability. It is essential that the health care team be clear about the justification for palliative sedation and the details of care.

The attending physicians should take the lead in discussing palliative sedation with other members of the health care team and with the patient or surrogate (BOX 1). Several points are key:

- The patient is experiencing unbearable suffering that is refractory to other interventions.
- The patient will likely not regain consciousness and will die.
- Many people are ambivalent or uncertain about palliative sedation.
- Palliative sedation is ethically and legally acceptable, and is distinguished from active euthanasia.

Frontline health care workers, such as nurses and house staff, need to be educated about palliative sedation and concur with its use in the particular case. Nursing staff that will administer the sedatives may have questions, concerns, objections, or emotional reactions.[50] In our experience, many nurses and house staff feel that they are causing the patient's death, even if they intellectually understand the rationale for palliative sedation. If, after an opportunity to talk about their reactions, a health care worker continues to object to participating in palliative sedation, it would be prudent to try to arrange for other personnel to assume care.

Discussions With the Patient or Surrogate

The agreement of the patient or surrogate is ethically important both to respect the patient's autonomy and to help

Box 1. Discussing Palliative Sedation With Patient, Family, and Medical Team*

Be Explicit About Goals and Outcomes

"We want to relieve her pain and spasms, but the usual medicines haven't worked. Our recommendation is to give her sedatives so that she can find relief. We will gradually increase the dose until she is comfortable. But to relieve her pain and spasms, we may need to give her enough medicine to make her unconscious. If she becomes unconscious, she will likely die without waking up."

Discuss Common Concerns and Misunderstandings

"What have you heard about this way to treat suffering that is out of control? Do you have any questions or concerns? How do you feel about this plan?"

"Some patients receiving this level of sedation for other purposes have reported dreamlike perceptions of their surroundings, so we encourage you to talk with her or hold her hand."

Anticipate Questions About the Dying Process and Requests to Hasten It

"It is difficult to predict how long she will live after we start the medication; it may be only a few hours or it may be several days. We will let nature take its course and not do things either to delay or to hasten death. The most important thing is for you to know is that we will do everything possible to make sure that she is comfortable."

Focus on Other Measures to Provide Closure and Comfort

"Are there things that we should do before she dies? Are there people who need to say good-bye? Are there religious rituals she would want carried out?"

*Based on Lo et al,[26] Lo et al,[48] and Back et al.[49]

him or her reach closure. The health care team needs to offer emotional support and help the patient or surrogate think through complicated ethical issues. Consultation with the ethics committee, the hospital chaplain, or the patient's own religious or spiritual advisor may be useful.

Because patients and families may be unfamiliar with palliative sedation, a general explanation may be needed. The physician may begin with open-ended questions to elicit what the patient or surrogate knows about palliative sedation and what his or her concerns are. The health care team should address any misconceptions about palliative sedation. The plan of care should include measures to provide comfort, closure, and dignity for the patient, such as saying good-byes and arranging for appropriate religious ceremonies.[48,51] Palliative sedation requires the consent of patients or surrogates and explicit acknowledgment that other interventions will be withheld.[32,47]

Practical Aspects of Using Palliative Sedation to Relieve Refractory Symptoms

NURSE: *[T]hey told me exactly what was going to happen. They told me what signs to look for, and when to stop pushing the drug.*

INTERN: *After the fact, it's important to have a forum to . . . talk about what happened, and process it.*

The ICU is the most common site where medication to relieve symptoms in dying patients may render them unconscious.[52] Often, this occurs when life-sustaining interventions are withdrawn or withheld although it is not often thought of as palliative sedation. The basic principles are the same regardless of the location.

Dosage of Medication

Pharmacologic principles suggest that a combination of an opioid and a sedative such as a benzodiazepine, barbiturate, or propofol administered as continuous intravenous drips will achieve symptom control in most patients. There are no clinical trials to guide this selection. Nevertheless, clinical experience and expert recommendations have been useful to assist clinicians in providing palliative sedation in the ICU.[52-54]

Midazolam is the most commonly used drug for palliative sedation.[9] It has a rapid onset of action, a short half-life, and a high therapeutic index.[55] In a recent review of published series, the median dose of midazolam was 1.45 mg/h, with a range of 0.42 to 20 mg/h.[11] Shafer et al[55]recommended a starting dose of 0.4 mg/h, with the expectation that the final dose would likely range from 4.5 to 10 mg/h. As a point of reference, a typical regimen for procedural sedation for bronchoscopy is a bolus of 2 to 3 mg of midazolam followed by increments of 1 mg; many patients are awake and talking after 4 or 5 mg. In the ICU, typical doses of midazolam for sedation are 0.02 to 0.08 mg/kg for intermittent doses and 0.04 to 0.2 mg/kg per hour for continuous infusion. In some patients, midazolam produces paradoxic agitation.[56]

Other sedatives, including propofol and barbiturates, can be used; however, most internists have less experience with these medications than with benzodiazepines. Propofol causes hypotension more often than does midazolam.[55,56] Clinicians will need to consider whether their hospital permits the use of these medications on the hospital ward and if the required level of nursing care is available. In some cases, transfer to an ICU or special care area for palliative sedation may be necessary. Adjunctive medication to treat specific problems, for example dantrolene for myoclonus or haloperidol for agitated delirium, may reduce the amount of sedative required to achieve comfort.[55] Paralytic agents such as pancuronium or succinylcholine are contraindicated because they do not relieve symptoms, will prevent respiratory effort, and, most importantly, hide manifestations of discomfort such as grimacing and tachypnea.[57-59]

Some clinicians may have concerns about the high doses of medication that may be required for palliative sedation.

Box 2. Points to Consider When Instituting Palliative Sedation

Consult with a palliative care or pain specialist, if readily available.

Discuss the decision with nurses, house staff, and other caregivers.

Clarify as needed the distinction between palliative sedation and euthanasia.

Obtain informed consent from the patient or surrogate.

Form an explicit plan for palliative sedation, including drugs, doses, and criteria for increasing medication by boluses or increased hourly infusions.

Ensure that the site of care provides an appropriate level of nursing care and monitoring.

Document the procedure in the medical record.

Continue to elicit and respond to concerns, questions, and suggestions.

After the patient's death, plan follow-up discussions with the family and with the health care team.

Review and possibly revise hospital policies impacting on palliative sedation.

Because of drug tolerance and individual responses to therapy, ceilings on dosage are not appropriate. In addition, empirical studies have failed to show an association between increases in doses of sedatives during the last hours of life and decreases in survival.[60] Therefore, when dosed appropriately to relieve specific symptoms, such palliative medications do not appear to hasten death.

Forming a Detailed Plan for Palliative Sedation

Because nurses and house staff may lack experience with palliative sedation, attending physicians must specify what might happen and how to respond. For continuity of care, the cross-covering physicians should receive a detailed sign out, and the attending physicians should be available by pager for questions or urgent developments.

Clinicians must also anticipate how to respond if things do not go as planned. For instance, dying may be prolonged, engendering requests to hasten the process. Reminding family members of the goals of palliative sedation and providing emotional support to deal with the stresses of prolonged dying can preempt such requests.

Because palliative sedation is uncommon, it is advisable for physicians and staff to consult with a palliative care specialist. If such specialists are not easily available, a list of points to consider may be helpful (BOX 2). After a patient dies, a follow-up discussion with the family and with the team helps people cope with their emotions and can suggest how to improve the quality of palliative care.[61] As an additional quality improvement measure, physicians should consider whether hospital policies concerning palliative sedation need to be revised.

Because palliative sedation should be considered a last resort, it usually occurs in complicated cases, under stressful conditions, and with time constraints. Although palliative sedation should never be easy for caregivers, it is immensely rewarding to relieve a dying patient's suffering, without crossing the line into ethically controversial ground.

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