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ESMO Clinical Practice Guidelines for the management of refractory symptoms at the end of life and the use of palliative sedation†

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Level of evidence statement:

Since there are no randomised studies addressing this issue, all assertions are level V based on case series and expert opinion.

introduction

In patients with advanced cancer, a readiness to address pain and other intolerable symptoms is a medical and moral imperative [1]. This has been described by Roy as the 'emancipation principle of palliative care' which states: '(one should) spare no scientific or clinical effort to free dying persons from twisting and racking pain that invades, dominates, and shrivels their consciousness, that leaves them no psychic or mental space for the things they want to think and say, and do before they die.' [2]. Indeed, there is a broad ethical consensus that, at the end of life, the provision of adequate relief of symptoms is an overriding goal, which must be pursued even in the setting of a narrow therapeutic index for the necessary palliative treatments [1, 3–12].

The provision of adequate relief of physical symptoms such as pain is a central aspect of medical care of all patients. In the care of patients with incurable illnesses that generate intense and prolonged patient suffering, this aspect of care assumes a critical significance.

symptoms at the end of life

Among patients with advanced cancer, clinical experience suggests that optimal palliative care can effectively manage the symptoms of most cancer patients during most of the course of the disease. Although physical and psychological symptoms cannot be eliminated, they are usually sufficiently relieved to adequately temper the suffering of the patient and family [13–18]. This phase may be referred to as the ambulatory phase of advanced cancer.

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It is useful to consider five phases in the natural course of progressive cancer:

(i) Diagnostic: ambulatory or inpatient.
(ii) Curative primary therapy.
(iii) Ambulatory palliative therapy.
(iv) Sedentary palliative therapy—interactional.
(v) Sedentary palliative therapy—non-interactional.

Far advanced cancer is generally characterised by loss of ambulation, increasing time in bed, and gradual loss of interactional capacity. As the disease progresses and the end of life approaches, patients commonly suffer more physical and psychological symptoms (including pain), and it often becomes more difficult to achieve adequate relief [19–25]. For some patients, the degree of suffering related to these symptoms may be intolerable. Despite intensified efforts to manage such problems, some patients do not achieve adequate relief and they continue to suffer from inadequately controlled symptoms that may be termed 'refractory'.

refractory symptoms at the end of life

The term 'refractory' can be applied to symptoms that cannot be adequately controlled despite aggressive efforts to identify a tolerable therapy that does not compromise consciousness. The diagnostic criteria for the designation of a refractory symptom include that the clinician must perceive that further invasive and non-invasive interventions are (i) incapable of providing adequate relief, or (ii) associated with excessive and intolerable acute or chronic morbidity or (iii) unlikely to provide relief within a tolerable time frame [26]. The implication of this designation is that the pain will not be adequately relieved with routine measures, and that sedation may be needed to attain adequate relief [26].

epidemiology of refractory symptoms at the end of life

Among patients with advanced cancer, clinical experience suggests that optimal palliative care can effectively manage the symptoms of most cancer patients during most of the course of the disease. Although physical and psychological symptoms

cannot be eliminated, they can be relieved enough to adequately temper the suffering of the patient and family. This phase may be referred to as the ambulatory phase of advanced cancer.

As the disease progresses and the end of life approaches, patients commonly suffer more physical and psychological symptoms (including pain), and it often becomes more difficult to achieve adequate relief [19–22, 27, 28]. For some patients, the degree of suffering related to these symptoms may be intolerable. Despite intensified efforts to manage such problems, some patients do not achieve adequate relief and they continue to suffer from inadequately controlled symptoms that may be termed 'refractory'.

Pain, dyspnoea, anxiety, and agitated delirium are among the most common symptoms of cancer patients approaching the end of life [29]. Overall, the prevalence of refractory symptoms necessitating sedation ranges from 10% to 50%, with a median estimate of 20%–30% [30–34].

palliative sedation

Palliative sedation is a measure of last resort used at the end of life to relieve severe and refractory symptoms. It is carried out by the administration of sedative medications in supervised settings and is aimed at inducing a state of decreased awareness or absent awareness (unconsciousness). The intent of palliative sedation is to relieve the burden of otherwise intolerable suffering for terminally ill patients and to do so in such a manner so as to preserve the moral sensibilities of the patient, medical professionals involved in his or her care, and concerned family and friends [26].

indications

Palliative sedation is indicated in both adults and children [35, 36], with advanced incurable (i.e. terminal) illness in order to alleviate severe symptoms that are refractory to other forms of treatment. It is most commonly utilised for the treatment of pain, dyspnoea, agitated delirium, and convulsions. However, there is much variability in the use of sedation among patients at the end of life who undergo sedation for refractory symptoms (Table 1).

Still, other than in emergency situations, intermittent or mild sedation should generally be attempted before palliative sedation. For some patients, a state of 'conscious sedation', in which the ability to respond to verbal stimuli is retained, may provide adequate relief without total loss of interactive function.

impact of palliative sedation on patient survival

The limited data show that neither the administration of palliative sedation [48] nor the degree of sedation hastens death in otherwise terminally ill patients. These findings are illustrated in the following studies:

- The impact of sedation on survival for terminally ill patients was evaluated in a 2012 systematic review of observational studies involving over 1000 patients (34% of whom underwent sedation) [48]. There was no statistically significant difference in overall survival between hospice patients who underwent sedation (median, 7–27 days) and those who did not (median, 4–40 days) [48].
- Of three studies evaluating the degree of sedation and its impact on survival after withdrawal of ventilatory support, [49–51] the largest study evaluated 42 patients, of whom 88% were administered morphine during the procedure [49]. No association was reported between the dosages of morphine used and the duration of survival.

process

patient assessment

Terminally ill patients suffering from severe distress should be evaluated urgently, preferably by a clinician with specific expertise in palliative care. This evaluation is to determine whether

Table 1. Surveys of the use of sedation in the management of refractory symptoms

	Year	*N*	Place	% Sedated for refectory symptoms	References
Ventafridda et al.	1990	120	Home	52	[30]
Fainsinger et al.	1991	100	Inpatient (IP)	16	[31]
Morita et al.	1996	143	Hospice	43	[32]
Stone et al.	1997	115	IP and home	26	[33]
Fainsinger et al.	1998	76	IP hospice	30	[34]
Chiu et al.	2001	251	IP palliative care	28	[37]
Muller-Busch	2003	548	IP palliative care	14	[38]
Sykes and Thorns	2003	237	Hospice	48	[39]
Morita	2004		Multicentre	<10–50	[40]
Kohara et al.	2005	124	IP palliative care	50	[41]
Vitetta et al.	2005	102	Hospice	67	[42]
Rietjens et al.	2008	157	IP palliative care	43	[43]
Maltoni et al.	2009	518	Multicentre	25	[44]
Mercadante et al.	2009	77	IP palliative care	54	[45]
Claessens et al.	2011	266	IP palliative care	7.5	[46]
Jaspers et al.	2012	1944	IP palliative care	18	[47]
			Hospice	22	

reversible (or treatable) factors may be playing a role in the patient's deterioration or severe distress (e.g. acute bowel obstruction, elevated intracranial pressure or a previously undiagnosed pulmonary infection). In addition, this allows for a re-evaluation of the patient's prognosis, which is essential in order to allow for the discussion of appropriate therapy.

In general, if palliative sedation is under consideration, review of the case by a multidisciplinary team (e.g. involving a palliative care team or specialists such as psychiatrists or pain specialists) should be conducted in order to ensure that all other reasonable treatments have been provided, and that palliative sedation meets the patient's goals [52, 53]. When local expertise is limited, telephone consultation with experts in palliative medicine is strongly encouraged.

talking to patients approaching the end of life

Oncologists caring for patients with advanced cancer typically need to engage in repeated, emotionally challenging conversations with patients and their families. This is one of the most difficult aspects of the oncologist's role [54, 55].

Patients are dealing with the emotional impact of the life-threatening illness, often complex treatment decisions, and limited likelihood of benefit, while at the same time trying to maintain a balance of maintaining hope with realistic and achievable goals [56–58]. The interactions occur in the context of patient preferences, family, and culture, all of which profoundly influence the discussions. They influence the amount of information patients want, how they want to receive that information, and, ultimately, how they make decisions regarding their medical care. How these discussions are carried out is a matter of profound consequence for the emotional well-being of the patient and their family [59, 60].

obtaining consent or assent

When patients with advanced illness are at risk of intolerable suffering, physicians should approach the option of palliative sedation at a time before the patient is in a crisis situation. The discussion of this option should include review of the aims, benefits, and risks of palliative sedation, as well as the alternatives to its use. If the patient permits, it is generally preferable to conduct this discussion with the participation of significant family members. This approach maximises communication and often facilitates important, meaningful discussions between patients and their families while the opportunity still exists.

For patients who are in distress but remain conscious, alert, and communicative despite these conditions, a discussion on palliative sedation should be a part of a more comprehensive conversation that includes the following:

- The patient's general condition and the cause of the distress.
- Acknowledgment that prior treatments have not been successful.
- Current prognosis, including predictions about survival.
- Rationale, aims, and methods available for the use of palliative sedation, including the depth of planned sedation, patient monitoring, and, if appropriate, the possibility of planned weaning and even discontinuation of sedation.
- Alternative treatment options, the likelihood that they may relieve distress, and the expected survival associated with each.
- Anticipated effects of sedation, including the degree of reduction in consciousness levels and the estimated effects on mental activities, communication, and oral intake.
- Potential risks such as paradoxical agitation, delayed or inadequate relief, and the possibility of hastened death (caused by aspiration or over-sedation).

Some patients have valid concerns that they may be harmed by excessively candid diagnostic or prognostic information, or by the burden of decision-making. They may not want to know the exact nature of the disease, its extent, and the details of their likely prognosis [61–64]. To protect their perceived self-interest, they may request that some issues remain unaddressed, undisclosed, or uncertain. Respecting this sort of request has been called 'necessary collusion' [61], but it is better described as voluntary diminished autonomy. Although the decision to request less information is autonomous, having less information renders the patient less able to make informed decisions. Indeed, these requests often go hand in hand with a request for either a directive approach to decision-making by the physician, or a request to delegate the decision-making to another person [65–69], often a family member, religious leader, or the treating physician.

Voluntary diminished autonomy has important implications for the consent process. A patient who chooses not to receive all of the relevant information cannot give informed consent to treatment and the usual approach of asking the patient to sign an informed consent document is inappropriate in this setting. In this setting, an assent form should include the following statements:

- The patient has been offered information about his/her condition and the treatment options.
- The patient has been provided with all of the information that he/she wanted to receive about his/her condition, the treatment options, and the likelihood of benefit and risks involved.
- The patient entrusts the informed decision-making to a nominated person who has been fully informed of the likelihood for benefit, the potential risks of harm and burden, and alternate therapeutic options. That person may be asked either to make the decision on behalf of the patient, or to recommend the treatment to the patient for his/her approval.

When informed treatment decision-making is delegated, it is prudent that the surrogate decision-maker affirms that there has been an informed decision-making process based on full disclosure of the potential benefits, risks, and alternatives.

For patients who lack decisional capacity, the advanced care plan of the patient should be followed. If there is no advanced directive, the discussion regarding palliative sedation (including consent) must be obtained from a legally recognised proxy. When the patient is a child, parental consent is required; however, care options might be discussed in an age-appropriate manner for older children to facilitate their agreement (or assent) [70, 71].

For terminally ill patients who are in the process of dying and are in severe distress, an opportunity to obtain consent by the patient or his/her health-care proxy may not present itself. In the absence of an advanced directive or health-care proxy, the provision of comfort measures (including, if necessary, the use

of sedation) should be considered standard practice and the default strategy for clinician treatment decisions.

Regardless of whether the patient has decisional capacity or not, patients and their families should be reassured that they will receive the best possible care during this time, irrespective of decisions to proceed with palliative sedation or an alternative treatment. In addition, patients should be informed that medical treatments and nursing care will be provided to ensure that the patient's comfort is maintained and that the patient's and family's wishes are respected.

discussions with family members

In situations in which the family members were not part of the consent process, permission should be sought to communicate the decision with the patient's family [72]. Informing the family should be suggested to the patient as usual practice, and the patient's permission sought in the form of assent.

With the patient's assent, discussion should be held with the family to inform them of the patient's condition, treatment options, potential outcomes of those treatment options, and the consequences of a patient's expressed preference. It is often helpful to conduct part of the discussion with the patient's participation, and part without the patient's presence to address the family's concerns alone.

In the uncommon event of patients not permitting discussion with their family, the reasons should be explored and the patients should be strongly encouraged to reconsider their decision. In some cases, this may include the need to counsel them about the potential distress that the withholding of information may cause to family members.

sedative medications

Midazolam is a short half-life benzodiazepine with a rapid onset of action and is often prescribed for palliative sedation [28, 32, 34, 73–78]. Alternatives include levomepromazine [79, 80], chlorpromazine [81, 82]; phenobarbital [83, 84] and propofol [75, 85–88]. These medications are reviewed in Table 2.

administration

Sedation for the management of refractory symptoms is usually carried out in an inpatient setting. However, substantial experience has been reported in home care settings [89–92], which may be a reasonable alternative for some patients. Irrespective of the site of administration, it is prudent that physicians be aware of any local regulatory restrictions that may impact on decision-making and patient care planning.

Administration of the selected medication initially requires dose titration to achieve adequate relief, followed by ongoing therapy to ensure maintenance of the effect. In general, the level of sedation should be the least necessary to provide adequate relief of suffering. Regular, 'around the clock' administration can be maintained by continuous infusion or intermittent bolus.

The route of administration can be intravenous, intramuscular, subcutaneous, or rectal; in some situations, drugs can also be administered via a stoma or gastrostomy. In all cases, provision for emergency bolus therapy to manage breakthrough symptoms is recommended.

If mild sedation is ineffective, deeper levels of sedation should be carried out. This is especially true in cases of refractory suffering when death is imminent, and in the case of a catastrophic event (e.g. massive haemorrhage or asphyxia).

In appropriate cases, doses can be titrated down to re-establish lucidity if it was desired by the patient before sedation. This enables an opportunity to re-evaluate the patient's condition and his or her preferences regarding sedation. It may also allow for family interactions. However, the patient should be advised before palliative sedation is initiated that lucidity may not be restored, that symptoms may reoccur, or that death may intervene.

patient monitoring

Once adequate relief has been achieved, the parameters for patient monitoring and the role of further dose titration are determined by the clinical situation:

- Patient is imminently dying [72]—we do not perform routine monitoring of vital signs (e.g. pulse, blood pressure, and temperature) for patients nearing death. The only critical parameters for ongoing observation are those pertaining to comfort. Since downward titration of drug doses places the patient at risk for recurrent distress, it is not recommended in most instances. Respiratory rate is monitored primarily to ensure the absence of respiratory distress and tachypnoea. A gradual deterioration of respiration is expected as patients near death and this alone should not constitute a reason to decrease sedation.
- Patient is not imminently dying [72]—monitoring may be undertaken to preserve physiological stability for terminally ill patients who are not imminently dying, especially in cases in which sedation is being administered as a temporary respite therapy. This may include repeat assessment of the level of sedation and routine physiological parameters such as heart rate, blood pressure, and oxygen saturation. If life-threatening obtundation with respiratory depression occurs, a lower treatment dose may be required. If patients become more unstable, the careful administration of a benzodiazepine antagonist (flumazenil) may be appropriate.

the role of nutrition and hydration

Decisions regarding the administration of hydration and/or artificial nutrition therapy are independent of the decision about whether to administer palliative sedation. Opinions and practices vary. This variability reflects the heterogeneity of attitudes of involved clinicians, ethicists, patients, families, and local norms of good clinical and ethical practice.

Individual patients, family members, and clinicians may regard the continuation of hydration as a non-burdensome humane supportive intervention that represents (and may actually constitute) one means of reducing suffering. Alternatively, hydration may be viewed as a superfluous impediment to inevitable death that can be appropriately withdrawn, because it does not contribute to patient comfort or the prevailing goals of care.

Often, the patient will request relief of suffering and give no direction regarding hydration and nutrition. Under these circumstances, family members and health-care providers must work to reach a consensus on what constitutes a morally acceptable plan based on the patient's best interests.

Table 2. Medications used for sedation in palliative care

The published literature describing the use of sedation in the management of refractory symptoms at the end of life is anecdotal and refers to the use of opioids, neuroleptics, benzodiazepines, barbiturates and propofol.		
Benzodiazepines		
Midazolam [28, 32, 34, 73–78].	Pharmacology	Water soluble, short-acting benzodiazepine. Metabolised to a lipophilic compound that rapidly penetrates the central nervous system. Brief duration of action because of rapid redistribution; therefore, administration by continuous infusion is generally required to maintain a sustained effect.
	Advantages	Rapid onset. Can be administered i.v., s.c. Can be co-administered with morphine or haloperidol.
	Starting dose	0.5–1 mg/h, 1–5 mg as needed
	Usual effective dose	1–20 mg/h
	Adverse effects	Paradoxical agitation, respiratory depression, withdrawal if dose is rapidly reduced after continual infusion, tolerance.
	Antagonist	Flumazenil
Neuroleptics/antipsychotics		
Neuroleptics may be effective when the patient is manifesting signs and symptoms of delirium. Delirium is an acute confusional state that can be difficult to differentiate from anxiety, yet the distinction is important, because the administration of opioids or benzodiazepines as an initial treatment of delirium can worsen the symptom.		
Levomepromazine [79, 80]	General	Levomepromazine is an antipsychotic phenothiazine.
	Advantages	Rapid onset, antipsychotic effect in cases of delirium, some analgesic effect, can be administered orally or parenterally (i.v., s.c., i.m).
	Starting dose	Start dose 12.5–25 and 50–75 mg continual infusion.
	Usual effective dose	12.5 or 25 mg every 8 h and every 1 h p.r.n. for breakthrough agitation or up to 300 mg/day continual infusion.
	Adverse effects	Orthostatic hypotension, paradoxical agitation, extrapyramidal symptoms, anticholinergic effects.
Chlorpromazine [81, 82].	General	Widely available antipsychotic can be administered orally, parenterally (i.v. or i.m.), and rectally.
	Advantages	Antipsychotic effect for delirious patients.
	Starting dose	i.v. or i.m. 12.5 mg every 4–12 h, or 3–5 mg/h i.v. or 25–100 mg every 4–12 h per rectum.
	Usual effective dose	Parenteral 37.5–150 mg/day, per rectum 75–300 mg/day.
	Adverse effects	Orthostatic hypotension, paradoxical agitation, extrapyramidal symptoms, anticholinergic effects.
Barbiturates and anaesthetic agents		
Barbiturates and propofol reliably and rapidly cause unconsciousness, and, since their mechanism of action differs from the opioids and benzodiazepines, they may be useful in patients who have developed extreme levels of tolerance to these other medications. They do not have an analgesic effect; therefore, opioids will probably be necessary for patients with pain.		
Phenobarbital	General	Barbiturate [83, 84]
	Advantages	Rapid onset, anticonvulsant
	Dose	1–3 mg/kg s.c. or i.v. bolus dose, followed by starting infusion of 0.5 mg/kg/h
	Usual maintenance dose	50–100 mg/h
	Adverse effects	Paradoxical excitement in the elderly, hypotension, nausea, and vomiting, Stevens–Johnson syndrome, angio-oedema, rash, agranulocytosis, thrombocytopaenia.
Propofol	General	Propofol is very similar to the short-acting barbiturates, but it has a short duration of action and a very rapid onset [75, 85–88]. These characteristics make it relatively easy to titrate [86].
	Dose	In one report, the patient was started on a loading dose of 20 mg, followed by an infusion of 50–70 mg/h [87].

If adverse effects of artificial hydration and/or nutrition therapy exacerbate patient suffering, then reduction or withdrawal of artificial hydration/nutrition should be considered.

administration of routine medications

Medications for symptom palliation used before sedation should be continued, unless they are ineffective or have distressing side-effects. Medications that are either inconsistent with, or irrelevant to, the goal of patient comfort can be discontinued.

In most cases, patients who were on pain medications (e.g. opioids) before sedation should be continued on them unless adverse effects or signs of overdose (e.g. respiratory suppression) are observed, in which case dose modifications may be necessary. If symptoms of an overdose are observed, opioid doses should be reduced but should not be rapidly withdrawn because of the risk of withdrawal.

approach to the patient's family and friends

Palliative sedation can be a welcomed method to assure patient comfort, but can also be profoundly distressing to the patient's

family members and/or friends. A few principles are useful when considering the approach to a patient's loved ones:

- They should be allowed and be encouraged to be with the patient. In many situations, an opportunity to say goodbye is of critical importance.
- They often need repeated reassurance that other methods have been sufficiently tried and/or carefully considered but were ineffective, and that sedation is unlikely to shorten the patient's life.
- They should be kept informed about the patient's well-being and what to expect.

The care team must provide supportive care to the members of the patient's family and/or friends. This includes listening to their concerns, attention to grief and physical/psychological burdens, and awareness for any perceived feelings of guilt. In addition, they should be offered advice as to ways to be of help to the patient (e.g. by being with, talking to, and touching the patient, providing mouth care, and managing the atmosphere of the patient's care).

The care team should provide regular information updates to the family including information about the patient's condition, degree of suffering, anticipated changes, or, when appropriate, notification that death is approaching and what can be expected in the dying process.

After the death of the patient, the family should be offered the opportunity to meet with his or her care providers to give them the opportunity to express grief and to discuss any outstanding concerns that they may harbour about the care delivered in the last days of life.

care of staff providing palliative sedation

Situations in which a patient has undergone palliative sedation can also be profoundly distressing to staff members. This is particularly true if there is lingering disagreement regarding the treatment plan among providers and in situations when the process is protracted.

The care team should recognise the potential for staff distress. All participating staff members need to understand the rationale for sedation and goals of care. Whenever possible this should be addressed at team meetings or case conferences, both before and after the event, to discuss the professional and emotional issues related to such decisions. Distress can be mitigated by fostering a culture of sensitivity to the emotional burdens involved in care, participating in the deliberative processes leading up to a treatment decision, sharing information, and engaging in multidisciplinary discussions that offer the group or individual opportunities to express their feelings.

special applications of sedation in palliative care

emergency sedation

Emergency sedation refers to the use of sedation to provide urgent relief of overwhelming symptoms in dying patients. Emergency situations may include massive haemorrhage, asphyxiation, severe terminal dyspnoea, or overwhelming pain crisis [93–95]. If a catastrophic situation is anticipated, advanced care directives should be discussed with the patient, family members, and health-care providers.

For patients who are at home and at risk of a catastrophic event, sedating medications should be prepared in advance and accompanied by a clear plan for emergency administration. In situations in which family members or other home carers feel that they would be unable to administer emergency medications, consideration should be given to inpatient care.

respite sedation

Respite sedation refers to the transient use of sedation to relieve severe symptoms (e.g. malaise, pain, agitation, and nausea) that are not necessarily refractory, to provide adequate relief before continuing with further trial of non-sedating palliative approaches. After such respite, some patients will be sufficiently rested to consider further trials of symptomatic therapy [32, 83, 84].

Since the aim of respite sedation is to ultimately restore the patient to their pre-treatment state of consciousness, precautions are required to ensure patient safety and to minimise risks. These include:

- Administration of the lowest effective dose of the sedative agent chosen that provides adequate comfort.
- Monitoring routine physiological parameters.

If midazolam is used, flumazenil should be readily available in the case of inadvertent overdose. Despite these precautions, this approach is associated with significant risks (including the risk that level of consciousness may not be completely restored) that should be considered in the consent process.

use of sedation in the management of refractory existential or psychological distress

Sedation in the management of refractory psychological symptoms and existential distress is controversial and is different from other situations for four major reasons [96–98]:

- Due to the nature of the symptoms being addressed, it is much more difficult to establish that they are truly refractory.
- The severity of distress of some symptoms may be very dynamic and idiosyncratic; in such cases, psychological adaptation and coping are common.
- The standard treatment approaches to address severe psychological symptoms or existential distress are not intrinsically life-threatening, such as the use of psychotherapy, religious counselling, and spiritual support.
- The presence of these symptoms does not necessarily indicate a far advanced state of physiological deterioration.

The European Association for Palliative Care (EAPC) guidelines address this issue with the following caveats [72].

- This approach should be reserved for patients in advanced stages of a terminal illness.
- The designation of such symptoms as refractory should only be made following a period of repeated assessment by clinicians skilled in psychological care who have established a relationship with the patient and his or her family, along with trials of routine approaches for anxiety, depression, and existential distress.

- Because of the complexity and frequently multifactorial nature of this situation, the evaluation should be made in the context of a multidisciplinary case conference, including representatives from psychiatry, chaplaincy, and ethics, as well as those providing care at the bedside.
- In the rare situations that this strategy is indeed appropriate and proportionate to the situation, it should be initiated on a respite basis for 6–24 h with planned downward titration after a pre-agreed interval.
- Only after repeated trials of respite sedation with intensive intermittent therapy have been carried out should continuous sedation be considered.

ethical considerations

Good clinical practice is predicated on careful patient evaluation, which incorporates the assessment of current goals of care. Since all medical treatments involve risks and benefits, each option must be evaluated for its potential to achieve the goals of care. The risks of treatment must be proportionate to the gravity of the clinical indication. In these deliberations, clinician considerations are guided by an understanding of the goals of care and should be within accepted medical guidelines of beneficence and non-maleficence.

Ultimately, the decision to act on these considerations relies on either obtaining informed consent from the patient (or his or her surrogate) or by previously determined advanced directive. In this context, the decision to offer the use of sedation to relieve intolerable suffering to terminally ill patients presents no new ethical problem [99, 100] and is supported by legal precedent [3, 101, 102].

distinction from 'slow euthanasia'

Palliative sedation is distinct from euthanasia. Voluntary euthanasia refers to the deliberate termination of the life of a patient by active intervention at the request of the patient. Palliative sedation, in contrast, is utilised for refractory suffering and:

- the intent of the intervention is to provide symptom relief, not to end the life of the suffering patient;
- the intervention is proportionate to the prevailing symptom, its severity, and the prevailing goals of care;
- unlike euthanasia, death of the patient is not the criterion used to gauge the success of the treatment.

Some authors assume that palliative sedation requires the concurrent discontinuation of nutrition and hydration [103–107]. Therefore, they argue that while sedation in the relief of uncontrolled symptoms may be justifiable, it almost certainly hastens death by allowing for starvation and dehydration. As a result, palliative sedation is practically the same as 'slow euthanasia'. However, it is important to reassert that the discontinuation of hydration and nutrition is not an essential element to the administration of sedation in the management of refractory symptoms [72, 108].

ethically problematic practices

Palliative sedation is not meant to be a means of hastening the patient's death [72]. Clinicians involved in the palliative care of patients, especially those using palliative sedation, need to be aware of the potential for harm from abusive, injudicious, or unskilled use of sedation. Potential harm is illustrated in the following examples:

Sedation as a means of hastening the patient's death—This is the most common abuse of sedation and is essentially the practice of 'slow euthanasia' [109–116]. This may occur by the deliberate use of deep sedation in patients who have no refractory symptoms, or in the deliberate use of doses that far exceed what is necessary to provide adequate comfort.

Sedation applied inappropriately—Injudicious palliative sedation occurs when sedation is applied with the intent of relieving symptoms but in clinical circumstances which are not appropriate. In this situation, sedation is applied with the intent of relieving distress and is carefully titrated to effect but the indication is inadequate to justify such a radical intervention. The following are representative examples of injudicious use:

- Instances of inadequate patient assessment in which potentially reversible causes of distress are overlooked [110, 117].
- Situations in which, before resorting to sedation, there is a failure to engage clinicians expert in relief of symptoms despite their availability [110, 118].
- The case of an overwhelmed physician resorting to sedation because he is fatigued and frustrated by the care of a complex symptomatic patient [119].
- Situations in which the demand for sedation is generated by the patient's family and not the patient him/herself [119].

Sedation withheld when it is appropriate—This may occur when clinicians rule out or do not offer the option of palliative sedation in favour of other therapeutic options that do not provide adequate relief. This may occur when anxiety about having to deal with all of the difficult discussions about sedation and end of life care results in continued futile therapeutic trials of non-sedating therapies or when there are reservations based on undue concerns about potentially hastening death.

Table 3. European Association of Palliative Care (EAPC) 10-item framework for guidelines in palliative sedation

Recommend pre-emptive discussion of potential role of sedation in the end of life care and contingency planning
Describe the indications in which sedation may or should be considered
Describe the necessary evaluation and consultation procedures
Specify consent requirements
Indicate the need to discuss the decision-making process with the patient's family
Present direction for selection of the sedation method
Present direction for dose titration, patient monitoring, and care
Guidance for decisions regarding hydration and nutrition and concomitant medications
The care and informational needs of the patient's family
Care for the medical professionals

Adapted from Cherny and Radbruch [72].

guidelines from medical groups

For palliative sedation to be used humanely and appropriately, appropriate attention to these processes is essential. While acknowledging that specific best practices have not been rigorously developed, procedural guidelines at the institutional level are necessary for clinicians to have a framework for decision-making and implementation. This promotes and protects the interests of patients, their families, and the health-care providers administering care. Sound procedural guidelines such as checklists can reduce the risk of adverse outcomes in medicine [120, 121].

Representative guidelines have been developed at a national, local, and institutional level [72, 122–130]. The EAPC developed a 10-item framework that addresses the key clinical issues in palliative sedation for the management of refractory physical symptoms at the end of life. These are summarised in Table 3 [72].

conclusions

Sedation is a critically important therapeutic tool of last resort. It enables the clinician to provide relief from intolerable distress when other options are not adequately effective. Because sedation undermines the capacity to interact, it must be used judiciously. Clear indications and guidelines for use are necessary to prevent abuse of this approach to facilitate the deliberate killing of patients, which, while benevolently intended, may have untoward sociological and ethical consequences for palliative care clinicians and the image of palliative medicine as a profession.

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