INTRODUCTION — Palliative sedation is a measure of last resort used at the end of life to relieve severe and refractory symptoms. It is performed by the administration of sedative medications in monitored 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 [1].

This topic will review the indications and administration of palliative sedation in patients nearing the end of life, as well as special applications of palliative sedation in other palliative care settings, such as in emergency situations, for respite, and for psychological distress. Other aspects of symptom care in the palliative setting are covered separately. (See "Overview of managing common non-pain symptoms in palliative care".)

INDICATIONS — Palliative sedation may be utilized in both adults and children [2-6] 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 utilized for the treatment of refractory pain, dyspnea, agitated delirium, and convulsions. However, there is much variability in the use definition of “refractory” symptoms, and thus, in the prevalence of use of palliative sedation (table 1) [7].

Some emergency situations for which palliative sedation could be considered may include massive hemorrhage, asphyxiation, an overwhelming pain crisis, and severe terminal dyspnea [8-10]. (See 'Emergency sedation' below.)

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.

Defining refractory symptoms — A symptom is considered "refractory" when it cannot adequately be
controlled by therapies that do not seriously compromise consciousness. The diagnostic criteria for "refractoriness" are based on the clinician’s determination that further invasive and noninvasive interventions meet any of the following [1]:

- Incapable of providing adequate relief,
- Associated with excessive and intolerable acute or chronic adverse effects, or
- Unlikely to provide relief within a tolerable time frame.

A refractory symptom may also be defined as one that is associated with intolerable suffering on the part of the patient.

**CONCERNS OF STAFF AND FAMILY** — Witnessing or just considering palliative sedation can be profoundly distressing to family and staff. This is particularly true if there is concern regarding the effects and ethics of palliative sedation, lingering disagreement regarding the treatment plan among providers, and in situations where the process is protracted.

**Are we hastening death?** — Multiple studies have attempted to measure the impact of palliative sedation on patient survival, and their overall conclusion is that survival is the same (or even better) when sedated patients are compared to non-sedated patients [11-18]. These studies, while important, share methodological limitations that detract from the certainty of their conclusions: they are all cohort studies, most did not incorporate cohort matching for prognostic factors, and many did not detail the degree of sedation in the intervention arm.

**Other ethical concerns** — Some family members and staff may be concerned that palliative sedation is a form of euthanasia. (See "Physician-assisted dying: Understanding, evaluating, and responding to requests for medical aid in dying", section on 'Defining and describing practices'.)

The discussion of ethical issues with family and care team members should address the distinction from euthanasia. Palliative sedation is distinct from euthanasia in that euthanasia refers to the deliberate termination of the life of a patient by active intervention, usually at the request of the patient (voluntary active euthanasia [VAE]). Palliative sedation, in contrast, is utilized for refractory suffering and the intent of the intervention is to provide symptom relief, not expressly to end the life of the suffering patient [19-26].

Discussions with family members should emphasize that uncontrolled suffering at the end of life constitutes a critical situation and that the option of palliative sedation, after obtaining informed consent by the patient (or his or her surrogate) or by previously determined advance directives, constitutes a proportionate and effective response to suffering that is within accepted medical guidelines and supported by the principles of patient autonomy and self-determination. In this context, the decision to offer the use of sedation to relieve intolerable suffering to terminally ill patients presents no new ethical problem [27,28] and is supported by legal precedent [29-31]. (See 'Obtaining consent' below and "Ethical issues in palliative care", section on 'Palliative sedation'.)

Some authors assume that palliative sedation requires the concurrent discontinuation of nutrition and hydration [32-35]. Therefore, they argue that while palliative sedation for the relief of uncontrolled symptoms may be justifiable, it almost certainly hastens death by allowing for starvation and dehydration. 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 [36]. (See 'The role of nutrition and hydration' below.)
Ethically problematic practices — Clinicians 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 death – This is the most common abuse of palliative sedation. It 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 [19-26].

- Sedation applied inappropriately – Palliative sedation may be used for an inappropriate indication, due to inadequate patient assessment that may have overlooked a potentially reversible cause of distress [20,37]. For patients in whom palliative sedation is being considered, consultation with palliative care experts or a multidisciplinary team may help identify potential and available alternatives to palliative sedation [20,38].

- Sedation given in response to the family’s (or others’) wishes and not in response to the patient him or herself (or his/her advance directives) [39].

- Sedation withheld when it is appropriate – This may occur when clinicians rule out or do not offer the option of palliative sedation in favor 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 ineffective therapies or when there are reservations based on undue concerns about potentially hastening death.

Approach to the care team — The care team should recognize the potential for staff distress [40]. 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 individuals opportunities to express their feelings.

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 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. The conversation should also emphasize the importance of comfort and our obligation to prevent or alleviate suffering.

- 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 (eg, 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 ventilate grief and to discuss any outstanding concerns that they may harbor about the care delivered in the last days of life. (See "Palliative care: The last hours and days of life", section on 'Preparing the family for the dying process'.)

**PROCESS**

**Patient assessment** — Palliative sedation may be discussed as a component of a “goals of care” discussion when death is not imminent but a patient with advanced illness is at risk of intolerable suffering, and the clinician anticipates a potential need for it in the future. 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. (See "Discussing goals of care").

However, most often the discussion about palliative sedation takes place because of a symptom crisis.

Terminally ill patients suffering from severe distress should be evaluated urgently, preferably by a palliative care clinician. This evaluation is to determine whether reversible (or treatable) factors may be playing a role in the patient’s deterioration or severe distress (eg, 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 (eg, involving a palliative care team or such specialists as psychiatrists or pain specialists) should be conducted in order to assure that all other reasonable treatments have been provided and that palliative sedation meets the patient's goals. When local expertise is limited, telephone consultation with experts in palliative medicine is strongly encouraged.

**Obtaining consent** — 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.

For patients experiencing severe or refractory distress but who are still conscious, alert, and communicative, 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 from sedation and even discontinuation
- Alternative treatment options, the likelihood that they may relieve distress, and the expected survival
associated with each

- Anticipated effects of sedation, including 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

For patients who lack decisional capacity, the advance care plan of the patient should be followed. If there is no advance directive, the discussion regarding palliative sedation (including consent) must be obtained from a legally recognized 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) [6,43]. (See "Pediatric palliative care".)

For terminally ill patients who are actively dying and in severe distress, an opportunity to obtain consent by the patient or his/her health care proxy may not be present. In the absence of an advance directive or health care proxy, the provision of comfort measures (including, if necessary, the use of sedation) should be considered standard of 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.

**Sedative medications**

- **Opioids** — Many patients are already taking sedating opioids for pain or dyspnea, and can be treated simply with upward dose titration. These medications should not be discontinued even when comfort is achieved. (See 'Administration of previous medications' below.)

- **Benzodiazepines and other agents** — **Midazolam** is a short half-life benzodiazepine with a rapid onset of action and is often prescribed for palliative sedation. In one prospective study, 24 of 176 patients (14 percent) receiving palliative care at home underwent palliative sedation using a stepwise administration of midazolam [44], which was administered predominantly due to agitated delirium. Based on the home care team and the individual patient’s relative’s experience, the use of midazolam was felt to be effective at minimizing distress and most expressed satisfaction with the procedure.

At least in the United States, **midazolam** is rarely used outside of the hospital, and is sometimes restricted to the intensive care unit (ICU), preoperative, or preprocedure settings. Another benzodiazepine option is **lorazepam**, which has a slower onset of action (10 minutes) as compared with midazolam (two minutes).

Alternative agents used in this context include **levomepromazine** [45,46], **chlorpromazine** [47,48], **phenobarbital** [49,50], and **propofol** [51-55]. These medications are reviewed in a table (table 2).

**Administration** — Sedation for the management of refractory symptoms is usually performed in an inpatient setting. However, substantial experience has been reported in home care settings [56], which may be a reasonable alternative for some patients.

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 performed. This is especially true in cases of refractory suffering when death is imminent, and in the case of a catastrophic event (eg, massive hemorrhage or asphyxia). (See "Palliative care: Overview of cough, stridor, and hemoptysis", section on 'Management'.)

**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** — We do not perform routine monitoring of vital signs (eg, 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 tachypnea. 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** — Monitoring may be undertaken to preserve physiological stability for terminally ill patients who are not imminently dying. 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.

Once sedation and symptom control is achieved, doses can later be titrated down to reestablish lucidity if appropriate, and, if it was desired by the patient, prior to sedation. This enables an opportunity to reevaluate the patient's condition and his or her preferences regarding sedation. It may also allow for patient–family communication. However, lucidity may not be restored, symptoms may reoccur, and death may intervene.

**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. This author believes that providing artificial nutrition and/or hydration to maintain a patient who is close to death and is in a state of unconsciousness does not serve the goals of care and is not generally appropriate. However, opinions and practices vary and reflect the heterogeneity of attitudes of involved clinicians, ethicists, patients, families, and local norms of good clinical and ethical practice. The topic of nutrition and hydration as part of end of life care is discussed separately. (See "Stopping nutrition and hydration at the end of life".)

**Administration of previous 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. (See "Palliative care: The last hours and days of life", section on 'Reviewing medication orders'.)
In most cases, patients who were on pain medications (eg, opioids) prior to sedation should be continued on them unless adverse effects or signs of overdose (eg, 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.

**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 hemorrhage, asphyxiation, severe terminal dyspnea, or overwhelming pain crisis [8-10]. If a catastrophic situation is anticipated, advance care directives should be discussed with the patient, family members, and health care providers. (See 'Obtaining consent' above.)

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 (eg, malaise, pain, agitation, and nausea) that are not necessarily refractory, to provide adequate relief before continuing with further trial of nonsedating palliative approaches. After such respite, some patients will be sufficiently rested to consider further trials of symptomatic therapy [49,50,57].

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 minimize 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 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. (See 'Obtaining consent' above.)

**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 the use of palliative sedation in other situations for several reasons [58,59]:

- 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 (ie, difficult to predict); 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 counseling, and spiritual support [59].
- Unlike physical symptoms such as pain or dyspnea, the presence of these severe psychological symptoms or existential distress does not necessarily indicate a far advanced state of physiological
The European Association for Palliative Care (EAPC) has provided a framework for addressing the use of palliative sedation in these circumstances [60]:

- 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 to 24 hours with planned downward titration after a pre-agreed interval.
- Only after repeated trials of respite sedation with intensive intermittent therapy have been performed should continuous sedation be considered.

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 [61,62].

Representative guidelines have been developed at a national, local, and institutional level [60,63-75]. There are several inconsistencies throughout the positions taken by organizations on palliative sedation, most notably the timing of initiating palliative sedation, the level and pattern of sedation, whether or not existential distress is an indication, and the continuation versus discontinuation of life-sustaining therapies [76,77]. Discrepancies in these areas are largely due to a number of ethical and clinical factors that make these decisions very difficult.

However, several core factors are in agreement among most position statements on palliative sedation:

- The patient must have a terminal illness where death is imminent (though the definition of imminent is variable).
- The physical symptoms that the patient is experiencing are intractable and refractory to the most aggressive interventions, with no other options for treatment that would be effective within the estimated time left before expected death.
- The intention of the intervention is symptom relief.
- The plan of sedation and the risk-benefit profile should be made explicitly in an informed consent obtained from the patient, or if incapable, the surrogate or family prior to initiation of palliative sedation.
- The decision to use palliative sedation must be discussed among an interdisciplinary team, ideally led by an experienced palliative care physician.
• Documentation of the informed consent and the provision of sedation must be thorough.

The European Association for Palliative Care has developed a 10-item framework that addresses the key clinical issues to be considered when institutions are developing guidelines for palliative sedation in the management of refractory physical symptoms at the end of life. These are summarized in a table (table 3).

SOCIETY GUIDELINE LINKS — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Palliative care").

SUMMARY AND RECOMMENDATIONS

• Palliative sedation is the monitored use of sedating medications to induce a state of decreased awareness or complete unconsciousness in order to relieve the burden of otherwise intolerable suffering at the end of life. (See 'Introduction' above.)

• Palliative sedation may be utilized in both adults and children with advanced incurable (ie, terminal) illness in order to alleviate severe symptoms that are refractory to other forms of treatment. The most common symptoms include pain, dyspnea, agitated delirium, and convulsions. (See 'Indications' above.)

• Although the data are limited, compared to patients at the end of life who did not receive palliative sedation, the use of palliative sedation does not appear to shorten survival in this setting. (See 'Are we hastening death?' above.)

• Patients who are acutely suffering should be evaluated urgently, preferably by a clinician with experience and expertise in palliative care. (See 'Patient assessment' above.)

• Irrespective of the agent selected for palliative sedation, administration initially requires dose titration to achieve adequate relief, followed by ongoing therapy to ensure maintenance of effect. In general, the level of sedation should be the least necessary to provide adequate relief of suffering. (See 'Administration' above.)

• For patients undergoing palliative sedation, monitoring should be tailored to their clinical status (see 'Patient monitoring' above):
  • For patients who are actively dying, we do not perform routine monitoring of vital signs (eg, pulse, blood pressure, and temperature). The only critical parameters for ongoing observation are those pertaining to comfort.
  • For patients who are not actively dying, monitoring is reasonable, including repeat assessment of the level of sedation and routine physiological parameters such as heart rate, blood pressure, and oxygen saturation.

• The decision about artificial hydration and/or nutrition therapy is made independently of the decision about palliative sedation itself. (See 'The role of nutrition and hydration' above.)

• Medications for symptom palliation used before initiating palliative 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 generally be discontinued. (See 'Administration of previous medications' above.)
• Loved ones often need repeated reassurance that other methods have been sufficiently trialed but were ineffective in alleviating suffering and that palliative sedation is unlikely to shorten the patient’s life. (See ‘Approach to the patient's family and friends’ above.)

• The care team should recognize 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. (See ‘Approach to the care team’ above.)

• Special applications of palliative sedation include (see ‘Special applications of sedation in palliative care’ above):
  ● The use of sedation to provide urgent relief of overwhelming symptoms in dying patients (emergency palliative sedation)
  ● Transient use of sedation to relieve severe symptoms that are not necessarily refractory (respite palliative sedation)
  ● The use of sedation to manage refractory psychological symptoms and existential distress is controversial but may be appropriate.

• Palliative sedation is not synonymous with voluntary active euthanasia (VAE). VAE refers to the deliberate termination of the life of a patient by active intervention, usually at the request of the patient. Palliative sedation is not meant to be a means of hastening the patient’s death. (See "Physician-assisted dying: Understanding, evaluating, and responding to requests for medical aid in dying" and ‘Other ethical concerns’ above.)

• We encourage the development of guidelines on a local level to establish criteria for the use of palliative sedation. We agree with the European Association for Palliative Care’s 10-item framework that addresses the key clinical issues in palliative sedation for the management of refractory physical symptoms at the end of life. (See ‘Guidelines from medical groups’ above.)

REFERENCES


60. Cherny NL, Radbruch L, Board of the European Association for Palliative Care. European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care. Palliat Med 2009; 23:581.


## Prevalence of palliative sedation in the management of refractory symptoms

<table>
<thead>
<tr>
<th>Year</th>
<th>n</th>
<th>Place</th>
<th>Percent sedated for refractory symptoms</th>
<th>Reference</th>
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<td>120</td>
<td>Home</td>
<td>52</td>
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<tr>
<td>1991</td>
<td>100</td>
<td>Inpatient (IP)</td>
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<tr>
<td>1996</td>
<td>143</td>
<td>Hospice</td>
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<td>115</td>
<td>IP and home</td>
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<td>76</td>
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<tr>
<td>2005</td>
<td>124</td>
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<td>10</td>
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<tr>
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References:

### Medications used for palliative sedation in patients with refractory symptoms at end of life*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pharmacology</th>
<th>Dosing (adult)</th>
<th>Role in palliative sedation</th>
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<tbody>
<tr>
<td><strong>Benzodiazepines</strong></td>
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</table>
| Midazolam | Short-acting GABA<sub>α</sub> agonist  
Rapidly penetrates CNS  
Brief duration of action  
Continuous infusion is generally required to maintain effect | **Acute:** 1 to 5 mg IV every 5 to 15 minutes as needed until calm.  
**Continuous infusion:** Initially 1 mg/hour IV or SQ then 0.5 to 5 mg per hour titrated to calm.  
Doses of up to 20 mg/hour have been used.  
A ceiling effect can occur. | **Role:** First-line choice.  
Often given in combination with an antipsychotic to relieve accompanying symptoms of agitated delirium.  
**Advantages:** Rapid onset. Water soluble and compatible with most drugs given by CSQI. Potent sedative and anxiolytic also useful for control of seizures, muscle spasms, nausea, vomiting, and intractable central pruritus. Reversal agent available (flumazenil).  
**Disadvantages:** Risk of paradoxical agitation and delirium. Risk of apnea with large individual doses in combination with opioid or if low cardiac output. Accumulation, prolonged sedation, and tolerance can occur after several days of continuous use. |
| Lorazepam | Intermediate-acting GABA<sub>α</sub> agonist  
Relatively slow onset  
Longer duration of effect compared to midazolam | **Intermittent:** 1 to 4 mg IV every 2 to 6 hours or 1 to 2 mg SQ every 6 to 8 hours.  
**Continuous infusion:** 0.01 to 0.1 mg/kg/hour IV or SQ. Doses of up to 10 mg/hour have been used.  
A ceiling effect can occur. | **Role:** An alternative to midazolam for patients likely to require a longer period of sedation or receiving care where midazolam continuous infusion is unavailable. Often given in combination with an antipsychotic.  
**Advantages:** Potent sedative and anxiolytic also useful for control of seizures (IV/SQ but...
Palliative sedation - UpToDate

not orally), muscle spasms, nausea, and vomiting. Prolonged onset and duration of effect may permit management with intermittent IV or SQ injections in some patients. Reversal agent available (flumazenil).

**Disadvantages:**
Relatively slow onset. Risk of oversedation when titrating due to delayed response. Risk of paradoxical agitation and delirium. IV and CSQI line incompatibilities, risk of line precipitate, tissue injury, and phlebitis. Accumulation of toxic propylene glycol solvent. Drug accumulation, prolonged sedation, and tolerance can occur after several days of continuous use.

| First-generation antipsychotics | Levomepromazine (methotrimeprazine) | Sedating dopamine D₂, 5HT₂A, H₁, alpha₁, alpha₂, and muscarinic antagonist with analgesic and amnestic effects. Usual onset within 20 to 40 minutes. | **Initial loading dose:** 12.5 to 25 mg SQ, IM or IV. **Continuous infusion:** 2 to 3 mg/hour SQ; usual effective dose 50 to 300 mg daily. **Intermittent:** 6.25 mg SQ every hour as needed with background dose of 12.5 to 25 mg daily in 1 or 2 divided doses (titrate based on as-needed dose requirements). **Role:** Sedating antipsychotic for control of delirium and/or agitation in imminently dying patient. Often given when large doses of benzodiazepine (eg, midazolam 30 mg daily) do not provide sufficient anxiolysis or calm. NOTE: Not available in the United States. **Advantages:** Effective sedative, analgesic, and anxiolytic with rapid onset and useful for control of nausea, vomiting, delirium, and agitation. Flexible delivery options include CSQI that is compatible for delivery with analgesics and anticholinergics often used in palliative care. |
### Chlorpromazine

**See levomepromazine**

**Intermittent:** 12.5 to 25 mg IV or IM every 4 to 12 hours.

**Continuous infusion:** 3 to 5 mg/hour IV. Usual effective dose 37.5 to 150 mg daily (parenteral).

**Rectal:** 100 mg every 6 to 12 hours.

**Role:** A sedating antipsychotic alternative in settings where levomepromazine is not available.

**Advantages:** Effective sedative and anxiolytic with rapid onset; also useful for control of delirium, agitation, nausea, vomiting, and intractable hiccups.

**Wide availability.**

**Disadvantages:** SQ administration is not an option due to tissue damage and pain. Anticholinergic effects, orthostatic hypotension (which can be severe) with rapid IV administration, akathisia, acute dystonic reactions, seizures, and cardiotoxicity associated with QT prolongation.

### Barbiturate

**Phenobarbital**

Enhances GABA and inhibits glutamate, providing long acting sedative, hypnotic, and anticonvulsant actions (higher doses)

**Initial loading dose:** 1 to 3 mg/kg IV or IM (100 to 200 mg); repeat after 30 minutes if needed.

**Continuous infusion:** 0.5 mg/kg/hour IV or SQ (800 mg daily); may increase if needed up to 2400 mg daily.

**Role:** A second-line option for refractory agitation in imminently dying patients who have not adequately responded to full doses of midazolam with either levomepromazine or chlorpromazine.

**Advantages:** Provides effective sedation to patients who have developed extreme...
tolerance to benzodiazepines and antipsychotics; controls refractory seizures. Maintenance dose may be administered by CSQI.

**Disadvantages:** Paradoxical excitement, especially among older adults. Other adverse effects include hypotension, bradycardia, nausea, vomiting, and serious cutaneous allergic reactions. Phenobarbital increases drug metabolism and can decrease serum concentrations of other drugs. It should not be abruptly discontinued due to occurrence of rebound seizures.

### Short-acting anesthetic

| Propofol | Ultra rapid-acting general anesthetic providing global CNS depression by GABA<sub>A</sub> potentiation and possibly inhibition of glutamate | Initiate as continuous infusion at 5 micrograms/kg/minute IV and titrate every 5 to 10 minutes in increments of 5 to 10 micrograms/kg/minute. Effective dose range: 5 to 50 micrograms/kg/minute. | Role: A second-line option for refractory intolerable agitation and delirium in imminently dying patient who has not adequately responded to full doses of benzodiazepines and antipsychotics receiving care in a specialty setting (ie, critical care unit) with access to necessary expertise and equipment. **Advantages:** Produces reliable and rapid unconsciousness. Useful in patients who have developed extreme tolerance to benzodiazepines and antipsychotics; controls refractory nausea, vomiting, and seizures. **Disadvantages:** Infusion site pain and phlebitis if given via peripheral vein. |
Delivered in an oil-in-water emulsion that can support bacterial growth, requiring strict adherence to aseptic technique and frequent bottle and tubing changes. Requires computer-controlled infusion pump. Other adverse effects: apnea with bolus injection, hypotension, allergic reactions, and bradycardia.

CNS: central nervous system; IV: intravenous; SQ: subcutaneous; CIVI: continuous intravenous infusion; CSQI: continuous subcutaneous infusion; SHT: serotonin; IM: intramuscular.

* The medications listed in this table for palliative sedation in general do NOT provide analgesia. Analgesia must be provided prior to and during use of palliative sedation with appropriate opioid and non-opioid options. For additional information, refer to UpToDate topic reviews of pain assessment and management at end of life.

¶ Immediate deep sedation is rarely needed, ie, for sudden massive hemorrhage.

Courtesy of author with additional data from:


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### European Association of Palliative Care (EAPC) 10 item framework for guidelines in palliative sedation

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
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<tbody>
<tr>
<td>1.</td>
<td>Recommend preemptive discussion of potential role of sedation in end of life care and contingency planning.</td>
</tr>
<tr>
<td>2.</td>
<td>Describe the indications in which sedation may or should be considered.</td>
</tr>
<tr>
<td>3.</td>
<td>Describe the necessary evaluation and consultation procedures.</td>
</tr>
<tr>
<td>4.</td>
<td>Specify consent requirements.</td>
</tr>
<tr>
<td>5.</td>
<td>Indicate the need to discuss the decision making process with the patient's family.</td>
</tr>
<tr>
<td>6.</td>
<td>Present direction for selection of the sedation method.</td>
</tr>
<tr>
<td>7.</td>
<td>Present direction for dose titration, patient monitoring, and care.</td>
</tr>
<tr>
<td>8.</td>
<td>Guidance for decisions regarding hydration and nutrition and concomitant medications.</td>
</tr>
<tr>
<td>9.</td>
<td>The care and informational needs of the patient's family.</td>
</tr>
<tr>
<td>10.</td>
<td>Care for the medical professionals.</td>
</tr>
</tbody>
</table>

*Source: Cherny NI, Radbruch L. European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care. Palliat Med 2009; 23:581.*

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