

## Review Article

# Palliative Sedation in Patients with Advanced Cancer Followed at Home: A Systematic Review

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## Abstract

**Context.** Patients with advanced cancer who are near the end of life may experience intolerable suffering refractory to targeted palliative therapies. Palliative sedation (PS) is considered to be an effective treatment modality for these refractory symptoms when aggressive efforts fail to provide relief.

**Objectives.** The aim of this study was to systematically review articles regarding PS performed at home in patients with intractable symptoms.

**Methods.** Literature databases searched included MedLine, PubMed, and EMBASE. The text words and MeSH/EMTREE terms “home care” and “sedation” were used for electronic database searches.

**Results.** Six articles met the inclusion criteria for research and reported data regarding patients who were sedated at home. Although an early study reported a rate of more than 50%, the majority of the most recent literature, even though retrospective, shows an incidence of PS of 5%–36%. Agitated delirium, dyspnea, and pain were the most common problems requiring PS. The duration was variable (the mean across studies 1–3.5 days), and has not been statistically associated with hastened death. Benzodiazepines, specifically midazolam, have been most frequently used, alone or in combination with neuroleptics and opioids; in one article, opioids were given alone.

**Conclusion.** PS at home seems to be a feasible treatment option among selected patients and makes a potentially important contribution to improving care for those who choose to die at home. Although the existing studies provide only low-quality evidence, the decision to use PS does not seem to anticipate patients' death. More homogeneous prospective studies on a large number of patients

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### **Key Words**

*Palliative sedation, end of life, home care*

## **Introduction**

Some terminally ill patients with cancer who are near the end of life may experience intolerable suffering refractory to targeted palliative therapies. Palliative sedation (PS) is considered to be an effective treatment modality for these refractory symptoms when aggressive efforts fail to provide relief.<sup>1</sup> According to the definition proposed by the European Association for Palliative Care (EAPC), PS is the use of sedative medication to relieve intolerable suffering in the last days of life.<sup>2</sup> An even more specific definition is the use of nonopioid drugs to control refractory symptoms in the dying.<sup>3</sup> Some elements of PS have been specified by a recent expert panel, providing detailed recommendations for terminology and definitions, indications and conditions, decision making and informed consent, cultural issues, ethical aspects, type of sedation and drugs, outcomes and monitoring, nutrition, and hydration.<sup>4</sup>

PS for intractable distress in the dying has been debated during recent years for the obvious ethical, sociocultural, and decision-making implications.<sup>1</sup> It has been reported to be provided to 2%–52% of terminally ill patients,<sup>3</sup> and studies have suggested that PS is successful in managing untreatable symptoms close to death and is satisfactory for relatives.<sup>5</sup>

Despite the efforts made by some hospice and palliative care units to offer a natural setting for PS, with continuous monitoring and participation in the process, a home death with PS can be challenging. This points to the importance of palliative care and the experience of people skilled in both symptom control and end-of-life care at home. As most patients die at home in many countries, and this remains the death place of preference,<sup>6</sup> information gathered in this setting should be of evaluable relevance.

The existing literature on PS must be characterized to provide the foundation for future research. The aim of this study was to systematically review the literature regarding

PS performed at home in cancer patients with intractable symptoms.

## **Methods**

The databases searched included MedLine, PubMed, and EMBASE. The text words and MeSH/EMTREE terms that were used for the search included “home care” and “sedation.” In total, 13,316 abstracts were retrieved. The use of the MeSH/EMTREE term “palliative care” restricted the research to 1427 abstracts. Only articles that were pertinent to the aim of this review and provided some data were taken into consideration. Hand search of the congress proceedings of the EAPC for the last three years also was performed to include the gray literature. Given the expected paucity of data, case reports of retrospective, prospective, and noncontrolled studies were included. Only articles published in the English language were screened.

## **Results**

Only six articles met the inclusion criteria for research and reported data regarding patients who were sedated at home. The principal characteristics of the selected articles are presented in [Table 1](#). In some articles, various data were unavailable, including indications for PS,<sup>7,8</sup> mean duration of PS,<sup>7</sup> and drug used for PS.<sup>7,9</sup>

## **Definitions**

No definition was provided in a pioneer study by Ventafridda et al.<sup>9</sup> In an article in which PS was not the primary outcome, it was defined as the administration of drugs to obtain total loss of consciousness.<sup>7</sup> However, the large variability observed in the use of PS among centers suggests a lack of appropriate criteria adopted for definition. In subsequent articles, most of the definitions adopted for PS were similar and reflected a unanimous

Table 1  
Published Articles on PS at Home

Authors/Year/Country	Design	Sample of Patients at Home, n (% Sedated)	Principal Drugs and Doses (mg/day)	Principal Indications	Mean Duration (days)
Ventafriidda et al./1990/Italy <sup>9</sup>	Prospective	154 (52)	NA	Dyspnea, pain	2
Peruselli et al./1999/Italy <sup>7</sup>	Prospective, multicenter	100 (25)	NA	NA	NA
Bulli et al./2007/Italy <sup>8</sup>	Prospective	1075 (12–14.2)	Neuroleptics Midazolam Opioids	NA	1
Rosengarten et al./2009/Israel <sup>10</sup>	Retrospective	720 (5)	Morphine (12–240) Midazolam (12–144)	Pain, agitation	3
Porzio et al./2010/Italy <sup>12</sup>	Retrospective	44 (36)	Midazolam (24–48)	Delirium, dyspnea	3.5
Alonso-Babarro et al./2010/Spain <sup>11</sup>	Retrospective	245 (12)	Midazolam (58–97)	Delirium, dyspnea	2.5

NA = not available.

concept, that is, the use of specific sedatives to relieve intolerable suffering from refractory symptoms by reducing a patient's level of consciousness.<sup>8,10–12</sup> In an Italian study, to be eligible for PS at home, patients had to reside no farther than 20 minutes away from the hospital and there could be no other sources of suffering in the family.<sup>12</sup>

#### Frequency of PS

The frequency of PS varied,<sup>7–12</sup> ranging from 5%<sup>11</sup> to 52.5%.<sup>9</sup> In a multicenter study, the use of sedation ranged from 0% to 60%, implying a lack of defined criteria and marked variation among centers.<sup>7</sup>

#### Indications

Dyspnea (52%), pain (49%), and delirium (17%) in different combinations were more frequently reported in a pioneer study as an indication for PS,<sup>9</sup> whereas in another two Italian studies, percentages were not reported.<sup>7,8</sup> In a more recent study, pain (58%) and agitation/delirium (63%) were the most frequent indications for PS.<sup>10</sup> However, in other studies, pain was relatively infrequent as an indication for PS. In one of these studies, delirium was predominant as an indication for PS (82%), and the remaining patients had dyspnea (18%).<sup>12</sup> Similarly, in another study, delirium (62%) and dyspnea (14%) were also the most frequent indications for PS.<sup>11</sup>

#### Outcomes

No formal evaluation and outcome measures have been reported. By using a scale of 1–4, based on the assessment of family

members and medical staff, marked and good improvement in symptom control were achieved in 61% and 17% of patients, respectively.<sup>10</sup> None of the studies monitored the process of dying after starting PS.

#### Drugs

A stepwise approach has been used in the studies of PS, starting with midazolam (1 mg/hour, followed by 2 mg/hour) and adding neuroleptics in cases of failure. The first step was effective in 62.5% of patients.<sup>12</sup> Midazolam in doses of 58–97 mg/day was sufficient for achieving PS in 97% of patients, whereas 7% required levomepromazine 100–150 mg/day.<sup>11</sup> In one article, however, to achieve sedation, opioid doses, given alone, were increased, possibly because pain was the prevalent indication for PS.<sup>10</sup> A 25%–41% increase in the dosage of opioids during the last 24 hours of life also has been reported in an Italian experience.<sup>8</sup> This trend decreased in a later report, with reliance in this study on a combination of benzodiazepine, neuroleptics, and opioids (65%). Data were unavailable in two early Italian studies.<sup>7,9</sup>

#### Duration of PS

The duration of PS varied in this literature. In a large study, the duration of PS was less than two days, and more than 65% of all patients sedated endured PS for a period of one day or less.<sup>8</sup> In another study performed in Israel, the mean duration of sedation was three days (range four hours to 13 days).<sup>10</sup> In other studies, the mean duration of PS ranged from 49 hours<sup>9</sup> to 3.6 days.<sup>12</sup>

### *Factors Influencing PS at Home*

In a large study of 1075 patients during two different periods, death occurred at home in more than 85% of cases. Sedated patients were younger and had a survival significantly higher than those patients who were not sedated. During PS, 33%–65% of the sedated patients were not hydrated.<sup>8</sup> No differences in survival were evidenced in patients who received PS and those who did not require sedation.<sup>9</sup> Similarly, in another review of medical records of home care patients who died at home, there was no significant difference in survival after initiation of palliative care between the patients who received PS at home and those who did not receive PS. The mean age of the patients who received PS was significantly lower than that of the patients who did not receive PS.<sup>11</sup>

### *Ethical Concerns*

In a pioneer study, PS was carried out with the patient's consent formulated in advance or ad hoc, with no changes of consent. If the patients were delirious or extremely ill, a living will was considered, as well as the consent of the family.<sup>9</sup> In a large Italian study,<sup>8</sup> 62% of the patients sedated at home had not been informed.

In a retrospective study performed in Spain, there was also more awareness of their prognosis in patients who were sedated before death, and the decision to start sedation was made with the patient in 45% of cases.<sup>11</sup> Informed consent was obtained by patients or relatives after an agreement among staff members was achieved.<sup>12</sup> Verbal informed consent to initiate PS was received directly from patients deemed to be competent or from their immediate family member.<sup>10</sup> No data were available from a multicenter Italian study.<sup>7</sup>

### *Discussion*

Patients with cancer spend most of their lives at home and often are at home during the last week of life.<sup>6</sup> Admission to hospital or staying at home in the last days of life depends on many different factors, including resource availability and personal preference, other than clinical needs. PS is a common procedure in palliative care and has caught the attention of

several authors and investigation groups in the last years. Inpatient palliative care units are well recognized as settings where PS may be used when symptoms are uncontrolled close to death. Continuous personnel availability, environment, resources, and facilities facilitate this difficult process. Based on this experience, it is commonly held that PS may be appropriate when other treatments fail to relieve suffering in the imminently dying patient, and PS does not accelerate death.<sup>4,13</sup>

The clinical experience in providing PS at home has been limited, and very few data exist. We were able to retrieve only six articles providing meaningful data, half of them reports of retrospective observational studies. Of interest, four articles were produced in Italy, possibly because home care has been for years the only setting to provide palliative care because of a slow development of palliative care units.

### *Clinical Features of PS at Home*

The frequency of PS observed in the few available studies is quite different. The high discrepancy among the studies has been explained by the variation in the facilities in countries with different cultures or health care systems. The highest rates of PS at home reported have been in countries where inpatient end-of-life care is scarce.<sup>10</sup> Although an early study reported a rate of more than 50%,<sup>9</sup> the majority of the most recent literature, even though retrospective, shows an incidence of PS of 5%–36%,<sup>7,8,10–12</sup> which seems lower than the 20%–50% rate reported by hospital-based palliative care units during the same periods,<sup>5,14–17</sup> with the highest rate in acute units.

It is likely that hospitalized patients tend to have a greater symptom burden than those who remain at home. Alternatively, home care may offer a better environment, limiting the occurrence of disorientation and delirium.<sup>11</sup> Although in one of the studies the frequency of PS at home was higher than that reported in the in-hospital beds (36% vs. 21%), only 36% of patients who were followed by the palliative care team died at home.<sup>12</sup> In another experience of patients with advanced cancer followed at home, more patients were sedated when moved to hospital than when remaining at home (32% vs. 23%).<sup>9</sup>

Unlike the hospital setting, it is relevant to consider the scenario of home-based

treatment, including available facilities, drugs, and delivery systems; greater autonomy and responsibility; and the additional emotional burden of the staff members and involvement of family members in direct care. A critical factor is represented by the need for a continuous bedside presence and a level of cooperation from both staff and family members as the intensity of treatment increases. Also, the setting and different clinical situations in which the decision has to be taken are of paramount importance: whether the sedation was planned ahead or was needed urgently, whether the preferences of the dying patient were known, or whether there are emotional and cultural difficulties encountered in taking control of the patient's symptoms in the last stages of his or her life. Finally, lack of awareness on the part of the home care staff or lack of agreement on the part of patients and/or families may influence the rate of PS.

Agitated delirium, dyspnea, and pain were the most common problems requiring PS. These indications have been invariably reported in the literature in other settings,<sup>4,13</sup> although pain seems to hardly be a unique indication to sedate, and often difficult to distinguish from other manifestations of suffering. Existential suffering can be just as debilitating as physical suffering and, in some cases, is not distinguishable. Rather, it seems that delirium and dyspnea are the most frequent indications for PS in the dying patients, as it occurs in hospitalized patients.<sup>3,5</sup>

Most studies did not provide information about patient assessment and tools to measure the effectiveness of PS, other than a general satisfaction score based on assessment of family members and medical staff<sup>10</sup> of the intensity of symptoms before starting sedation.<sup>10,12</sup> The Ramsay Sedation Scale was used to measure the level of unconsciousness.<sup>11</sup> Despite the lack of appropriate means, these studies suggested that PS may be used safely and efficaciously to treat dying cancer patients with refractory symptoms at home. More prospective data with specifically designed tools and appropriate study design should confirm this observation regarding PS at home.

As reported in hospitalized patients, the duration of PS varies,<sup>9,12</sup> with the longest period reported up to 13 days.<sup>10</sup> In most cases, however, death occurred within 48 hours.<sup>8</sup>

Younger patients are more likely to receive PS at home.<sup>9,11</sup> This observation confirms previous data reported in palliative care units.<sup>5,16</sup> The reasons may rely on the need for more complex treatments and a different psychological status in younger people than in older patients, although this aspect should be better examined. Communication seems to have some influence on the decision to start PS. Patients who received PS were more likely to have been aware of their prognosis than those who did not receive PS.<sup>11</sup>

Survival in patients who were sedated was similar or higher than that observed in patients who were not sedated.<sup>8,9,11</sup> This observation seems to suggest that PS performed at home does not hasten death if carefully administered by palliative care specialists.<sup>11</sup> However, the scientific design and the limited powered statistics do not allow a clear conclusion. This aspect is worthwhile of further studies, as it is a very difficult issue to demonstrate in the context of a dying patient.

In recent years, benzodiazepines have been more frequently used to induce and maintain sedation. A benzodiazepine has been added to an opioid, which was likely to be previously administered for analgesic purposes and/or dyspnea.<sup>5,18</sup> The preferred benzodiazepine has been midazolam, which has been used in doses titrated against the effect with a maximum of 240 mg/day. In some countries, like Italy, midazolam is unavailable for extra-hospital use, and it is supposed that it could be provided by hospital-home teams authorized to do that.

One article described patients who were given opioids alone for PS.<sup>10</sup> Additionally, a 25%–41% increase in the dosage of opioids during the last 24 hours of life has been reported in an Italian experience.<sup>8</sup> This trend decreased during a second period examined, with a prevalence of a combination of benzodiazepine, neuroleptics, and opioids. The decision to sedate using an opioid could pose problems and raise concerns about the use of a drug whose primary purpose is analgesia.<sup>19</sup> Opioids are not appropriate to relieve suffering from exhaustion, delirium, anxiety, agitation, and psychological suffering; rather, they may aggravate delirium. This should be emphasized in an effort to avoid clinical decisions that may not be adequately defensible and

could be open to criticism. In appropriate hospice settings or acute palliative care units, opioids were given in combination with midazolam in almost all patients.<sup>5,17</sup> The opioids may play a basic role in treating dyspnea or death rattle. However, although opioids are a first choice for the treatment of pain and/or dyspnea, even during sedation, unfortunately opioids still are administered alone as sedative agents in general practice.<sup>20,21</sup>

### *Ethical Concerns*

It is essential to educate the patient or relatives about the meaning of PS, and verbal informed consent to initiate PS should be received directly from patients deemed to be competent or their immediate family members.<sup>10</sup> No clear documentation has been reported regarding the involvement in the decision-making process immediately before starting PS. Consent is necessary even in the most difficult situations, when PS is needed urgently, the preferences of the dying patient are unknown, and emotional distress exists.<sup>8</sup> The onset of PS often corresponds to a moment in which the patient is not entirely mentally lucid. The ideal would be to allow the patient to plan ahead his own treatment, but a timely intervention is often an insurmountable task.

The question regarding hydration and nutrition was raised in two articles. Although forced nutrition was considered inappropriate, fluids at a low-maintenance dose, which also allows a delivery route for drugs, was unanimously approved by the patients and their families.<sup>10</sup> In an Italian study, however, the trend to use hydration was less common; two-thirds of patients received no fluids.<sup>8</sup> It is likely that hydration in some circumstances is a relatively unimportant factor in influencing quality of life and may even have negative repercussions.<sup>5</sup> A separate decision in each case is warranted.

### *Conclusion*

Palliative sedation at home seems to be a feasible and successful treatment option among selected patients and makes a potentially important contribution to improving care for those who choose to die at home. The decision does not seem to hasten death. The latter

assertion remains weak, however, because of the limitations of the studies performed. The available literature describing the practice of PS at home, as well as other settings, is far from adequate. The quality of some articles is weak, just reporting data from a cohort with a historical comparison. More homogeneous prospective studies on a large number of patients should be performed to provide a more reliable conclusion. Monitoring of the process of dying and specific tools should help in recognizing and appreciating the value of PS. Comparison studies on the outcome of PS performed at home and in inpatient units should add further data to expand this treatment at home.

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