

# Hospice pharmaceutical care: the care for the dying

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Increasing symptom burden may require intensified pharmacological and non-pharmacological interventions in the terminal phase. In addition, treatment goals have to be reconsidered as patients' needs and priorities may have changed considerably in the terminal phase. Indications for some medical treatment such as chemotherapy, antibiotics or fluid substitution may also change or disappear in the terminal phase. Team discussions may be helpful to evaluate the balance of beneficial and non-beneficial effects of the medicines and facilitate the decision on withholding or discontinuation. Pain intensity in dying patients is not always stable, and an adaptation of the analgesic medication may be necessary as the pain may exacerbate with the progression of the disease or diminish with the deterioration of bodily functions. Patients may have to be switched to short acting application forms to allow flexible dose adaptation. If patients are unable to take oral medications, a switch to subcutaneous application of morphine or hydromorphone is recommended. Pulmonary secretions (death rattle) should be treated with anticholinergic drugs such as hyoscine. Terminal restlessness and agitation should be treated causally whenever possible—for example, with subcutaneous infusions in dehydrated patients. However, most dying patients with terminal restlessness will require symptomatic treatment with benzodiazepines or neuroleptics. As many dying patients will suffer from new symptoms, the standard prescription of a rescue medication for all patients in the terminal phase is recommended. This will allow a rapid response from nurses or other qualified healthcare staff.

Following the definition of the WHO, palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life threatening illness through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.<sup>1</sup> Hospice care is sometimes used synonymously with palliative care. However, in many European countries hospice also stands for inpatient units or home care services that care for patients who face the end of life in the terminal stage of their disease.<sup>2</sup>

Palliative care is often misunderstood to be restricted to the imminently dying patient and to patients with advanced cancer. However, both are not true. Early access to palliative care has proven to be

beneficial,<sup>3</sup> and palliative care needs have been described for patients with chronic pulmonary disease<sup>4</sup> and heart disease.<sup>5</sup>

However, regardless of how early in the disease trajectory palliative care has been initiated, the vast majority of patients will need palliative or hospice care most in the terminal phase, in the last days and weeks of life. Symptom burden often increases with disease progression, as existing symptoms become more intense and new symptoms develop.

Physical and cognitive functions have often deteriorated slowly with progression of the disease—for example, with cachexia related changes in metabolism that are very frequent in cancer patients as well as in cardiac patients. This is augmented by physiological changes such as decreased circulation or irregular breathing patterns in dying patients. The symptom load can be increased disproportionately with these changes. In addition, psychosocial problems and spiritual concerns may add to the burden of pain and other physical symptoms at the end of life.

Increasing symptom burden may require intensified pharmacological and non-pharmacological interventions in the terminal phase (table 1). In contrast, physiological changes can also improve bioavailability, decrease distribution volume and elimination half-time, and these changes in pharmacokinetics increase the

effectiveness of medications, requiring dose reductions to avoid adverse effects. In addition, treatment goals have to be reconsidered as patients' needs and priorities may have changed considerably in the terminal phase.

Flexible adaptation of symptom control and adaptation of the care plan to changing goals requires palliative care expertise. Whereas for most dying patients competent care can be provided by primary care givers such as general practitioners, community nurses or hospital staff with basic palliative care training, a significant minority of patients with complex needs and problems require a higher degree of expertise. These patients should be treated by a multiprofessional palliative care team with adequate competencies in symptom control, communication with patient and family as well as psychosocial and spiritual care. Palliative care teams can work in a range of settings, from hospices and palliative care units to home care teams.<sup>6</sup> A major challenge in the development of palliative care is to ensure access to adequate palliative care not only in urban centres but also in rural areas or in settings such as nursing homes.

## Needs and treatment goals

Evaluation and repeated re-evaluation of patients' needs and priorities is a major

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**Table 1** Medications for symptom control in dying patients

Symptom	Application route	Dosage (starting dose)	Indication
Pain			
Morphine	Subcutaneous, intravenous	5–10 mg per bolus, 10–30 mg/day (or more)	Pain
Hydromorphone	Subcutaneous, intravenous	0.5–2 mg per bolus	Pain, dyspnoea
Fentanyl	Transdermal	12.5–400 µg/h (or more)	Stable pain
Ibuprofen	Oral	1200–2400 mg/day	Soft tissue pain or bone pain
Dyspnoea			
Morphine	Subcutaneous, intravenous	5–10 mg as bolus, 10–30 mg/day (or more)	Dyspnoea
Lorazepam	Sublingual	0.5–2.5 mg per bolus	Dyspnoea
Scopolamine	Subcutaneous	2–4 mg per bolus	Respiratory secretions
Butylscopolamine	Subcutaneous	20–40 mg per bolus	Respiratory secretions
Nausea, vomiting			
Metoclopramide	Oral, subcutaneous, intravenous	3×10 mg /day	Nausea, vomiting
Haloperidol	Oral, subcutaneous, intravenous	0.5–5 mg per bolus	Nausea, vomiting
Gastrointestinal obstruction			
Octreotide	Subcutaneous	50–500 µg/day	Excessive secretions in gastrointestinal tract
Terminal restlessness, agitation			
Lorazepam	Sublingual	1 mg	Anxiety, agitation, restlessness
Midazolam	Subcutaneous, intravenous	2.5–5 mg per bolus, 15–30 mg/day	Anxiety, agitation, restlessness
Haloperidol (Haldol)	Oral, subcutaneous, intravenous	2.5–5 mg per bolus up to 2×5 mg (or more)	Anxiety, agitation, restlessness
Levomopromazine (Neurocil)		25–50 mg bolus bis 200 mg/day	Anxiety, agitation, restlessness
Rescue medication			
Morphine	Subcutaneous	10 mg	Pain, dyspnoea
Butylscopolamine	Subcutaneous	40 mg	Excessive secretions in respiratory tract or elsewhere
Lorazepam	Sublingual	1 mg	Anxiety, agitation, restlessness

The list is an example; other medicines or application routes might be indicated, and other dose ranges might be indicated in selected patients. Additional information on essential medications in palliative care have been published by the International Association for Hospice and Palliative Care.<sup>10</sup>

focus point of palliative care. As long as cure of the underlying disease is still an option, patients tend to accept even small chances of improvement with pharmaceutical or non-pharmaceutical interventions as well as severe side effects from these treatments. However, with the transition to palliative care, the priorities of patients often change. Interventions with low effectiveness or burdening side effects are much less accepted. In the terminal phase, again other priorities may become evident. For example, patients will accept prolonged severe nausea and vomiting as side effects of chemotherapy with curative intent but rarely as a side effect of symptomatic analgesic therapy. Sedation as a side effect of an opioid treatment that effectively relieves chronic pain may be acceptable even for prolonged periods of time but in the terminal phase patients may prefer to reduce opioid dosage, even if pain relief is less, in order to maintain level of consciousness as high as possible.

### Treatment withdrawal or withholding

In contrast, fatigue is often underdiagnosed, under assessed and undertreated in palliative care patients, and the recommendations of the European Association for Palliative Medicine describe pharmacological and non-pharmacological treatment options.<sup>7</sup> However, the recommendations also state clearly that in the final stage of life, fatigue may provide protection and shielding from suffering for the patient, and treatment of fatigue

may be detrimental. Identification of the time point where treatment of fatigue is no longer indicated is important to alleviate distress at the end of life.

Indications for other medical treatment may also change or disappear in the terminal phase. Chemotherapy and radiotherapy should be discontinued in the terminal phase, even if they are applied with palliative intention only. Antibiotic therapy may no longer be indicated when the expected survival time is only a few days or less, and antibiotics then should be withdrawn or withheld.

In our tertiary palliative care centre, we had discussed the need for antithrombotic prophylaxis as most patients suffer from advanced cancer disease and are bedridden, both significant risk factors for thromboembolism. In consequence, low molecular heparin was administered routinely to high risk patients. However, nursing staff challenged this standard procedure as they reported that some patients were burdened severely by repeated subcutaneous antithrombotic injections, sometimes with extensive bruising or pain with the injections. Discussions in the team led to a more balanced approach, where low molecular heparin is administered to high risk patients but the indication is re-evaluated when side effects are severe, and heparin is discontinued in the dying phase in all patients.

In many patients, substitution of fluids and nutrition is an important point of discussion. As patients in the terminal phase are increasingly unable to take oral fluids

and nutrition, family members and staff members are often in favour of substitution with parenteral infusions, sometimes even discussing parenteral nutrition. However, this is not necessary, as the vast majority of dying patients do not suffer from hunger or thirst. Patients with fluid substitution do not seem to have less thirst than those without. On the other hand, fluid substitution may produce adverse effects with increased respiratory secretions.<sup>8</sup>

However, re-evaluation of the medical indication for medicines or infusions is not self-evident, and physicians are often reluctant to withdraw or withhold treatments. Team discussions may be helpful to evaluate the balance of beneficial and non-beneficial effects of the medicines and facilitate the decision on withholding or discontinuation.

### Pain in the terminal phase of life

Pain is one of the most frequent and most burdensome symptoms in patients with advanced cancer or other incurable progressive diseases. More than 80% of patients with advanced cancer report pain.

The WHO recommends that cancer pain should be treated by the oral route (and with injections), with an around the clock regimen (and not only as required) and with the analgesic ladder (step 1: non-opioid analgesics; step 2: opioids for slight to moderate pain such as codeine or tramadol; step 3: opioids for moderate to severe pain such as morphine)<sup>9</sup>.

As the level of consciousness is increasingly reduced, patients will not be

able to swallow at some point, and oral medications are no longer feasible. At this point in time the treatment regimen should be checked to see which medications are still essential in this stage of life and which can be discontinued. Opioid treatment can be continued with transdermal therapeutic systems, such as fentanyl or buprenorphine patches, if pain intensity is stable.

However, in dying patients pain intensity is not always stable, and an adaptation of the analgesic medication may be necessary as the pain may exacerbate with progression of the disease or diminish with deterioration of bodily functions. Short term re-evaluation of pain relief and adverse effects of analgesic medications is required in these patients. Patients receiving slow release opioid medications with long durations of action may have to be switched to short acting application forms if pain intensity changes rapidly, as flexible dose adaptation will not be possible with the long acting forms. If patients are unable to take oral medications, a switch to subcutaneous application of morphine or hydromorphone is recommended. Similarly, transdermal systems with their sluggish pharmacokinetics may not allow flexible dose titration, mandating a switch to subcutaneous application. Intravenous application offers no advantage over the subcutaneous route but may be preferred if the patient has an intravenous line for other reasons. Opioids can be applied either by bolus injections or by a syringe driver.

From its pharmacodynamics properties, hydromorphone has a theoretical advantage over other opioids as it has a very low protein binding percentage. This would cause fewer interactions with other drugs and less interference by changes in the plasma protein fraction in severely ill patients. However, no evidence on any advantage of hydromorphone or other opioids in dying patients is available in the literature.

As the dosage of morphine, hydromorphone or other opioids has to be titrated in relation to the pain syndrome, it is difficult to describe dose ranges. Even for initiation, lower starting dosages may be indicated. It should be stressed that there is no upper dose limit, as some patients require titration in a very high dose range before adequate pain relief is achieved.

### Other symptoms in the terminal phase of life

Symptoms that require special attention in the care of dying patients are pulmonary secretions and terminal restlessness.

Pulmonary secretions can have many causes in dying patients: exudations from

pneumonia, effusions from cardiac failure or deterioration of respiratory tract function, with reduced coughing reflexes and impaired function of the mucosal ciliae. Secretions can cause loud noises (death rattle) which can be very burdensome for the patient and family members. At that stage, patients often are comatose and do not seem to suffer much from the rattle but family members may feel that the patient is suffocating horrendously. Scopolamine, butylscopolamine or glycopyrrolate can all alleviate the rattle, as their anticholinergic action reduces pulmonary secretion quickly. Subcutaneous application is preferred as clinical experience shows little effect with transdermal or sublingual application of scopolamine. Sedation may be a welcome side effect in the terminal stage. Unfortunately, these drugs have little effect in about half of patients, most probably those with exudations from pneumonia. In these patients, positioning with the upper body elevated by 30° will be helpful to reduce the rattle and improve respiratory function as secretions will flow down and not stay in the tracheal and bronchial system.

Pulmonary secretions may add to dyspnoea but more often other causes are predominant such as pneumonia, pleural effusions, anaemia, ascites or bowel extension. Opioid treatment is very effective, usually with small bolus doses (5 mg morphine) subcutaneously. Application of oxygen is not effective in most patients and may burden dying patients additionally.

Terminal restlessness and agitation also cause considerable distress in patients and families. These symptoms may be caused by factors such as dehydration, circulatory deterioration, infection or adverse effects of medications. Causal treatment should be preferred whenever possible—for example, with subcutaneous infusions in dehydrated patients or dose reduction in medications causing adverse effects. However, most dying patients with terminal restlessness will require symptomatic treatment. Benzodiazepines are used as the firstline pharmacological approach. Flexible titration requires benzodiazepines with short durations of action but most benzodiazepines have very long elimination half-lives and thus are not useful for dying patients. Lorazepam has a shorter elimination half-life and can be applied orally with a fast dissolving sublingual tablet, making it a suitable medication. Midazolam is even shorter acting, and can be applied with subcutaneous or intravenous bolus injections or continuous infusions and can be used for rapid titration in patients with severe agitation. For agitated patients,

## Key messages

Increasing symptom burden may require intensified pharmacological and non-pharmacological interventions in the terminal phase. In contrast, physiological changes can also increase the effectiveness of medications, requiring dose reductions to avoid adverse effects. In addition, treatment goals have to be reconsidered as patients' needs and priorities may have changed considerably in the terminal phase.

neuroleptic drugs with predominantly antipsychotic activity such as haloperidol or with more sedative properties such as levomepromazine may be indicated.

In some patients, the dying phase is dominated by a major crisis. Patients with cancer that has infiltrated major blood vessels may suddenly experience major haemorrhage. This can be a traumatic experience for the patient and family members although the patient will lose consciousness in a few minutes. Prophylactic planning is paramount, with good information for the patient and family members, provision of towels and sedative medications at the bedside.

### Rescue medication

As many dying patients will suffer from new symptoms, the standard prescription of a rescue medication for all patients in the terminal phase is recommended. This rescue medication should include very few drugs such as morphine (for pain or dyspnoea), butylbromide hyoscine (for respiratory or other secretions, or nausea) and lorazepam or midazolam (for anxiety, agitation or restlessness). This will allow a rapid response from nurses or other qualified healthcare staff when patients develop new symptoms during out of office hours or in a setting where the visit from a physician will take some time. The rescue medication can be applied repeatedly if a first bolus is not effective.

Nursing staff and other healthcare staff should be trained in the indication and use of the rescue medications, and they should be familiar with the effect and side effect of the drugs. In some cases family members can also be trained in the use of these medications although this will not be feasible from a legal point of view in some European countries.

### Conclusion

Dying patients may often suffer from pain and other symptoms, and adequate assessment and treatment of these symptoms is paramount to prevent needless suffering in the terminal phase.

Palliative care and hospice care are developing and expanding rapidly in most European countries, with more and more inpatient, outpatient and home care services providing this type of care for an increasing number of patients. However, most patients die at home or in nursing homes, and it will not be possible to care for all of these patients with specialised palliative care services. General practitioners and community nurses will have to be educated and trained to provide basic palliative care, including the pharmacological interventions described in this paper. In Germany, a change in the legislation in 2009 made palliative care a compulsory subject for medical students, and those students graduating from 2014 onwards will have to be certified in basic palliative care. This may be a pivotal change to implement the pharmacological

interventions for the care of dying patients, improving their quality of life and preventing suffering.

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