Pain relief and the end of life

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Good pain control is possible in most patients in the months, weeks and days preceding death. This leads not only to better patient care but also to a better bereavement experience for families.

Pain is the most feared form of suffering and is common at the end of life. More than half of patients with cancer at any stage of the disease experience pain, and a third of these would describe it as moderate or severe. Patients dying from chronic diseases such as heart failure, lung disease, neurological illness and diabetes may also have significant pain that limits activities of daily living and reduces quality of life. Pain and the medications used for its treatment have significant impacts on pleasurable activities at the end of life, including cognition and interactions with others, and on sleep.

The principles of palliative care are described in the World Health Organization (WHO)’s widely accepted 2002 definition of palliative care:

‘Palliative care is an approach that improves the quality of life of patients and their families facing the problems 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.’

This article explores the issues associated with pain control at the end of life, and provides practical advice on assessing, treating and managing pain at this time.

BARRIERS TO GOOD PAIN RELIEF

Although evidence exists for both pharmacological and nonpharmacological interventions to effectively treat pain, this is not translated into effective pain relief for many people. Pain at the end of life is still undertreated. Lower income countries worldwide may lack access to medications for financial, social and political reasons. It is estimated that around 60% of those dying would benefit from the involvement of specialist palliative care services.

In addition to resource issues, some physicians are hesitant to prescribe opioids for fear it may be perceived as euthanasia. Another prescriber fear is opioid-induced respiratory depression, but such concerns are unfounded provided opioids have been used appropriately. Pain itself induces tachypnoea, and if opioids are used sensibly and titrated slowly, even large doses may be safely prescribed. If pain increases, more opioid is used and tolerance to respiratory depression also increases.

Key points

- Patients with a terminal illness worry about their level of discomfort, especially pain, at the end of life. However, effective pain control is possible in most palliative care patients.
- Misconceptions about medications for pain relief can be barriers to treatment; addiction is rare and most adverse side effects can be managed.
- Good pain management is important in the weeks and months leading up to the terminal phase. There is good evidence that effective pain relief at the end of life does not shorten life.
- A comprehensive assessment includes a detailed history and examination, with particular attention to musculoskeletal and neurological findings, and judicious symptom-directed investigations where appropriate.
- Patients and their families need education regarding what to expect when commencing strong analgesics.
Inappropriately high doses of opioid are often associated with increasing somnolence, and this symptom should be a trigger for health professionals to reduce the opioid dose.\(^{17}\) Careful titration of doses is important. Reversal agents such as naloxone hydrochloride rarely need to be given, but when they are then they should be titrated carefully against effect. The expected deterioration in level of consciousness at the end of life should not be confused with the effects of opioids. Opioids used appropriately at the end of life do not shorten survival.\(^{18}\)

Patient and carer-related barriers to opioid use include fears of addiction, side effects and being interpreted as being troublesome to their care providers.\(^{16}\) These fears may prevent patients from taking analgesics and achieving pain relief.\(^{19}\)

**ANALGESIA**

Effective and appropriate management of patients with pain at the end of life involves a comprehensive assessment of the patient, with a detailed history and clinical examination supported by review of any investigations already performed, including blood tests and radiology (see the box on page 18). Where appropriate, judicious symptom-directed investigation may be necessary: laboratory findings may be required to confirm infection, anaemia or metabolic derangements that potentiate pain, and radiological work-up may include plain x-rays or CT, MRI or ultrasound scans, although imaging is rarely indicated at the end of life. Frequent review and monitoring for control of symptoms and side effects is essential.

It is best that there is a multidisciplinary team approach to pain relief at the end of life, with the GP working and communicating closely with other disciplines such as medical and radiation oncology, nursing (community- and hospital-based), allied health, psychology and palliative care.\(^{20,21}\)

**General principles of analgesia**

This article focuses on the pharmacological therapy for pain relief but there are many other modalities that may be of use in pain relief at the end of life. These include repositioning to minimise or prevent painful pressure areas, use of heat or cool packs and gentle massage by carers, and also general care and attention to the ‘little things’, such as nasal prong irritation for oxygen that may not be necessary.

The WHO’s three-step ladder for cancer pain relief is widely used as a framework for analgesia (see http://www.who.int/cancer/palliative/painladder/en).\(^{22}\) In this approach, there is a stepwise progression of use of analgesics as pain increases, from a nonopioid (such as paracetamol or an NSAID) to an opioid for mild to moderate pain (such as codeine or tramadol) to a stronger opioid for moderate to severe pain (such as morphine, oxycodone, fentanyl or hydromorphone), with or without an adjuvant at each stage (such as an anti-convulsant for neuropathic pain). A recent systematic review has confirmed the benefit of using an NSAID in combination with an opioid in patients with moderate to severe pain.\(^{23}\)

Pain relief should commence as early as possible. If a patient is opioid-naïve then a suggested starting dose of oral morphine would be 2 to 5 mg every four hours, with the lower doses used particularly in the frail elderly. If the patient is unable to swallow, use of subcutaneous morphine (2.5 mg every four hours as required) should be considered. If the pain is unchanged after an hour, the dose is doubled;
if the pain is reduced but not completely relieved, the dose is repeated. For patients with pain that is severe, use of a strong opioid is the starting step. Often patients are already taking long-acting (modified release) opioids twice-daily or using a transdermal opioid patch (available for buprenorphine and fentanyl). In these situations, a short-acting opioid for breakthrough pain should be made available at a dose of one-sixth to one-tenth of the total daily dose.

All patients should have regular review of their analgesia to ensure good pain relief. If the opioid used or the route of administration are changed then more frequent monitoring is important not only for safety but also for dose titration. Changing opioids requires consideration of the various potencies of the different opioids and their formulations. Equianalgesic doses of opioids are listed in Table 1, and opioid conversion calculators are available online (e.g. on the Cancer Institute NSW website, eviQ Cancer Treatments Online, https://www.eviq.org.au). The authors suggest that when calculating opioid equianalgesic doses, it is best to use oral morphine as a baseline.

<table>
<thead>
<tr>
<th>Type of opioid</th>
<th>Equianalgesic dose</th>
<th>Breakthrough pain dose (every hour as needed)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate release (IR) oral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>15 mg every four hours</td>
<td>15 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>10 mg every four hours</td>
<td>10 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>3 mg every four hours</td>
<td>3 mg</td>
</tr>
<tr>
<td>Methadone</td>
<td></td>
<td>Seek specialist advice</td>
</tr>
<tr>
<td>Modified release oral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>45 mg twice daily</td>
<td>15 mg IR morphine</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>30 mg twice daily</td>
<td>10 mg IR oxycodone</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>16 mg once daily</td>
<td>3 mg IR hydromorphone</td>
</tr>
<tr>
<td>Subcutaneous injection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>30 to 45 mg over 24 hours via syringe driver, or 5 mg every four hours regularly</td>
<td>5 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20 to 30 mg</td>
<td>3.5 to 5 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>5 mg over 24 hours via syringe driver, or 1 mg every four hours regularly</td>
<td>1 mg</td>
</tr>
</tbody>
</table>

* These are not suggestions for initial doses to be used in opioid-naïve patients.
† Breakthrough dose calculation based on use of one-sixth (or the nearest sensible dose) of the total daily dose.
requirements in the previous 24 hours.


There is no clear evidence that one opioid is better than another. If medications are freely available, the choice of agent and the route of administration are dependent on several factors, including the location of the patient (for example, community settings may lack qualified staff to manage syringe drivers or administer subcutaneous medications). Another important consideration is the presence of renal failure, which may necessitate dose reduction of the opioid or opioid rotation.

**Analgesia at the end of life**
The general principles of analgesia described above apply at the end of life, although additional practical issues also need to be considered.

Appropriate prescribing involves careful review of medications. Medications that are considered nonessential or do not provide symptom relief should be stopped. Many patients in the terminal phase are unable to swallow or have issues with absorption if medications are taken orally. Many oral opioid medications have parenteral counterparts, and these can be prescribed as either regular intermittent subcutaneous injections or a constant infusion using a syringe driver when patients are no longer able to tolerate oral medications. Parenteral counterparts are not available for many of the adjuvant agents used (such as amitriptyline, pregabalin and gabapentin used for neuropathic pain), and when these oral medications are ceased, alternative medication may need to be given parenterally. Suggested opioid medication changes for clinical situations at the end of life are given in Table 2.

Syringe drivers are usually programmed to deliver the medications in the syringe over 24 hours, although 48 hours may be used for patients whose condition is stable or when there are limited services available for reloading the driver. Diluents are usually either normal saline or water for injection. Further information about diluents and the compatibilities of medications for concurrent administration is available in Therapeutic Guidelines: Palliative Care. If in doubt, advice can be sought from the local specialist palliative care team. Not all residential aged care facilities have personnel able to operate syringe drivers, and regular intermittent dosing of subcutaneous medications, usually four-hourly, may be required instead.

It is important that patients have appropriate medications available for use on an as-needed basis for background pain or incident (movement-related) pain. Records of use of these medications are essential to guide the prescriber in the titration of background analgesia. Due care must be taken to differentiate whether the medications are used for background pain (in which case it would be justified to adjust the dose of regular subcutaneous opioid) or for incident pain. Patients or caregivers may record pain levels and medication taken in a pain diary.

Incident pain can be a major problem for palliative care patients, and is recognised as a cause of poorly controlled pain. At the end of life, patients are generally less active and become increasingly bed-bound, and therefore may experience fewer episodes of incident pain. The importance of incident pain should, however, not be disregarded. Education of aged care facility staff, carers and family members about the pre-emptive use of as-required medications before movements known to precipitate pain is important. Precipitants may include the essential day-to-day care procedures, such as washing and wound and pressure area care. The dose of pre-emptive opioid given is usually the same as the patient’s usual as-needed opioid dose but should be carefully titrated to effect; it should be given at least 15 to 30 minutes before the
pain-precipitating movement. In some situations, if anxiety is felt to be contributing to distress, then a small dose of a benzodiazepine appropriate for use on an as-needed basis (such as midazolam 2.5 mg subcutaneously if nearing the end of life) may be effective in calming the patient. By no means should this be given to sedate the patient in the presence of unresolved pain; if there is any doubt, the palliative care team should be consulted.

**MANAGEMENT OF OTHER SYMPTOMS**

Pain is often associated with other symptoms. A symptom cluster may be defined as two or more concurrent symptoms that occur together with a high degree of predictability; symptoms within a cluster should have a stronger association with each other than with symptoms in different clusters.26 Constipation is a common side effect of opioids, but also occurs with increasing immobility and ill health. All patients taking strong opioids should have regular assessment of their bowel habits. Aperients such as docosate sodium with senna (two tablets twice daily) or macrogol 3350 (one sachet, dissolved in 125 mL water, once daily) should be regularly prescribed. If the patient is unable to swallow and there is uncomfortable constipation, then suppositories or an enema may be required, but care must be taken

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Medication in use</th>
<th>Suggested medication change</th>
</tr>
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<tbody>
<tr>
<td>Unable to swallow, pain stable</td>
<td>Modified release oral morphine 15 mg twice daily with immediate release oral morphine 5 mg as needed</td>
<td>Change to morphine 15 mg subcutaneously over 24 hours via syringe driver, with morphine 2.5 mg subcutaneously as needed. If no syringe driver available, use 1/6th (or nearest sensible dose) of total regular opioid dose in 24 hours as a regular four-hourly subcutaneous dose and also as needed – in this case 2.5 mg morphine subcutaneously regularly every four hours and extra doses as needed</td>
</tr>
<tr>
<td></td>
<td>Modified release oral oxycodone 10 mg twice daily with immediate release oral oxycodone 5 mg as needed</td>
<td>Change to morphine 15 mg subcutaneously over 24 hours with 2.5 mg as needed</td>
</tr>
<tr>
<td>Unable to swallow and renal function impairment increasing, pain stable</td>
<td>Modified release oral morphine 10 mg twice daily with immediate release oral morphine 5 mg as needed</td>
<td>Change to fentanyl 100 µg subcutaneously over 24 hours via syringe driver with 25 µg subcutaneously as needed, or Hydromorphone 2 mg subcutaneously over 24 hours via syringe driver with 0.5 mg subcutaneously as needed</td>
</tr>
<tr>
<td>Unable to swallow, pain stable</td>
<td>Fentanyl 12 µg/h patch changed every 72 hours and immediate release oral morphine 5 mg as needed</td>
<td>Continue fentanyl patch, changing every 72 hours. Change as-needed immediate release oral morphine to as-needed subcutaneous morphine 2.5 mg</td>
</tr>
<tr>
<td>Unable to swallow, incident pain only (i.e. with care procedures)</td>
<td>Morphine 15 mg subcutaneously over 24 hours via syringe driver with 2.5 mg subcutaneously as needed</td>
<td>Continue on baseline opioid dose and give as needed pre-emptively i.e. prior to care procedures precipitating pain</td>
</tr>
<tr>
<td>Unable to swallow, baseline pain not controlled</td>
<td>Morphine 15 mg subcutaneously over 24 hours via syringe driver with 2.5 mg subcutaneously as needed (2.5 mg subcutaneously needed four times daily for baseline pain)</td>
<td>Increase baseline morphine dose from 15 mg to 20 mg. Increase as-needed morphine dose to 5 mg</td>
</tr>
<tr>
<td>Known hepatic metastases, right upper quadrant pain predominant</td>
<td>–</td>
<td>Consider use of dexamethasone 4 to 8 mg daily for five days (give in the morning) to reduce liver capsule inflammation</td>
</tr>
<tr>
<td>Pain unresponsive to measures taken</td>
<td>–</td>
<td>Refer for specialist assessment or to hospital</td>
</tr>
</tbody>
</table>

* To be used as a guide only.
PAIN RELIEF AND THE END OF LIFE CONTINUED

not to precipitate undue bowel spasms in a patient in the last few days of life (the terminal phase).

Urinary retention may be additive to or caused by constipation. Regular clinical examinations will detect this, and bladder scans and insertion of indwelling catheters should be performed when necessary.

Delirium is common in patients at the end of life, and its many contributors include dehydration, infection, metabolic abnormalities, CNS involvement from malignancy and psychoactive medications as well as opioids. Delirium may be very distressing for the patient’s family members, with many expressing helplessness at this time. Management includes addressing the primary cause where possible, nonpharmacological methods such as providing a calm environment, and pharmacological methods such as use of antipsychotics. Benzodiazepines may be used in small doses but never in isolation as they sedate and calm but do not treat the psychosis.

Nausea can be another common symptom. A careful history should be taken to assess cause, metabolic contributors and concurrent medications, and all potentially reversible factors should be addressed. Antiemetics such as metoclopramide 10 mg three to four times daily may be of use, either on an as-needed basis or, if nausea is more persistent, regularly. If symptoms are refractory, other antiemetics may be required, and the local specialist palliative care team should be contacted.

Multifocal myoclonus can occur in patients in the terminal phase for many reasons, including metabolic abnormalities, dehydration, infection and hypoxia. It can also be a side effect of various medications, including neuropathic agents and opioids (particularly morphine, due to its metabolite morphine-3-glucuronide); occurrence is possibly dose-dependent, but the triggering doses vary widely. Its presence should be confirmed by examination. Rehydration may not be appropriate in the end-of-life setting. Management options available for suspected drug-induced myoclonus include dose reduction or cessation of the suspect drug. If opioids are reduced or rotated then careful monitoring is needed to ensure that this does not cause distress or pain. If it is thought that it is in the patient’s best interests with regard to symptom control to remain on the probable causative agent then the use of a low dose of a benzodiazepine may be helpful in settling possibly distressful myoclonus.

CARE OF THE FAMILY

The story of a dying patient is often also that of loving family members. In addition to feeling the emotional stress associated with this time, many family members are involved with the patient’s informal care. This may include helping with day-to-day activities, personal care, transportation, nutritional support and emotional care. Many family members have out-of-pocket expenses and loss of earnings.

Doctors have an important role in caring for the family. Instances in which there may be conflict regarding patient care can be difficult. Vulnerable caregivers may not be able to provide care for the patient without putting their own health at risk. Timely referral to support services is important, although such resources are often severely lacking.

COMMUNICATION

In all areas of health care but perhaps even more so in palliative care, good communication with patients, their families, carers and caregivers is vital.

The goals of care should be discussed. The aim of relief of distressing symptoms is shared and the means by which this is done should be explained in a frank and easy to understand way.

Patients and their families often have questions about practical matters such as how to identify the dying phase and what to expect during this phase. Caregivers and patients may be reassured that good pain relief is achievable in the home as well as in hospital, and should be given information about what to do should symptoms be difficult to control.

If the patient wishes to die at home, families may request information about who to contact and what to do after death. A comprehensive discussion with pertinent information needs to be provided in these situations, including advice about the after-hours availability of the GP to provide a death certificate.

CONCLUSION

Inadequate pain relief at the end of life is a common fear. Patients at this stage, together with their families, require comprehensive assessment and management. Good pain control is generally possible and will lead not only to better patient care but also to a better bereavement experience for families.

REFERENCES

References are included in the pdf version of this article available at www.medicinetoday.com.au.

COMPETING INTERESTS: None.
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