MedicineToday 2013; 14(4): 16-24

PEER REVIEWED FEATURE
POINTS: 2 CPD/2 PDP

Pain relief and the end of life

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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.

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.[1] 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.[2] 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.[3] 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.[4,5]

The principles of palliative care are described in the World Health Organization (WHO)'s widely accepted 2002 definition of palliative care:[6]

'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.[7-9] 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.[10]

In addition to resource issues, some physicians are hesitant to prescribe opioids for fear it may be perceived as euthanasia.[11] Another prescriber fear is opioid-induced respiratory depression, but such concerns are unfounded provided opioids have been used appropriately.[12-14] Pain itself induces tachypnoea, and if opioids are used sensibly and titrated slowly, even large doses may be safely prescribed.[15] If pain increases, more opioid is used and tolerance to respiratory depression also increases.[16]

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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;

ASSESSMENT OF PATIENTS WITH PAIN AT THE END OF LIFE

- Pain – site, nature, severity, onset, duration, frequency, relieving factors, exacerbating factors
- Analgesia – history, current baseline opioid use, as needed use and frequency
- Associated symptom burden – including cough, respiratory secretions, dry mucous membranes, nausea, vomiting, constipation, urinary symptoms
- Associated psychological symptoms, distress or depression
- Physical examination
- Review of all previous records, concurrent medical problems, investigations performed
- Radiological and blood tests – where appropriate
- Collateral history from family or carer where possible

TABLE 1. EQUIANALGESIC DOSES OF ORAL AND INJECTED OPIOIDS*

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

* 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.

if the pain is reduced but not completely relieved, the dose is repeated.[21] 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.[24] The quantity and frequency of breakthrough doses used to control baseline pain in a 24-hour period may be used as a guide to the titration of total daily dose. If at any time, pain is unstable or not being effectively relieved by the long-acting opioid being used or by a judicious increase in its dose then reassessment and consideration of an alternative administration route or change back to a four-hourly short-acting opioid regimen with retitration is warranted.

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:

- oral oxycodone is approximately 1.5 times more potent than oral morphine
- subcutaneous oxycodone is approximately 1.5 times more potent than subcutaneous morphine
- oral hydromorphone is approximately five to seven times more potent than oral morphine
- subcutaneous hydromorphone is approximately five to seven times more potent than subcutaneous morphine
- fentanyl is many times more potent than morphine (100 µg subcutaneous fentanyl is roughly equivalent to 10 mg subcutaneous morphine) but has a short duration of action, limiting its use outside the transdermal patch or syringe driver setting.

Opioid conversions should be undertaken by experienced medical practitioners. As mentioned previously, changes in opioid used or route of administration require a period of vigilance with close observation of the patient. Doses may need to be titrated up or down dependent on response. The regular dose should be increased according to the pain relief

requirements in the previous 24 hours.

Cancer pain management guidelines for adult patients in Australia are currently under public consultation (available at http://wiki.cancer.org.au/australia/Guidelines:Cancer_pain_management).

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*.[25] 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 bedbound, 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

TABLE 2. END OF LIFE CLINICAL SITUATIONS AND SUGGESTED OPIOID MEDICATION CHANGES*

Clinical situation	Medication in use	Suggested medication change
Unable to swallow, pain stable	Modified release oral morphine 15 mg twice daily with immediate release oral morphine 5 mg as needed	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
	Modified release oral oxycodone 10 mg twice daily with immediate release oral oxycodone 5 mg as needed	Change to morphine 15 mg subcutaneously over 24 hours with 2.5 mg as needed
Unable to swallow and renal function impairment increasing, pain stable	Modified release oral morphine 10 mg twice daily with immediate release oral morphine 5 mg as needed	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
Unable to swallow, pain stable	Fentanyl 12 µg/h patch changed every 72 hours and immediate release oral morphine 5 mg as needed	Continue fentanyl patch, changing every 72 hours. Change as-needed immediate release oral morphine to as-needed subcutaneous morphine 2.5 mg
Unable to swallow, incident pain only (i.e. with care procedures)	Morphine 15 mg subcutaneously over 24 hours via syringe driver with 2.5 mg subcutaneously as needed	Continue on baseline opioid dose and give as needed pre-emptively i.e. prior to care procedures precipitating pain
Unable to swallow, baseline pain not controlled	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)	Increase baseline morphine dose from 15 mg to 20 mg. Increase as-needed morphine dose to 5 mg
Known hepatic metastases, right upper quadrant pain predominant	–	Consider use of dexamethasone 4 to 8 mg daily for five days (give in the morning) to reduce liver capsule inflammation
Pain unresponsive to measures taken	–	Refer for specialist assessment or to hospital

* To be used as a guide only.

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 docusate 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

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.[27] Delirium may be very distressing for the patient's family members, with many expressing helplessness at this time.[28] 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.[25]

CARE OF THE FAMILY

The story of a dying patient is often also that of loving family members.[29] 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. MT

REFERENCES

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

COMPETING INTERESTS: None.

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REFERENCES

1. Clark K, Smith J, Lovell M, Currow DC. Longitudinal pain reports in a palliative care population. J Palliat Med 2012; 15: 1335-1341.
2. van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. Ann Oncol 2007; 18: 1437-1449.
3. Solano JP, Gomes B, Higginson IJ. A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. J Pain Symptom Manage 2006; 31: 58-69.
4. Ferrell BR, Rhiner M, Cohen M, Grant M. Pain as a metaphor for illness. Part I: Impact of cancer pain on family caregivers. Oncol Nurs Forum 1991; 18: 1303-1309.
5. Potter V, Wiseman C, Dunn S, Boyle F. Patient barriers to optimal cancer pain control. Psychooncology 2003; 12: 153-160.
6. World Health Organization. WHO definition of palliative care. WHO, 2002. Available online at http://www.who.int/cancer/palliative/definition/en (accessed March 2013).
7. Heading G, Mallock N, Sinclair S, Bishop J. New South Wales cancer patient satisfaction survey 2007. Interim report. Sydney: Cancer Institute, NSW; 2008. Available online at: http://www0.health.nsw.gov.au/pubs/2008/pdf/cancer_patient_survey_1-5.pdf (accessed March 2013).
8. National Institute of Clinical Studies. Managing acute and cancer pain in hospitalised patients. In: Evidence-practice gaps report. Volume 1: A review of developments 2004-2007. Canberra: Australian Government; 2008; p. 32-36. Available online at: http://www.nhmrc.gov.au/_files_nhmrc/file/nics/material_resources/epgr_review_chapter_11.pdf (accessed March 2013).
9. Deandrea S, Montanari M, Moja L, Apolone G. Prevalence of undertreatment in cancer pain. A review of published literature. Ann Oncol 2008; 19: 1985-1991.
10. Steinhauser KE, Christakis NA, Clipp EC, et al. Preparing for the end of life: preferences of patients, families, physicians, and other care providers. J Pain Symptom Manage 2001; 22: 727-737.
11. Goldstein NE, Cohen LM, Arnold RM, Goy E, Arons S, Ganzini L. Prevalence of formal accusations of murder and euthanasia against physicians. J Palliat Med 2012; 15: 334-339.
12. Currow DC, McDonald C, Oaten S, et al. Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. J Pain Symptom Manage 2013; 42: 388-399.
13. Mahler DA, Selecky PA, Harrod CG, et al. American College of Chest Physicians consensus statement on the management of dyspnea in patients with advanced lung or heart disease. Chest 2010; 137: 674-691.
14. Clemens KE, Klaschik E. Symptomatic therapy of dyspnea with strong opioids and its effect on ventilation in palliative care patients. J Pain Symptom Manage 2007; 33: 473-481.
15. Schauer PK, Agostinucci W, Gannon R, Schauer AR. Practical aspects of pain management in cancer patients. Conn Med 1989; 53: 211-215.
16. Hill CS Jr. The barriers to adequate pain management with opioid analgesics. Semin Oncol 1993; 20(2 Suppl 1): 1-5.
17. Citron ML, Johnston-Early A, Fossieck BE Jr, et al. Safety and efficacy of continuous intravenous morphine for severe cancer pain. Am J Med 1984; 77: 199-204.
18. Thorns A, Sykes N. Opioid use in last week of life and implications for end-of-life decision-making. Lancet 2000; 356: 398-399.
19. Johnson DC, Kassner CT, Houser J, Kutner JS. Barriers to effective symptom management in hospice. J Pain Symptom Manage 2005; 29: 69-79.
20. Sheinfeld Gorin S, Krebs P, Badr H, et al. Meta-analysis of psychosocial interventions to reduce pain in patients with cancer. J Clin Oncol 2012; 30: 539-547.
21. Lovell MR, Boyle FM. Cancer pain management. Med Today 2010; 11(1): 33-38.
22. World Health Organization. WHO's pain ladder. WHO; 2013. Available online at: http://www.who.int/cancer/palliative/painladder/en (accessed March 2013).
23. Nabal M, Librada S, Redondo MJ, Pigni A, Brunelli C, Caraceni A. The role of paracetamol and nonsteroidal anti-inflammatory drugs in addition to WHO Step III opioids in the control of pain in advanced cancer. A systematic review of the literature. Palliat Med 2012; 26: 305-312.
24. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol 2013; 13: e58-e68.
25. Paaliative Care Expert Group. Therapeutic guidelines: palliative care. Version 3. Melbourne: Therapeutic Guidelines Limited; 2010.
26. Aktas A, Walsh D, Rybicki L. Symptom clusters: myth or reality? Palliat Med 2010; 24: 373-385.
27. Yennurajalingam S, Braiteh F, Bruera E. Pain and terminal delirium research in the elderly. Clin Geriatr Med 2005; 21: 93-119.
28. Morita T, Akechi T, Ikenaga M, et al. Terminal delirium: recommendations from bereaved families' experiences. J Pain Symptom Manage 2007; 34: 579-589.
29. McPhee SJ, Winker MA, Rabow MW, Pantilat SZ, Markowitz AJ, eds. Care at the close of life: evidence and experience. JAMAevidence. New York: American Medical Association; 2011.