Management of pain in the terminally ill

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Elinor Brabin
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Abstract
Pain is common in terminal illness. It is a multidimensional experience and requires an integrated approach for its management to be successful.

Pharmacological treatment follows the World Health Organization pain ladder, with early use of strong opioid analgesia in moderate-to-severe cancer pain. A variety of opioids are now available and choice will be tailored to the individual needs of the patient. Complex pain states, such as neuropathic and cancer-induced bone pain, often require multimodal treatment with adjuvant analgesia and interventional techniques. In the final days of life, drugs will be administered by continuous parenteral infusion, and titrated until symptom control is achieved.

Keywords Cancer; hospice; opioids; pain; palliative care; terminal illness

Introduction
Pain is common in terminal illness, affecting up to 85% of specialist palliative care in-patients.1 Cancer is the underlying cause in most patients, and pain prevalence increases in the advanced stages of malignancy.2 Pain is also reported in patients with non-malignant disease, affecting over 50% of those receiving specialist palliative care.3

Pain at the end of life is a multidimensional experience and requires an integrated approach for its management to be successful. Although the initial assessment will focus on the physical aspects of pain, the psychological and spiritual well-being of the patient must be considered, especially in cases of refractory pain. Depression and anxiety are common in advanced cancer and pain threshold may be reduced if they are not adequately treated.

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Learning objectives
After reading this article you should be able to:

• describe the principles and practice of strong opioid prescribing
• list non-pharmacological approaches for pain management
• outline methods for delivering analgesia in the final days of life

Assessment of pain
Mechanism of pain
Pain management begins with a clinical assessment of the patient. The main aim is to identify the aetiology and mechanism of pain. A clinical history and examination, in conjunction with the results of imaging studies, will reveal the cause(s) of pain in most patients. Knowledge of the underlying mechanism of pain is helpful, as it can influence treatment pathways and predict the complexity of pain management3 (Box 1). In simple terms pain can be described as either nociceptive (due to tissue injury) or neuropathic (due to nerve injury) (Figure 1). Approaches for management of nociceptive pain have traditionally followed the World Health Organization (WHO) pain ladder with early use of opioid analgesia. Conversely, first-line agents for neuropathic pain are usually anticonvulsants and tricyclic anti-depressants, with opioids reserved as second- or third-line agents. In practice, many pain syndromes in advanced cancer will have mixed nociceptive/neuropathic features with complex underlying pain pathways and the need for multi-modal treatment. An example is cancer-induced bone pain (CIBP), which consists of a background, tonic pain (usually opioid responsive) with spontaneous or movement-related exacerbations of pain (that respond poorly to opioids). The underlying mechanism is thought to be a unique pain state, characterized by excitability of sensory neurons in the dorsal horn, mediated by inflammatory and neuropathic stimuli.

Pain intensity
Pain intensity is an important domain of pain assessment as it predicts functional interference and is an end-point to measure treatment effect. It can be measured using numerical rating scales (0—10)/visual analogue scales, or form part of a multidimensional pain questionnaire such as the Brief Pain Inventory. A reduction greater than 30% is considered significant.4 Both types of scale are validated for use in palliative care patients and choice of scale will depend on patient suitability.

Treatment of pain
The majority of patients with moderate-to-severe cancer pain will require strong opioids. New theories are emerging about the best way to achieve rapid, effective pain control in patients with limited life expectancy. A ‘two-step’ WHO pain ladder has been suggested, avoiding the transition period on mild opioids.5 Another theory is that analgesic choice should be mechanistic, based upon the underlying cause of pain rather than its severity. The safety and feasibility of such methods have not been confirmed.
Opioids

The choice of strong opioids has increased significantly over the last 20 years. Clinical experience has demonstrated that patients respond variably, in terms of pain and side effects, to different opioid types. This phenomenon may due to genetic differences in opioid receptor subtypes. In the future, it is likely that pharmacogenetics will have a role in predicting opioid choice for individual patients.

WHO recommends that where possible analgesia should be given orally, ‘by the clock’ (i.e. regularly and not on demand) and should be tailored to the individual’s needs.

Morphine

Morphine is recommended as first choice of strong opioid in patients with moderate-to-severe cancer pain. It is available in a variety of preparations to enable flexible prescribing. Immediate release preparations e.g. Oramorph or Sevredol (which take 45 minutes to act and last 4 hours) are used initially and should be prescribed every 4 hours. These preparations allow rapid delivery of analgesia and the assessment of morphine tolerance. Patients are then converted to a twice-daily, slow-release preparation (12-hourly). A breakthrough dose of opioid should always be prescribed.

There are some situations in which an alternative strong opioid may be preferred to morphine. Morphine and its active metabolites are excreted by the kidneys and accumulate in renal failure. Dose reduction may be sufficient to prevent toxicity in mild renal impairment, but fentanyl and alfentanil (which undergo hepatic metabolism to non-active compounds), are recommended in end-stage renal failure.

Transdermal opioid patches are a useful alternative to subcutaneous infusions of morphine for patients unable to swallow oral medication. Due to their long duration of action, they are only recommended for patients with stable pain.

In most other cases, an alternative opioid is considered because the patient develops intolerable side effects on morphine.

Opioid toxicity

Opioid toxicity ranges from sleepiness and poor concentration to hallucinations, myoclonus and delerium. Toxicity can be exacerbated by dehydration, change in disease status and other methods of pain relief. Dose reduction, hydration and treatment of delerium may be adequate, but if toxicity persists or pain remains uncontrolled or escalates, an opioid switch is indicated. An equianalgesic table should be consulted to calculate the new opioid dose (Table 1). Oxycodone, fentanyl,
Hydromorphone and buprenorphine are alternative strong opioids to morphine.

**Opioid-induced hyperalgesia (OIH)**

OIH is a pro-nociceptive response to an opioid agonist. Pain perception increases, often beyond the distribution of the original pain site. There are associated neuropathic features, such as hyperalgesia or allodynia. OIH should be considered in patients with unremitting or escalating pain on high doses of morphine, especially if titration has been rapid. Treatment of OIH is opioid reduction or rotation, with co-administration of an N-methyl D-aspartate (NMDA) receptor-channel antagonist (e.g. ketamine).

**Breakthrough pain**

Breakthrough pain is a transitory exacerbation in pain on the background of adequately controlled background pain. It may occur spontaneously or be precipitated by a trigger, usually with rapid onset but short duration (less than 30 minutes). Convention is to use an immediate-release opioid, equivalent to one-sixth of the total daily dose of opioid, to treat episodes of breakthrough pain.

This approach may be superseded by the recent availability of rapid onset opioids. These drugs employ unique delivery systems that allow effective analgesia to be delivered within 15 minutes. They include oral transmucosal fentanyl (Actiq®), sublingual fentanyl (Abstral®) and intranasal fentanyl (Instanyl and PecFent®). Clinical comparisons between the different formulations are limited as they are mainly compared to placebo in clinical trials. Presently, choice is mainly influenced by patient preference and local formulary guidance.

**Adjuvant therapies**

Adjuvants are drugs with a primary indication for something other than pain, but they have analgesic properties in some painful, mainly neuropathic, conditions. Their use in cancer patients is usually off-licence as most are only licensed for treatment of diabetic neuropathy or post-herpetic neuralgia. Some have no UK licence for neuropathic pain at all.

They are a diverse collection and include: antidepressants, anti-epileptics, corticosteroids, NMDA receptor channel blockers and benzodiazepines. They can be used in isolation or added at any stage of the WHO pain ladder. Neuropathic pain and CIBP are complex cancer syndromes commonly encountered in terminal illness.

**Neuropathic pain**

Several drugs are recommended for the management of neuropathic pain. Evidence for their effectiveness comes mainly from patients without cancer. There is no evidence that any one adjuvant is more effective than another and the first-line choice may be influenced by other symptoms requiring treatment, for example insomnia with amitriptyline, anxiety with benzodiazepine.

However NICE recommendation for drug treatment of neuropathic pain is that first-line agents should be tricyclic antidepressants (TCAs), such as amitriptyline (10–75 mg) or dual uptake inhibitors, such as duloxetine (30–120 mg), which are efficacious when TCAs are not tolerated. Venlafaxine, which has been shown to be beneficial in cancer-related neuropathic pain, is another alternative but guidelines recommend that it is used under specialist care.

Second-line therapy includes the newer anticonvulsants, gabapentin and pregabalin, which have a better side effect profile than their older equivalents, sodium valproate and carbamazepine.

Limitations of oral neuropathic agents in the terminally patient are that:
- they require careful and time-consuming dose titration to minimize adverse effects.
- most have no subcutaneous equivalent to allow parenteral administration.

Other agents, used alone or in combination, include the following.

**NMDA antagonists** — ketamine and methadone, which can be given parenterally, relieve neuropathic pain and its associated features of hyperalgesia and allodynia. Due to the risk of side effects, their use should be restricted to cases where specialist supervision is available.

**Topical lidocaine** — this can be used in a gel or as a 5% topical patch. It is an effective treatment for post-herpetic neuralgia. Its use should be restricted to patients who have localized, cancer-related neuropathic pain with allodynia.

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Table 1

<table>
<thead>
<tr>
<th>Current opioid</th>
<th>New opioid and/or new route of administration</th>
<th>Divide 24-hour dose of current opioid by relevant figure below to calculate new opioid and/or new route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral codeine</td>
<td>Oral morphine</td>
<td>Divide by 10</td>
</tr>
<tr>
<td>Oral morphine</td>
<td>Oral oxycodone</td>
<td>Divide by 2</td>
</tr>
<tr>
<td>Oral morphine</td>
<td>Oral hydromorphone</td>
<td>Divide by 7.5</td>
</tr>
<tr>
<td>Oral morphine</td>
<td>Transdermal fentanyl</td>
<td>See manufacturer’s information</td>
</tr>
<tr>
<td>Oral morphine</td>
<td>Transdermal buprenorphine</td>
<td>See manufacturer’s information</td>
</tr>
<tr>
<td>Oral morphine</td>
<td>Subcutaneous morphine</td>
<td>Divide by 2</td>
</tr>
<tr>
<td>Oral morphine</td>
<td>Subcutaneous diamorphine</td>
<td>Divide by 3</td>
</tr>
<tr>
<td>Oral oxycodone</td>
<td>Subcutaneous oxycodone</td>
<td>Divide by 2</td>
</tr>
<tr>
<td>Oral hydromorphone</td>
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**Opioid conversion table**

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Non-pharmacological approaches to pain management

- Radiotherapy
- Intervventional analgesia
- Transcutaneous electrical nerve stimulation (TENS)
- Physiotherapy
- Psychological therapy
  - Cognitive behavioural therapy
- Complementary therapies
  - Acupuncture
  - Reflexology
  - Aromatherapy
  - Art therapy
  - Music therapy
  - Hypnosis

Box 2

Topical capsaicin — available as a cream (Axsain) or patch (Qutenza). There is limited evidence for efficacy but localized neuropathic pain may respond. Again treatment should be under specialist guidance.

Clonazepam — is a benzodiazepine with a long half-life that can also be effective for neuropathic pain although there is no supporting randomized controlled trial evidence. It can be used subcutaneously either as a bolus or in a syringe driver.

Intractable pain

Despite advances in the range of opioid and adjuvant therapy available, there are still some patients who will continue to experience uncontrolled pain or intolerable analgesic side effects.

These patients should be considered for interventional analgesic techniques including:

- a simple nerve block
- regional or neurodestructive techniques (e.g. coeliac plexus block in pancreatic pain, cordotomy for unilateral chest wall pain in mesothelioma)
- spinal routes of drug delivery (epidural or intrathecal).

Other non-pharmacological approaches may be considered (Box 2). An underlying psychosocial or spiritual problem must be actively excluded. In a small minority, the role of sedation may need to be considered. This is generally reserved for the final days of life, where the patient and their family accept a degree of sedation in order to gain some relief from intractable pain.

The final days

At the very end of life, comfort is the priority. Analgesics should be continued where possible.

- The total daily requirement of opioid should be calculated and converted to a subcutaneous dose, which can be administered over 24 hours in a syringe driver.
- A subcutaneous breakthrough dose of opioid should be prescribed.
- Fentanyl patches should be left in place, with any additional breakthrough requirements titrated in a syringe driver.
- Anti-inflammatory medication can be administered parenterally (e.g. diclofenac 150 mg over 24 hours). The risk of gastrointestinal or renal toxicity is likely to be acceptable if good symptom control is achieved.
- Most adjuvant medications have no subcutaneous equivalent. However benzodiazepines, ketamine and methadone may be given by this route.

Conclusion

Pain management in the terminally ill patient is complex and requires a multidisciplinary approach. Pharmacological management should follow the WHO pain ladder, in combination with early adjuvant therapy for neuropathic pain and CIBP. Some cancer pain syndromes will require multi-modal therapy, including interventional methods of analgesia in cases of refractory pain. In the final days, analgesics must be administered by continuous subcutaneous infusion and titrated until good symptom control is achieved.

FURTHER READING