Managing chronic cancer pain

By Fiona Montgomery, MSc, MRpharms

Pharmacists can enhance the quality of life of patients with terminal illness through their knowledge of drugs used in relieving pain.

Patients, and even some health care professionals, believe that severe, uncontrollable pain is the inevitable consequence of a diagnosis of cancer. In reality, one-third of patients with cancer do not experience severe pain, and in those who do, the application of the basic principles of pain management set out in the World Health Organization (WHO) guidelines on cancer pain have been shown to relieve that pain in 88 per cent of cases. However, there is evidence of poor pain control in about one-third of patients in a general setting, compared with 5–10 per cent in specialist units. Most patients requiring palliative care are treated outside a specialist setting, such as in their own homes, in nursing homes or in acute hospitals. It is essential that all health care professionals have a good understanding of the basic principles of pain management, as this is applicable to patients in all care settings with various diseases.

Acute pain is short-lived and accompanied by adrenaline-mediated symptoms such as sweating, increased heart rate and respiration, and dilated pupils. The pain draws attention to an injury or illness. Most acute conditions heal and become pain-free within two to three weeks. In contrast, chronic pain is mostly continuous, and is generally accompanied by vegetative symptoms such as lethargy, anorexia, sleep disturbance and preoccupation with the pain. The physiological features characteristic of acute pain may be absent and the patient may not appear to be in pain.

Pain is subjective, and has been shown to be overestimated by relatives of the patient and underestimated by health care professionals. Wherever possible, the patient's own description of the pain should be the basis of the overall assessment. Patients are often reluctant or reticent in describing their pain, out of the fear that new or increasing pain represents advancing disease or because they do not want to be a “bother”. A careful assessment of the patient is essential if good analgesia is to be achieved. A detailed history should be taken in order to determine the site(s), number, intensity, radiation, timing and quality of pain. Any factors that aggravate or relieve the pain should be explored. A full analgesic drug history is also useful in determining a pain management plan.

In cancer patients can have a number of different causes as shown in Table 1, p216.

A number of validated pain assessment scales have been developed to enable the making of consistent, repeated assessments. Complex tools such as the McGill pain questionnaire are useful in research but are generally too time-consuming for daily use. Simpler scales such as visual analogues or numerical rating scales are more routinely used.

It is rare for chronic pain to be simply a physical phenomenon: there are usually non-physical, as well as physical components. All pain assessment must include exploration of the social, psychological and spiritual components of the patient's suffering. This can only be achieved if the patient is managed by a multidisciplinary team.

Physical pain can be broadly categorised into three groups:

1. Somatic pain is associated with the activation of nociceptors in deep tissues such as bone. Pain is localised and constant and patients describe it as gnawing or aching.
2. Visceral pain results from activation of nociceptors in the visceral tissues of the thorax or abdomen. It is caused by inflam-
Pain is relieved at night, allowing sleep aiming for realistic goals, is helpful for the analgesic ladder (Figure 1).

Non-opioids such as, codeine, dihydrocodeine and dextropropoxyphene, should be considered where pain is not adequately controlled by regular paracetamol alone or with NSAIDs. Paracetamol may be continued, as its action is synergistic with weak opioids in enhancing drug regimen.

Step one (non-opioids) Non-opioids such as paracetamol 1g given regularly four times a day should be prescribed initially to patients with mild pain. To ensure adequate pain relief, regular rather than “as required” dosing is necessary.

Non-steroidal anti-inflammatory drugs (NSAIDs) also fall into this category. They can be considered both as step one analgesics and as adjuvants used at any step of the ladder. NSAIDs have analgesic and anti-inflammatory properties in mild to moderate pain, and can be particularly useful in treating bone pain. The choice of NSAID depends on the side effect profile, patient response and the local formulary.

Step two (opioids for moderate pain) Weak opioids, such as, codeine, dihydrocodeine and dextropropoxyphene have approximately one–10th the potency of morphine \(^\text{10}\), renal function and age. The dose can be doubled at bedtime to avoid the patient waking in pain for a 2am dose. Patients should be encouraged to ask for extra (“breakthrough”) analgesia whenever they need it to allow the correct dose to be determined. Once the patient’s pain is stable on short-acting morphine, an equivalent dose of a long-acting preparation should be prescribed to improve analgesia, reduce peak and trough effects and facilitate compliance. The choice of a long-acting preparation will depend on the local formulary or preference of the local palliative medicine specialist. A breakthrough or rescue dose of one-sixth of the total daily morphine dose should also be prescribed as a short-acting preparation. Patients should be encouraged to use this preparation if necessary. Regular need for breakthrough medication should be investigated and the long-acting dose adjusted if necessary. Paracetamol should be continued regularly at step three of the analgesic ladder.

Morphine has a number of predictable side effects, which should be considered when starting on strong opioids. Constipation is an inevitable consequence of the reduction in gut motility and the anticholinergic effects of opioids. All patients should be prescribed laxatives with a softening and stimulant effect. Nausea and sedation can occur at initiation of treatment with opioids and when there has been a dose increase. However, these adverse reactions rarely last. Patients should be offered an anti-emetic if necessary and advised that any feeling of sedation will pass. Continuing sedation indicates that the opioid dose is too high and a review of analgesia is required.

Morphine is the strong oral opioid of choice. A wide range of long or short-acting solid and liquid formulations is available. For continuous subcutaneous infusion, diamorphine is preferred owing to its high solubility.

Opioid toxicity can present as agitation, “seeing shadows” at the visual periphery, visual and auditory hallucinations, confusion, myoclonic jerks or vivid dreams. Initial management should include reduction of opioid dose, adequate hydration, and relief of agitation with haloperidol. If this is unsuccessful, or if intolerable side effects occur, with inadequate pain relief, it may be necessary to switch to an alternative opioid.

In the past few years, a number of different opioid preparations have become available in the UK. These do not replace morphine as the drug of choice for the relief of moderate to severe pain but provide alternatives where the use of morphine is not possible.

Morphine The dose of morphine required to control a patient’s pain, step three analgesics should be substituted. There is nothing to be gained from substituting one weak opioid for another.

Step three (strong opioids) Morphine is the strong oral opioid of choice. A wide range of long or short-acting solid and liquid formulations is available. For continuous subcutaneous infusion, diamorphine is preferred owing to its high solubility.

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**Table 1: Causes of pain**

<table>
<thead>
<tr>
<th>Cause of the pain</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain caused by cancer</td>
<td>Tumour infiltration into visceral tissue</td>
</tr>
<tr>
<td>Pain caused by treatment</td>
<td>Neuropathic pain from chemotherapy-induced nerve damage</td>
</tr>
<tr>
<td>Pain associated with cancer- induced debility</td>
<td></td>
</tr>
<tr>
<td>Pain unrelated to cancer or its treatment</td>
<td>Joint pain from rheumatoid arthritis or osteoarthritis or headache</td>
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**Figure 1: The WHO ladder or stepwise approach to the relief of pain**

- **Opioids for severe pain**
  - with or without non-opioid
  - with or without adjuvant
  - Step 3

- **Opioids for moderate pain**
  - with or without non-opioid
  - with or without adjuvant
  - Step 2

- **Non-opioids**
  - with or without adjuvant
  - Step 1
parenterally, and is metabolised in the liver to inactive metabolites. A transdermal delivery system is now available which avoids first pass metabolism and maintains steady-state plasma levels of fentanyl. Transdermal administration is possible because of the low molecular weight and high lipid solubility of fentanyl. Transdermal fentanyl has a long half-life with plasma steady-state concentrations 36–48 hours after application of the patch. The elimination half-life is 17 hours or more. Care is needed when changing from oral or parenteral opioids to fentanyl patches and when titrating the dose.

If a patient is to be started on fentanyl patches, it should be remembered that it will be 12 hours before the effects of fentanyl are felt. The first patch should be applied at the same time as the last modified release morphine tablet is given. The full therapeutic effect of the patch will be achieved only after 36–48 hours, thus adequate breakthrough medication must be available.

Due to the time it takes to reach steady-state concentrations, transdermal fentanyl is only suitable for the treatment of patients who have stable pain. Transdermal fentanyl is an effective alternative to morphine when the patient has swallowing difficulties or develops unmanageable constipation.

Fentanyl is also available as an oral transmucosal dosage form for the management of breakthrough or incident pain. Incident pain is defined as transient pain precipitated by a specific event or activity (for example, eating, walking, coughing etc.). If analgesia is not achieved 15 minutes after finishing the lozenge, use another lozenge of the same strength.

Hydromorphone Hydromorphone has been widely used in the US for the treatment of cancer pain. It is now licensed in the UK. Hydromorphone is approximately 7.5 times as potent as morphine and is available as 1.3mg and 2.6mg immediate release capsules and in a range of strengths as controlled release capsules. Patients who have reported cognitive blunting (for example, impaired language, memory and thought), vivid dreams or hallucinations with minimal doses of morphine may benefit from a change to hydromorphone. There are disadvantages in that the short-acting formulation, equivalent to 10mg and 20mg of morphine, makes it difficult to titrate a dose in the elderly or sensitive patient. In the UK, hydromorphone injection is available only as a special.

Oxycodone Oxycodone is another step three opioid, which has been used widely in the US. Although it has been available for a number of years as suppositories, oxycodone has recently been launched in oral format. It has a high oral bioavailability and is twice as potent as oral morphine. No toxic metabolites that can accumulate in renal failure have been identified. Modified-release oxycodone has been shown in a randomised, double-blind crossover trial to be associated with fewer hallucinations and less sleep disturbance than oral morphine. There is no commercially available injectable preparation but suppositories can be obtained as a special.

Methadone Methadone is used in some centres if the side effects of morphine are unacceptable. Its complex pharmacokinetics make it difficult to initiate outside the specialist, inpatient setting. Methadone also has a number of significant drug interactions: its metabolism is increased by carbamazepine, phenytoin and rifampicin and decreased by amitriptyline and cimetidine. Any use of methadone for this purpose should be with the guidance of a specialist in palliative medicine. Many centres have written protocols for the management of methadone initiation.

There is little evidence for the choice of one opioid over another and different patients may tolerate opioids differently. The choice of an alternative opioid will depend on local policies and the clinical experiences of the prescriber.

Adjuvant drugs Adjuvant analgesics are drugs which are not primarily indicated for pain but which act as analgesics in certain situations. These can be used at any stage on the analgesic ladder and are generally used for pain which is poorly responsive to opioids. These indications are often unlicensed and practice can vary between palliative care specialists.

Table 2: Equivalent doses of oral morphine and fentanyl patches

<table>
<thead>
<tr>
<th>24-hourly morphine</th>
<th>Fentanyl transdermal dose (mg)</th>
<th>patch (g per hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;135</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>135–224</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>225–314</td>
<td>75</td>
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<tr>
<td>315–404</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>405–494</td>
<td>125</td>
<td></td>
</tr>
</tbody>
</table>

![Figure 2: Titration of Actiq lozenges](image-url)
Gabapentin has been shown to be effective and clonazepam, have also been used. Carbamazepine, phenytoin, sodium valproate, amitriptyline is commonly used. It should be started in low doses (10–25mg) and increased gradually. Doses rarely need to exceed 75mg daily. Analgesic effects should be seen in three to seven days.

Anticonvulsants Anticonvulsants are also widely used in the treatment of neuropathic pain. Gabapentin is licensed for this indication, although others, such as carbamazepine, phenytoin, sodium valproate and clonazepam, have also been used. Gabapentin has been shown to be effective in recent randomised controlled trials. Gabapentin should be initiated at 300mg and increased daily to 1,800mg. Other antiepileptics should be started at low doses and increased until analgesia is achieved or intolerable side effects are seen. There is no correlation between anticonvulsant plasma level and analgesic effect.

No measurable differences have been shown between tricyclic antidepressants and anticonvulsants in the treatment of neuropathic pain in terms of efficacy or adverse effects. Choice is based on relative contraindications, potential drug interactions and risk of side effects in an individual patient. Individuals can vary in their analgesic response to various treatments and may require a combination of anticonvulsant and tricyclic antidepressant. It is good practice to introduce one drug at a time.

Corticosteroids There is evidence for the use of corticosteroids in the treatment of cancer pain. Dexamethasone is commonly used in palliative care because its potency, reduced mineralocorticoid effects and range of formulations make drug administration and compliance easier. Clinical experience has shown dexamethasone to be a useful adjuvant in raised intracranial pressure, severe bone pain, nerve infiltration, soft tissue infiltration and hepatic capsular pain. The dose and duration of treatment are dependent on clinical response. High doses of up to 10mg daily may be required. The oral route should be used if possible, with the last dose of the day given no later than 6pm to avoid insomnia.

Ketamine Ketamine has been used as an anaesthetic for 30 years. However, at subanaesthetic doses, it acts as an analgesic. This is an unlicensed indication and initiation of ketamine should only be undertaken under the direction of a pain or palliative medicine specialist. The analgesic effect is mediated by blocking N-methyl D-aspartate receptors which are implicated in clinical states such as allodynia (pain resulting from any stimulus), hyperalgesia (excessive sensitivity to painful stimulus) and hyperpathia (increased reaction to painful stimulus). If successful, ketamine will restore opioid sensitivity and opioid toxicity can occur.

Bisphosphonates Bisphosphonates have been shown to be effective in the treatment of bone pain caused by increased osteoblastic activity in multiple myeloma. Bone pain from widespread metastatic disease in breast cancer, unresponsive to strong analgesia and unsuitable for radiotherapy, has responded to intravenous infusions of bisphosphonates. There is no evidence that these drugs alleviate bone pain from other tumours.

CONCLUSION

Most acute hospitals do not have palliative care wards and patients are cared for throughout the hospital. Pharmacists can contribute to the management of these patients through knowledge of the WHO ladder, advice on use of strong opioids, rationalisation of therapy and knowledge of alternative routes of administration. Specialist palliative care input varies in different hospitals.

Pharmacists should be aware of the specialist resources available for advice and support in their area. A good understanding of therapy improves symptom control and patients (or their carers, if preferred) should be educated about their discharge medication by the pharmacist. Patients may also experience difficulty in obtaining supplies of palliative care drugs in the community setting, and liaison between hospital and community pharmacists can improve the availability of Controlled Drugs and special formulations.

Discharge planning can ensure that these patients enjoy good symptom control while staying in their home environment. The pharmacist’s contribution is essential in ensuring a smooth transfer between care settings for these patients.

References