Management of pain

Pain is a common symptom that patients describe and clinicians have to manage. Management plans are tailored to the complexity of the pain. This may require a multi-modal approach while involving the wider multidisciplinary team.

Pain is one of the most common symptoms of advanced disease. Although the causes and location of pain largely depend on the underlying condition, the approach to assessment and management should be broadly similar in a palliative care context.

In cancer patients, pain is one of the most feared and distressing symptoms (Foley, 1999; Breura and Kim, 2003). A systematic review found the prevalence of cancer pain irrespective of the stage of illness at >50% in all cancer types with the highest prevalence in head/neck cancer patients (70%) (van den Beuken-van Everdingen et al, 2007), and the European Pain in Cancer (EPIC) survey (2007) confirmed this. Prevalence of pain is reported as 40–80% for patients with other advanced diseases (The SUPPORT Principal Investigators, 1995; Higginson, 1997; Weiss et al, 2001). Up to 75% of patients have pain at more than one site (Banning et al, 1991).

Definition and classification of pain

Pain is defined as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage' (Merskey and Bugduk, 1994). This emphasizes that pain is multidimensional and highlights the importance of assessing physical and psychosocial factors affecting each patient.

The classification of pain continues to prove challenging and has to date concentrated on identifying the initiating pathophysiological mechanisms. Currently, pain is divided into inflammatory (nociceptive) or neuropathic in origin. A three-level classification has been developed which involves first the mechanism: inflammatory (nociceptive) or neuropathic, then the context (physiological or pathological), and finally the location (somatic, e.g. bone; or visceral, e.g. bowel) (*Figure 1*). This system does not involve traditional dichotomies such as malignant or non-malignant, or acute or chronic (Bennett, 2006).

Higher centres involved in pain

There is a network of brain regions involved in the sensory, emotional, cognitive and motor processing in the experience of pain (Toga and Mazziotta, 2000; Dickenson and Suzuki, 2005). Functional brain imaging over the last 15 years has given considerable insight into all types of pain, including experimental and clinical pain (Kulkarni et al, 2007). All types of pain are processed within the same matrix in the brain, but there are different patterns of pain response in the brain with different types of chronic pain, which mainly relate to the psychological context of the pain (Jones et al, 2003).

Pain assessment

Pain assessment is crucial in gathering all the relevant information to help aid a clinical diagnosis of the pain and form a management plan. The description of the pain and what effect it is having on the patient is important to grasp. To help structure a pain history, it is helpful to consider physical effects and manifestations of pain, functional effects, psychosocial factors and spiritual aspects (Cormie et al, 2008).

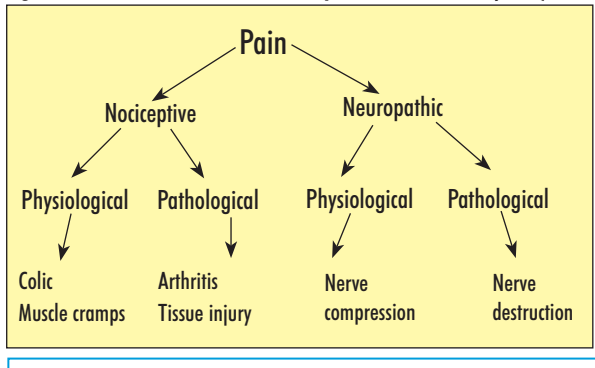
Assessment is a skill and experienced pain clinicians can quickly understand the patient's pain. Assessment tools help less experienced clinicians to gather this information concisely and efficiently. There are a variety of tools looking at the 'rating' of pain severity to tools assessing the holistic picture, picking up on the psychosocial and spiritual aspects of the pain. Tools can be health professional-reported or patient self-reported.

Pain severity

This can be assessed by very simple measures such as a:

- Visual analogue scale – an unmarked line with extremes marked as 'no pain' and 'worst pain'. Patients are asked to mark the point in the line that describes their pain
- Numerical rating scale – similar to a visual analogue scale but uses numbers or graduations that indicate the severity of the pain experience, e.g. 0–10
- Categorical verbal rating scale – involves a sequence of words describing different intensity levels of pain such as: 'none', 'mild', 'moderate' and 'severe' (Caraceni et al, 2002).

Figure 1. Three-level classification of pain. From Bennett (2006).



Dr Declan Cawley *is Specialist Registrar in Palliative Medicine, The Christie NHS Foundation Trust, Withington, Manchester M20 4BX, and*
Professor Michael I Bennett *is Professor of Palliative Medicine, Lancaster University, Lancaster*

Correspondence to: Dr D Cawley

The Brief Pain Inventory (Cleeland and Ryan, 1994) can be used to gain a greater understanding and context of pain. It has been extensively validated and is used globally. It captures aspects of pain interference from mood and cognition, to sleep and relations with other people. This tool attempts to combine the important points of the pain history with the psychosocial and functional aspects of the pain. Other tools look at a particular aspect like mood. There are numerous assessment tools to choose from but it is important to pick one that has looked at pain in your group of patients.

Pain management

Pharmacological management of pain

Pain management balances the use of analgesics in a step-wise fashion to ensure good pain control with minimal side effects.

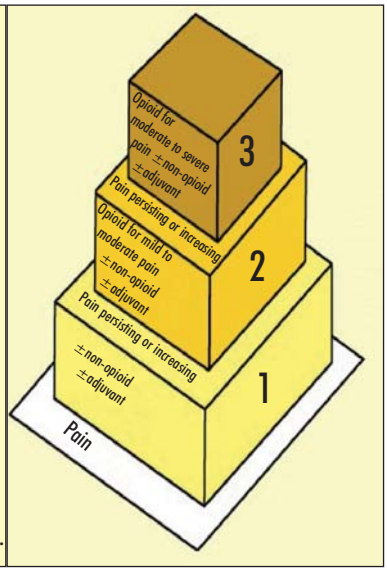
Pain that is opioid sensitive

Analgesia follows the World Health Organization Expert Committee (1990) analgesic ladder in a step-wise fashion for pain that is opioid responsive (*Figure 2*). It is a useful and effective approach to the treatment of mild, moderate and severe pain. Used alone, it controls pain in almost 80% of patients. The remaining 20% have difficult pains requiring more complex management (World Health Organization, 1996). When pain control is not achieved at step 1 or step 2, it is essential to move up the analgesic ladder rather than change to another drug of similar potency. This is a common pitfall for clinicians, who may be cautious about using strong opioids. The ladder should follow a step-wise approach but when pain is severe and uncontrolled low-dose strong opioids should be used.

An adjuvant is an analgesic drug whose primary indication is for something other than pain but which has an analgesic effect in certain conditions (Fallon et al, 2006).

Figure 2. World Health Organization Expert Committee (1990) analgesic ladder. NSAID = non-steroidal anti-inflammatory drug.

Step 1 – paracetamol (1 g 4-hourly) is the drug of choice for mild pain, particularly in elderly or frail patients (maximum 4 g/24 hours). A NSAID can be added or substituted when pain is not relieved by paracetamol alone.
Step 2 – e.g. codeine (30–60 mg 4-hourly) or dihydrocodeine (30–60 mg 4–6-hourly). Tramadol (50–100 mg 4–6-hourly) is often combined with paracetamol.
Step 3 – for severe pain, the gold standard is morphine. The starting dose of oral morphine is usually 5–10 mg 4-hourly, with the same dose for 'rescue' analgesia. Analgesic requirements can be assessed and if appropriate, start a long-acting or slow release (12-hourly) preparation. The starting dose may be lower in frail or elderly patients.



Consideration of use of these drugs is important, especially when pain is not responding to strong opioids or patients are having problematic side effects with opioids.

Titration of strong opioids

Morphine is the strong opioid of choice for moderate to severe cancer or non-malignant pain. It is commonly administered orally but this depends upon the patient's ability to swallow or absorb it. If an alternative route is required, subcutaneous or intravenous routes are used.

When starting a patient on immediate release morphine, in liquid (Oramorph) or tablet (Sevredol) form, use a regular 4-hourly dosing regimen and continually re-assess the patient and his/her pain. Initial doses depend on many factors with elderly, more frail patients starting with 2.5 mg 4-hourly to patients with uncontrolled pain and patients on regular weak opioids (e.g. codeine) starting with 10 mg 4-hourly. This approach requires regular review but offers greatest flexibility in dose titration. Dose escalation is patient and pain dependent. If pain is easing with morphine and no intolerable side effects, then incremental increases of between 25 and 50% are recommended (Fallon et al, 2006).

Modified release (or 12-hourly) preparations are usually started when pain is reasonably well controlled on a 4-hourly regimen. To calculate the modified release dose along with the PRN (as required analgesia) regimen:

- Total the 24-hour morphine requirements and divide the dose by 2–3 – this is the 12-hourly or twice daily dose (e.g. 10 mg 4-hourly immediate release morphine to 30 mg modified release twice daily)
- PRN dose is usually 1/6th of the 24-hour morphine requirement (e.g. 30 mg twice daily with 10 mg PRN).

When giving parenteral (intravenous or subcutaneous) morphine, the oral dose is divided by 2. Similarly if converting to a syringe driver, take the total 24-hour oral morphine requirement and divide by 2 to give the total dose of parenteral morphine over the 24-hour period (e.g. morphine sulphate tablets 30 mg twice daily → 30 mg parenteral morphine). The side effects of opioids need to be considered and managed appropriately (*Table 1*).

Opioids other than morphine

Alternatives are usually tried where patients have unacceptable side effects with morphine or an alternative route is required. Changing from one strong opioid to another to maximize pain control while minimizing side effects is called 'opioid switching'. Oxycodone, alfentanil, fentanyl, hydromorphone, buprenorphine and methadone are alternative strong opioids to morphine.

Symptoms such as nausea or drowsiness may occur in patients started on a strong opioid or who have had a dose increase, but may resolve within days and are not necessarily an indication for switching opioids. In most cases, a dose reduction and/or slower dose increases may be required. When a patient's condition changes, full re-assessment is needed to exclude other potential causes (e.g. acute

renal impairment, hypercalcaemia or sepsis) that may be adding to the clinical picture. The Scottish Intercollegiate Guidelines Network (Cormie et al, 2008) endorses the need for holistic reassessment of pain and the pain management regimen, and recommends opioid switching when pain is uncontrolled and optimization of dose and opioid-related side effects prevent further dose escalation. Discussion with the palliative care team may be helpful.

Neuropathic component to the pain

Description of pain by the patient as 'stabbing', 'burning' or 'shooting' can indicate a neuropathic component. Clinical examination can also help elicit any sensory skin changes or associated motor dysfunction. Screening tools for neuropathic pain (e.g. Leeds Assessment of Neuropathic Symptoms and Signs) can identify and assess underlying neuropathic mechanisms contributing to pain.

There is a lack of evidence for use of opioids in cancer-related neuropathic pain but not evidence of lack of effect. In non-cancer-related neuropathic pain there is support for morphine, methadone, fentanyl, oxycodone and tramadol. However, the studies have a relatively short follow up of days to a few weeks.

Synergy with combinations is especially important in managing neuropathic pain or 'difficult' pain. This approach enhances the 'effect' of each drug and leads to better pain control. The co-analgesic approach involves addition of adjuvants at any stage in the titration process, usually when there has been a trial with strong opioids.

Drugs commonly used in conjunction with opioids

There is a variety of drugs to choose from. The decision mainly depends on patient characteristics and symptoms, the effect of the pain on daily functioning, and the specific side-effect profile of the drug you intend to use. All of the additional drugs to opioids have significant side effects. It is important to consider the additional side effects as well as any potential drug interactions.

Anticonvulsants

Gabapentin and pregabalin are the most commonly prescribed drugs in this class. This may reflect the volume of studies of these drugs rather than superior potency (McQuay and Wiffen, 2006). Anticonvulsants need to be used with caution with frail, elderly and ill patients in particular because of their numerous drug interactions.

Antidepressants

Amitriptyline or imipramine are the most commonly prescribed tricyclic antidepressants. The selective serotonin-reuptake inhibitors (e.g. paroxetine, fluoxetine) and the serotonin noradrenaline-reuptake inhibitors (e.g. venlafaxine or the more potent duloxetine) are more selective antidepressants. The multiple actions of antidepressants make them a popular choice but they can have significant side effects and caution is advised in frail or elderly patients. Treating pain and depression with one drug may be much more acceptable to patients and decreases the pill burden. Lack of direct comparative data prevents selection of a single preferred treatment (McQuay and Wiffen, 2006).

Ketamine

Ketamine is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist and is most effective in pain states where hyperexcitability is established, as the NMDA receptor facilitates this pathophysiology. Ketamine undergoes first-pass metabolism to norketamine – a more potent analgesic than ketamine – which may explain why ketamine is more potent orally than parenterally. There is much clinical experience of the use of ketamine in neuropathic pain states but the evidence base is not well established (Fallon and Fergus, 2006).

Methadone

Controversy exists around the use of methadone, but it acts via opioid and NMDA receptors. It has significant inter-individual variability from half-life (average 24 hours, range 8–80 hours) to actual clinical effect on pain. It use should be reserved for specialists given its unpredictable half-life and uncertain potency compared to morphine.

Topical preparations

While the other classes of drugs may be considered initially for neuropathic pain, alternatives are required as not all patients will respond to these drugs or will be able to tolerate them. Currently available are lidocaine 5% patches and various strengths of capsaicin cream. These agents produce local analgesic effects. Their use should be restricted to individuals who have very specific, localized neuropathic symptoms (e.g. postherpetic neuralgia or cancer-related pain with allodynia).

Interventional analgesic approaches

This type of drug delivery is usually considered for patients with severe uncontrolled pain. Other conditions include plexopathies, debilitating incident pain, an unacceptable balance between analgesia and opioid-related side effects or as an adjunct to pain not responding to standard treatments. The approaches can vary and involve:

Table 1. Opioid side effects

Side effect	Dose related?	Management approach
Dry mouth	No	Frequent mouth care, artificial saliva
Constipation	Probably not	Prophylactic laxative (softening agent and stimulant)
Nausea	Yes	Tends to wear off, otherwise metoclopramide if not
Sedation or confusion	Yes	Reduce dose by 30%, check renal function, may respond to a change of opioid
Hallucinations	Yes	Reduce dose by 30%, consider haloperidol, may respond to a change of opioid
Pruritus	No	May respond to a change of opioid

- Nerve blocks (neuroaxial or neurolytic either by drugs or thermal ablation, e.g. trigger point injections, intercostal blocks, coeliac axis blocks, post-thoractomy block or neurolytic sympathetic blockage)
- Neuromodulation (spinal cord stimulation)
- Neurosurgery (cordotomy, vertebroplasty or kyphoplasty).

Spinal delivery of drugs can be epidural or intrathecal. Intrathecal delivery places drugs near central receptors and may reduce side effects, because smaller doses are needed compared to systemic administration in the ratio of potency of 100:1. The choice of technique depends on the patient's condition, as well as the patient's views on invasive procedures, his/her prognosis, underlying pathophysiology, and the availability and expertise of locally trained staff.

Breakthrough pain

This is an umbrella term for pain but is generally regarded as 'a transitory exacerbation of pain experienced by the patient who has relatively stable and adequately controlled baseline pain' (Portenoy et al, 2004). Other commonly used terms are 'transient pain' or 'episodic pain' (Mercadante et al, 2002). Breakthrough pain that occurs as a result of 'end of dose' failure indicates inadequate analgesia and the dose should be increased. Patients taking regular analgesics should always be prescribed breakthrough or rescue analgesia, which should be immediate release preparations (normally equivalent to 1/6th of the total daily dose of background strong opioid).

Incident pain (Mercadante et al, 2002) is usually short lived and may be volitional (e.g. moving), non-volitional (e.g. coughing) or procedure related (e.g. dressing changes). Owing to the nature of this type of pain, immediate release preparations of strong opioids may not act quickly enough and cause unnecessary side-effects. When activities can be planned anticipatory analgesia can be used, or transmucosal preparations can be used as these ensure more rapid onset of action (e.g. transmucosal fentanyl or effervescent preparations). If this type of pain proves difficult to control, discussion with a pain anaesthetist regarding a nerve block would be helpful.

Renal impairment

Use of opioids with caution and at reduced doses and/or frequency in these patients is advised. Alfentanil, buprenorphine and fentanyl are safest in patients with chronic kidney disease stages 4 or 5 (estimated glomerular filtration rate < 30 ml/min/1.73m^2) (Cormie et al, 2008). The variations in drug activity in patients with renal impairment should prompt discussion with pain or palliative care specialists about an appropriate choice of drug.

Non-pharmacological management

Non-pharmacological measures may help patients with pain of any cause, particularly when drugs alone are insufficient. Physical interventions may comprise of application of heat or cold to a painful site.

Another approach may be the use of TENS (transcutaneous electrical nerve stimulation) or acupuncture. These are simple and generally safe methods of stimulating peripheral nerves and muscles close to the site of pain and altering nociceptive input to the spinal cord. TENS can be useful for peripheral neuropathic pain and analgesic effects are felt immediately. The best results are seen when individuals have a supervised trial to guide electrode placement and stimulation settings (Johnson, 2006).

Complementary therapies are increasingly popular and include massage, aromatherapy, reflexology, meditation, mindfulness-based therapy and herbal remedies. The evidence for their efficacy is not strong but many patients find them helpful, possibly because of the attention received in terms of time and interaction with the therapist.

Pain often leads to reduced levels of activity and fear of doing harm. This cycle of de-conditioning is important to try and avoid. This philosophy is embraced by chronic pain teams by advocating safe and simple exercises to maintain function and mobility, and minimize the negative impact that pain has on the patient's quality of life.

Use of strong opioids in chronic non-malignant disease

All patients, irrespective of diagnosis or prognosis, should have access to good palliative care. Gaining the skills of good assessment and principles of pain and symptom management allows universal application. However, with chronic non-malignant disease comes a very different arena compared to cancer:

- Prognosis may be very uncertain and unpredictable, with very sudden acute life-threatening episodes coupled with recovery
- Functional debility associated with chronic disease and the interference with everyday living and quality of life brings practical difficulties
- Disease-modifying treatments are limited so attention is directed at symptom management.

Strong opioids should be considered for these patients but assessing how environmental influences can be altered will significantly contribute to their palliation.

In non-malignant disease, there are some very real concerns about the use of strong opioids. This is not unfounded but a standardized approach is vital. This includes impeccable assessment, inquiry into the attempts of non-drug therapies, establishing agreed goals for treatment and developing an understanding between clinician and patient of the true benefits and burdens of the long-term use of opioids. A single clinician where possible, with regular follow up and communication between the relevant specialists, is vital for this approach to succeed. Regular follow up allows for review of symptoms, monitoring for any signs of potential opioid dependency and constant consideration of adjuvant treatments (Ballantyne and Mao, 2003).

Specialist palliative care input

Palliative care of patients can vary from the very simple to the very complex. Specialist input can help the generalist

but can also assist when care is complex. This may be on an advisory or educational level or when pain is challenging and lesser known agents such as ketamine or methadone are required. Specialist palliative care teams exist to dovetail with the relevant specialties and work in collaboration, ensuring optimal symptom management.

Multi-modal and team approach

When pain is difficult to control or is of a chronic nature, it often affects an individual's emotional and psychological wellbeing. Screening for symptoms of anxiety or distress is important in understanding the very real difficulties that patients are experiencing. When issues are identified and complex, all members of the multiprofessional team may be required to help plan care (*Figure 3*).

Conclusions

Successful pain management depends on the initial assessment of potential underlying mechanisms and patient characteristics. Pharmacological and non-pharmacological approaches should be regularly reviewed. This allows clinicians to monitor pain relief while screening for unwanted or intolerable side-effects. No one professional is responsible for the management of difficult pain, but members of the extended professional team should coordinate a plan of care. Ultimately pain management can be challenging for patients, so assessing for psychological distress at regular intervals is important. Its identification and treatment can have a significant impact on pain management. **BJHM**

Figure 1 *is adapted from Bennett (2006) by kind permission of Oxford University Press.*

Conflict of interest: none.

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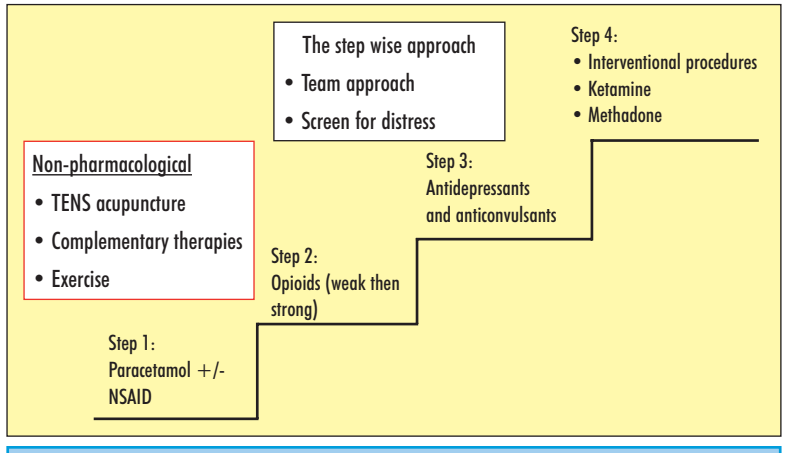
Figure 3. Integrated pain management. NSAID = non-steroidal anti-inflammatory drug; TENS =transcutaneous electrical nerve stimulation.



KEY POINTS

- Pain management is complex.
- Assessment is vital and should be ongoing, especially when treatment changes.
- Screening for neuropathic mechanisms is important so early addition of adjuvants can be facilitated.
- Pain can be distressing so regular assessment and treatment of psychological aspects of pain can significantly impact on management.
- A multi-modal and team approach is essential, involving specialists early to obtain best pain control with minimal side effects.