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ESSENTIALS Pain occurs in more than 50% of patients with advanced disease, interferes with daily functioning and quality of life, and is often undertreated. Patients can find it difficult to articulate the character of their pains, but it is important to determine whether it is somatic, neuropathic, or visceral since this has important implications for management. For most patients with cancer pain, a three-step approach combining simple or opioid analgesia (depending on severity) along with an adjuvant analgesic (depending on cause) will result in good pain relief, but the challenge is to achieve good pain relief without unacceptable adverse effects. Pathophysiology and aetiology of pain in advanced disease Pain occurs in more than 50% of patients with advanced disease, and although the 'analgesic ladder' approach to treatment promulgated by the World Health Organization (WHO) is both accepted as the mainstay therapy and widely disseminated, pain is undertreated globally. Poorly controlled pain interferes with daily functioning and quality of life. Pain has both multiple physical and psychological effects and the two aspects are often interlinked. Impact on physical activity together with its negative effects on sleep and relationships with others, forms a toxic mix which leads to general distress. Review data show a prevalence of pain in cancer patients of 35–96%, in heart disease 41–77%, AIDS 63–80%, chronic obstructive pulmonary disease (COPD) 34–77%, and renal disease 47–50%. The studies were not clear if the figures relate to purely the advanced disease stated, or if there were painful comorbidities. In chronic cancer pain, the data generally agree that somatic pains are more common (71%) than either neuropathic (39%) or visceral (34%) pains. We often think of chronic cancer pain as chronic pain with an extra neurobiological layer of complexity due to factors both produced by the tumour and in response to tumour presence. Patients with neuropathic pain have been shown to have greater pain intensity, a worse quality of life, and a greater negative impact on their daily living than patients with nociceptive pain. Similarly, those with neuropathic cancer pain have been shown to have a worse quality of life, poorer performance status, and a need for both higher opioid doses and a longer time to achieve pain control than those with nociceptive pain. The most common challenging pain overall is cancer-induced bone pain (CIBP). CIBP has three components: a background pain, spontaneous pain at rest, and pain associated with movement. The background component can usually be controlled, however, the spontaneous and movement-related components are challenging. Undertreatment of pain has many influencing factors. Discrepancies between patient, carer, and physician rating of pain severity is one factor. Fears around opioid use are also still prevalent on both the sides of professionals and patients. Inappropriate judgements might be made about the appearance of the patient which influence decisions about pain, these include: too mobile, too well, or too early on in disease process. Similarly, there can be inappropriate judgements made about pain management in advanced disease with poor judgements assuming

that all pains are due to advancing cancer and a lack of adequate assessment and management of reversible causes. A history and clinical examination are vital for pain assessment, and radiological and laboratory tests may be indicated. Inadequate pain control is most often due to a poor history and examination. Establishing the effect of pain on the person's quality of life and activities of daily living, recording previous effects of analgesic treatments, and exploring the patient's goals and expectations are crucial in being able to treat effectively all aspects of pain's impact on the person. The acronym SOCRATES is useful in prompting systematic assessment of pain characteristics: Site, Onset, Character, Radiation, Associated factors, Timing, Exacerbating/relieving factors, and Severity. As previously mentioned, patients often report more than one pain and it is important to ascertain a pain history for each pain a patient reports, because its cause and therefore treatment might vary. Character Patients can find it difficult to articulate the character of their pains. However, it is important to elicit descriptors as a step in 7.2 Pain management Marie Fallon

630 Section 7 Pain and palliative care diagnosing the underlying pathophysiology. If patients are struggling to describe a pain, direct questioning about presence or absence of particular characteristics can be helpful for the patient and assessor. Nociceptive pain is divided into somatic pain, which arises from injury to the soft tissues and bone, and visceral pain, which arises from injury to internal organs. Somatic pain is usually well localized and described as aching, sharp, or throbbing. However, visceral pain due to obstruction of a hollow viscus is poorly localized and can be described as gnawing, a pressure, or deep pain. Visceral pain is commonly referred, and follows classic patterns such as diaphragmatic irritation resulting in classic shoulder tip pain (Table 7.2.1). Patients often find visceral pain harder to describe than somatic pain. Neuropathic pain is often described as numb or burning with sharp, shooting pains either at rest or on movement. Itch, tightness, hot or cold sensations, creeping under the skin (formication) are all described in neuropathic pain. Patients might describe spontaneous pains in the absence of any stimuli or evoked pains such as allodynia (painful response to a nonpainful stimulus), hyperalgesia (increased painful response to a painful stimulus), and hyperpathia (delayed and prolonged response to painful stimulus). It is not always straightforward to distinguish between neuropathic and nociceptive pain on the basis of pain descriptors alone. Clinical examination Clinical examination is essential to ensure accurate diagnosis of the pathophysiology of pain. It not only aids accurate diagnosis but also allows for assessment of comorbidities and the patient's overall physical state. This information is essential when considering management strategies. Approach to cancer pain assessment Assessment is based on careful listening, observing, and encouraging open communication, along with a knowledge of common pain syndromes and patterns of presentation. The key information we seek is usually more accurate if we allow the patient to tell their story. A good consultation will enable not only the pain syndrome(s), along with probable underlying pathophysiology to be formulated, but also a good understanding of the impact of the pain on physical function and importantly on emotional functioning. These can be complex areas of assessment as there can be important interdependent relationships which may need very individual and specific management. Neuropathic pain Neuropathic pain in general is not a single condition, but represents a syndrome, which can be thought of as a collection of specific symptoms and signs with multiple underlying aetiologies. The aetiology of pain in cancer patients is complex and is often a mix of inflammatory and neuropathic mechanisms that evolve over time as the tumour progresses. The picture is further complicated because neuropathic pain symptoms and signs frequently exist as a spectrum and, therefore, the clinical question is not 'Does my

patient have neuropathic or nociceptive pain?’ but rather, ‘Is this pain predominantly neuropathic or nociceptive in origin?’ Nevertheless, neuropathic pain in cancer patients is conventionally categorized as disease-related, treatment-related, or comorbid. Cancer-induced bone pain (CIBP) Bones are the third most common site of metastatic disease, after liver and lung, with c.75% of these patients suffering from related pain. CIBP remains one of the major clinical challenges in palliative care, with several possible reasons for this. Bone pain can have a significant impact on physical, psychological, and social functioning (and therefore overall quality of life). CIBP can be difficult to manage and treatment may require the use of multiple types of interventions. The mechanisms of CIBP are complex and have unique characteristics that are different from neuropathic and inflammatory pain—this has clear implications for managing CIBP effectively. Additionally, the different components of CIBP (spontaneous pain, incident, or movement-related pain and background pain), which might have different mechanisms and be more or less important in any individual; all need to be addressed to improve the quality of life for the patient. The current gold standard treatment for CIBP is palliative radiotherapy, although only 55% of patients will achieve adequate analgesia from palliative radiotherapy, and this can take up to six weeks to work.

General approach to cancer pain management For most patients with cancer pain, a three-step approach combining simple or opioid analgesia, depending on the severity of pain, along with an adjuvant analgesic, depending on the cause of the pain, will result in good pain relief. The challenge, however, is to achieve good pain relief without unacceptable adverse effects. The solution usually lies in very careful assessment, appropriate

Pain mechanism	Site of lesion (examples)	Referral site
Visceral	Diaphragmatic irritation	Shoulder
Urothelial tract	Inguinal region and genitalia	Somatic
C7–T1 vertebrae	Interscapular	L1–L2
Sacroiliac joint and hip	Hip joint	Knee
Pharynx	Ipsilateral ear	Neuropathic
Nerve or plexus	Anywhere in the distribution of a peripheral nerve	Nerve root
Anywhere in the corresponding dermatome	Central nervous system	Anywhere in the region of the body innervated by the damaged structure

7.2 Pain management choice of analgesic, and adjuvant analgesic for the individual patient, along with anticipation and avoidance of any unwanted effects (Table 7.2.2). There are two main areas to think about:

1. Common opioid-related side effects: dry mouth, constipation, nausea/vomiting, and drowsiness. The latter two should resolve, but the first two are chronic.
2. The addition of adjuvant analgesics can potentiate the opioid-related side effects. A reduction in opioid dose should be considered as soon as pain is acceptable, if side effects worsen. Step 1: nonopioid drugs Nonopioids drugs can be used at any stage of the WHO analgesic ladder (Fig. 7.2.1). Their use might result in synergistic effects when used with opioids, producing better pain relief at lower doses of opioids with potentially fewer opioid side effects. Paracetamol and nonsteroidal anti-inflammatory drugs The first step on the WHO analgesic ladder is designed to treat mild pain, and recommends the use of paracetamol and/or nonsteroidal anti-inflammatory drugs (NSAIDs). Both paracetamol and NSAIDs can be considered either alone (step 1) or in combination with opioids (step 2 and 3) to improve analgesia and reduce opioid-related side effects. It is generally accepted that paracetamol is introduced first with an NSAID added to paracetamol or substituting paracetamol if indicated. NSAIDs are considered as second choice in mild pain, provided there is no contraindication. Adjuvant drugs Adjuvant drugs target specific

mechanisms commonly involved in neuropathic pain and the most frequently used are tricyclic antidepressants such as amitriptyline and imipramine, and anti-convulsants such as gabapentin and pregabalin (Table 7.2.3). The use of gabapentin or amitriptyline in combination with opioids is recommended in patients with cancer pain that is only partially responsive to opioid analgesia and has a neuropathic element. Amitriptyline can be a good choice for the patient who is unable to sleep. The use of these drugs is likely to cause significantly increased adverse effects. Duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI), is an alternative adjuvant to tricyclic antidepressants. Steroids, often dexamethasone, are used for liver capsule pain and nerve plexopathies. The lowest effective dose should be used.

Step 2: opioids for mild to moderate pain For pain unrelieved by step 1 and moderate pain, the important issue at this stage is to prescribe a therapeutic dose of codeine and paracetamol, which would be 60 mg and 1000 mg, respectively, four times a day. Tramadol with paracetamol is an alternative option advocated in some countries. The use of low doses of drugs that are normally used at step 3 (severe pain) has been debated. This could include low-dose oxycodone, or transdermal fentanyl. This method has the potential advantage of a simple upwards dose titration if pain is not controlled, but seems opioid responsive. This technique might be

Table 7.2.2 Opioid-induced side effects and their principle management

Side effect	Management
Nausea and vomiting	Antiemetics (e.g. metoclopramide; anticholinergics; opioid rotation)
Sedation	Discontinue other sedating medications; opioid rotation; psychostimulants; donepezil
Constipation	Prophylactic treatment with stool softener and bowel stimulant; nonabsorbable laxative (lactulose, polyethylene glycol); metoclopramide; opioid antagonists
Dry mouth	Discontinue other drugs with this side effect (e.g. anticholinergics); good regular mouth care; iced drinks; saliva replacement sprays

Mild pain Moderate pain Severe pain <3 out of 10 on NRS Paracetamol* NSAIDs* Codeine Dihydrocodeine Tramadol Morphine Diamorphine Fentanyl Hydromorphone Oxycodone

Step 1 Nonopioids **Step 2** Weak opioids *Nonopioids and adjuvants can be used at any step WHO = World Health Organization; NRS = numerical rating scales; NSAIDs = nonsteroidal anti-inflammatory drugs **Step 3** Strong opioids 3–6 out of 10 on NRS

“ 6 out of 10 on NRS Fig. 7.2.1 Adaptation of the WHO analgesic ladder to show analgesic treatment options.

632 Section 7 Pain and palliative care clinically appropriate for some patients and success depends on an appropriately low starting dose to avoid unwanted side effects. Transdermal fentanyl is not ideal in a situation of severe uncontrolled pain due to the longer time required to reach optimum dose. Evidence is accumulating for going straight to low dose step 3, rather than step 2.

Step 3: opioids for moderate to severe pain Strong opioids that are used in palliative care include: morphine, alfentanil, buprenorphine, diamorphine, fentanyl, hydromorphone, methadone, and oxycodone. Immediate release oral morphine administered every four hours is effective and safe and was the first rational pharmacological approach proposed to treat cancer pain. The improved availability of different opioids has resulted in greater experience with the use of these drugs. Oxycodone or hydromorphone are alternatives to oral morphine as an opioid of first choice. No evidence exists demonstrating the superiority of one oral opioid over another; oral morphine,

hydromorphone, and oxy- codone preparations are to be considered equivalent as first choice drug for moderate to severe cancer pain. In many countries mor- phine is most commonly used first line because of clinician fa- miliarity and cost. There is significant inter and intraindividual variation in opioid response. An open mind should be adopted to switching an opioid to achieve better pain relief. Transdermal opioids Fentanyl and buprenorphine are opioids with short-acting anal- gesic activity after intravenous or subcutaneous administration. Their low molecular weight, high potency, and lipid solubility, make them suitable for delivery via the transdermal therapeutic system. Transdermal fentanyl and buprenorphine are adminis- tered increasingly for moderate to severe cancer pain because of their formulation and favourable pharmacological profile. The de- livery system results in a slow build-up of drug in plasma levels, but once reached these will remain clinically stable. Transdermal delivery of drugs can be useful in patients with oral or other gastrointestinal problems. This form of fentanyl and buprenorphine can be used in patients with stable oral opioid re- quirements as an alternative to oral slow-release opioids. Methadone

Methadone has often been considered an alternative to oral mor- phine, but its pharmacokinetic characteristics of a very long and unpredictable individual half-life have meant that in clinical practice its use is usually initiated and supervised by a specialist. In this situation it is usually prescribed for the patient who has evidence of some elements of an opioid-responsive pain, but that requires doses at a level associated with unwanted side effects. Breakthrough pain The term ‘breakthrough pain’ has been used to describe a phenom- enon whereby pain intensity suddenly increases to a moderate to severe level beyond controlled background pain. Implicit in this definition is the administration of regular opioid analgesia for background pain. Breakthrough pain can result from slow-release medication wearing off and we call this end of dose failure. Another type of breakthrough pain can be more of an increase in back- ground pain due to an increase in activity or other factors. Both these types of breakthrough pain usually respond well to imme- diate release morphine or other prescribed opioid, usually given as one-sixth of the 24-hour around the clock dose. For breakthrough pain associated with metastatic bone disease or neuropathic pain, there can be a very sudden onset of pain of short duration: the fun- damental problem with standard immediate release opioid medi- cation is that the onset of action lags significantly behind the peak of the pain and the duration of analgesia is much longer than the breakthrough pain episode. This translates into poor pain control, with excessive drowsiness. A variety of fast-acting fentanyl preparations is now available. These formulations have a slightly more favourable pharmacokin- etic profile than oral immediate release morphine for rapid onset

Table 7.2.3
Summary of adjunctive therapies for neuropathic pain

Drug group	Probable mechanism of action	Typical regimen options
Corticosteroids	Reduce pain-provoking ‘inflammatory soup’ and oedema	Dexamethasone 8 mg twice daily; reduce slowly in 25% decrements.
Antidepressants	Enhance central inhibition by an increase in synaptic noradrenaline reuptake	Amitriptyline initiated at low dose: 10–25 mg at night; increased slowly to maximum 120 mg (dose usually limited by side effects). Duloxetine 30 mg once daily, increase to 60 mg after one week (max 120 mg/day in divided doses).
Anticonvulsants	Decrease in neuronal excitability	Gabapentin 100–300 mg at night; increased in 100–300 mg increments every three days as tolerated. Up to a maximum of 1800 mg/day. Pregabalin 150 mg/day in two divided doses. After three to seven days increase to 300 mg/day if needed. Then to a maximum of 600 mg/day after seven days if required.
Class 1b cardiac antiarrhythmics	Decrease neuronal excitability by blocking sodium channels	Seek specialist advice. IV lidocaine up to 5 mg/kg as infusion over 30 minutes. Lidocaine 5% patch: apply up to three patches once daily for up to 12 h, follow with minimum 12 h patch-free interval.
NMDA antagonists	Inhibit pathological neuronal phenomena, such as wind-up. Increase response to	

opioids Seek specialist advice. Typically ketamine 50–500 mg/day, depending on administration route a Specialist advice must be sought before using these groups of drugs because of potential side effect risks.

7.2 Pain management 633 breakthrough pain. However, they are not a solution for most patients with breakthrough pain. It is important to discuss potential use of fast-acting fentanyl preparations with a specialist. Opioid titration The traditional use of administering immediate release oral morphine every four hours was not founded on controlled clinical trials but on longstanding clinical practice combined with pharmacological rationale based on the short half-life of oral morphine. The advent of slow-release oral morphine, oxycodone, and hydromorphone preparations has made it possible to maintain appropriate plasma levels to deliver analgesia for periods of time ranging from 12 to 24 hours, and with transdermal delivery systems of fentanyl and buprenorphine for up to three days. This development encouraged the clinical practice of using slow-release oral opioid preparations or transdermal opioid delivery systems in opioid-naïve patients or those patients previously exposed only to drugs at step 2. The literature has not identified any problems with this approach as long as appropriate starting doses are chosen. For the nonspecialist, the 'conventional practice' of starting with immediate release morphine can allow a more accurate reassessment of effects and future titration decisions. Titration can be performed with slow-release opioid formulations according to their pharmacological profile in combination with oral immediate release opioids. The use of the immediate release opioid (for breakthrough pain)—prescribed at one-sixth of the total 24-hour opioid dose—will guide dose adjustment of the slow-release preparation. Pain management needs an interdisciplinary approach We can make pain management more complex by employing only systemic analgesics. The WHO three-step approach is only effective if integrated with appropriate other inputs, depending on the individual patient. Effective appropriate oncological or other disease-specific management, interventional anaesthesia, physiotherapy, occupational therapy and clinical psychology are among the key approaches which need to be available (Table 7.2.4). Uncontrolled pain Difficult-to-control pain can have a variety of complex causes, however, a common cause is a period of poorly controlled pain. Unrelieved pain can itself cause difficult to reverse neurobiological changes. All attempts should be made to control pain throughout the illness. Failure to do so can mean a very distressing end-of-life period. FURTHER READING Caraceni A, et al. for EPCRC Collaborative on behalf of EAPC (2012). Evidence-based guidelines for the use of opioid analgesics in the treatment of cancer pain: the 2011 EAPC recommendations. *Lancet Oncol*, 13, e58–e68. National Institute for Health and Care Excellence (NICE) (2013). Neuropathic Pain in Adults: Pharmacological Management in Non-Specialist Settings. Clinical guideline [CG173]. Last updated: February 2017. <https://www.nice.org.uk/guidance/cg173> Portenoy R (2011). Treatment of cancer pain. *Lancet*, 377, 2236–47. Scottish Palliative Care Guidelines. <http://www.palliativecareguidelines.scot.nhs.uk/> Scottish Intercollegiate Guidelines Network (2008). SIGN Guideline 106 Control of Pain in Adults with Cancer. <http://www.sign.ac.uk/assets/sign106.pdf> Table 7.2.4 Optimizing analgesic approaches Approach Therapeutic options Pharmacological techniques Pharmacological techniques to reduce systemic opioid requirement Co-administration of nonopioid analgesic or an adjuvant analgesic Neuraxial drug infusion or other route change Local nerve blocks Topical treatments Palliative chemotherapy Hormonal therapy Bisphosphonates Radioactive isotopes Non-pharmacological techniques Nonpharmacological techniques to reduce systemic opioid requirements Palliative radiotherapy Anaesthetic approaches Surgical approaches Transcutaneous electric nerve stimulation Acupuncture Therapeutic massage Rehabilitative approaches Psychological approaches

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