

Pain in palliative care: a review

In the first of two articles on managing pain in palliative care, Andrew Dickman looks at non-opioid and adjuvant analgesics

Palliative care has traditionally been associated with the model of care introduced for cancer patients by hospices within the UK. The aim of palliative care is to relieve symptoms and enable a patient to die with dignity. In 2002, the World Health Organization introduced a new definition of palliative care (see Panel 1). This was an important development because the definition recognises that other life-threatening conditions are of equal concern and that palliative care is also applicable early in the course of an illness, and it encompasses the treatment of physical, psychological and spiritual needs of both the patient and his or her family.

What is pain?

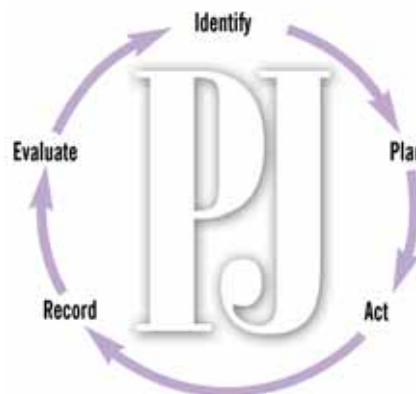
There have been tremendous leaps in knowledge since the pivotal gate theory proposed by Melzack and Wall in 1965.¹ It is now recognised that pain perception is governed by a multitude of factors that have been described as the neuromatrix theory of pain.² This theory proposes that individuals experience pain as a combination of cognition, emotion and sensation, mediated through the involvement of multiple regions within the brain (ie, the neuromatrix). Pain is experienced by an individual through many inputs to the neuromatrix, rather than directly by a sensory input caused by injury or inflammation. For example, chronic pain syndromes exist where no obvious tissue damage is apparent. Patients experiencing pain from these syndromes can display signs of psychological or physical stress, suggesting that genetic influences and the neural-hormonal mechanisms of stress are as important as the neural mechanisms of sensory transmission to the whole pain experience.

There are many definitions of pain; the International Association for the Study of Pain definition is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. In addition, there are many different ways to classify pain; common terms are shown in Panel 2 (p680). When assessing pain in the palliative care setting, a valuable definition is “pain is what the patient says it is”.

The concept of “total pain” has been adopted by palliative care practitioners in an attempt to explain what is experienced by the patient. Cancer pain is a complex chronic pain, often with multiple causes. In addition, a patient is likely to be depressed, anxious and possibly angry. Such factors will have a direct effect on a patient’s pain experience in addition to the physical pain caused by the disease. Addressing a patient’s concerns or fears, in addition to analgesia, can help to reduce suffering. In other words, pharmacotherapy alone is unlikely to be adequate treatment for



Pain perception is governed by a multitude of factors



Identify knowledge gaps

1. What is palliative care?
2. How useful is aspirin as a palliative care analgesic?
3. Give an example of an adjuvant analgesic.

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society’s areas of competence for pharmacists are listed in “Plan and record”, (available at: www.rpsgb.org/education). This article relates to “common disease states and their drug therapies” (see appendix 4 of “Plan and record”).

chronic pain of any cause. Indeed, the treatment of cancer pain will invariably be multimodal, incorporating combinations of analgesics and emotional, psychological and spiritual support.

Non-pharmacological treatments for pain (eg, transcutaneous electrical nerve stimulation) will also be of value. It is not surprising

Panel 1: What is palliative care?

Palliative care is an approach that improves the quality of life of patients and their families facing 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. Palliative care:

- Provides relief from pain and other distressing symptoms
- Affirms life and regards dying as a normal process
- Intends neither to hasten or postpone death
- Integrates the psychological and spiritual aspects of patient care
- Offers a support system to help patients live as actively as possible until death
- Offers a support system to help families cope during the patient’s illness and in their own bereavement
- Uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated
- Will enhance quality of life, and may also positively influence the course of illness
- Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications

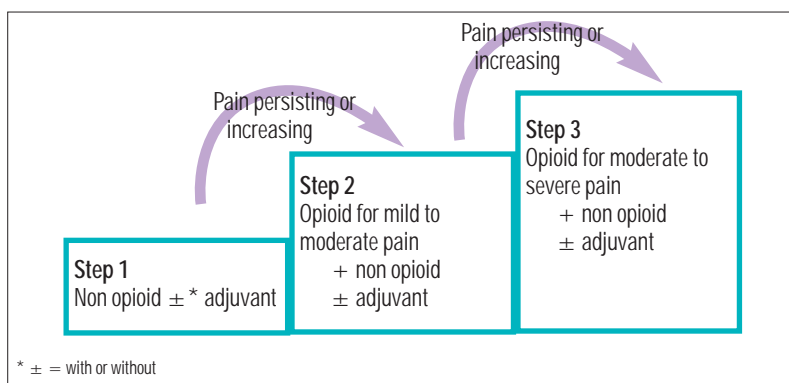


Figure 1: Representation of the WHO analgesic ladder

that a multidisciplinary team approach is necessary for the successful treatment of cancer pain. Despite this approach, patients should be advised that they may never be completely free of pain. Throughout the day, there may be brief episodes of discomfort and patients may have to change their lifestyles to ensure pain does not become an overwhelming problem.

Pharmacotherapy of cancer pain

Although not all patients with cancer will experience pain, it is believed that pain will intensify as the disease progresses. For patients with advanced disease, the incidence of pain is thought to be between 60 and 90 per cent.

Analgesics relieve pain by directly manipulating its physiological mechanisms. New anal-

gesics have been developed, along with novel formulations and delivery systems. A greater understanding of pain mechanisms has, along with serendipity, also initiated a proliferation of new indications for drugs previously developed for other conditions. Such drugs are referred to as adjuvant analgesics.

In 1986, the WHO introduced the concept of a three-step analgesic ladder for the treatment of patients with cancer pain (see Figure 1). This approach should be considered as a framework rather than a rigid protocol; pain management must be individualised. The ladder generally applies to chronic pain of non-malignant origin as well. The aim was to provide simple guidelines that practitioners could easily follow. Pain relief can be achieved in about 80 per cent of patients³ by adopting the basic principle of “by the mouth, by the ladder, by the clock” (ie, oral medication, in a step-wise approach at regular, fixed intervals). Analgesia must be given at fixed intervals to ensure continuous pain relief; analgesics are more effective at preventing the development of pain, rather than relieving existing pain.

A major consequence of the analgesic ladder was the legitimising of the use of strong opioids. The first step of the ladder involves the use of non-opioid drugs, such as paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs), with or without an adjuvant analgesic. If pain remains uncontrolled, step 2 is used: an opioid for mild to moderate pain (eg, codeine) is added to step 1 treatment. If pain persists, step 3 is introduced: a strong opioid (eg, morphine) replaces the weak opioid and is titrated according to pain relief.

A common misconception is that the prescriber must start at step 1. In fact, with careful assessment, it is acceptable to start at any point on the ladder because treatment is tailored to the severity of pain.

To combine or not to combine?

Chronic pain, whether caused by cancer or not, is likely to be composed of both nociceptive and neuropathic elements and a single analgesic is unlikely to be sufficient. Indeed, the analgesic ladder recommends the use of more than one analgesic if pain is difficult to control. The combination of two analgesics that have actions at different parts of the pain pathway should, in theory, allow a reduction in dose of both drugs, with a subsequent increase in safety, tolerability and efficacy. This is demonstrated by the fixed-dose combination of tramadol 37.5mg and paracetamol 325mg (Tramacet), which has been shown to have an improved tolerability profile compared with the equianalgesic dose of tramadol alone. Despite the lack of clinical trial evidence, in practice other drug combinations (eg, NSAID plus tramadol, opioid plus NSAID) are used with apparent success.

Non-opioid analgesics Non-opioid analgesics comprise paracetamol and NSAIDs.

Paracetamol Last year marked the 50th anniversary of paracetamol’s introduction in

Panel 2: Commonly encountered types of pain

Acute pain Acute pain is arbitrarily taken to last for less than three months. It serves as a warning of injury, or potential for further harm. It subsides as healing occurs and responds well to analgesia.

Chronic pain Chronic pain serves no purpose and does not generally relate to injury. One exception is chronic cancer pain, where the pain may be related to the disease. Chronic pain can respond unpredictably to analgesia.

Nociceptive pain Nociceptive pain is caused by stimulation of nociceptors in the peripheral nervous system and generally responds well to analgesia. Examples of nociceptive pain include “somatic” and visceral pain (see below).

Neuropathic pain Neuropathic pain is caused by damage to or changes in the central or peripheral nervous system. It typically responds poorly to conventional analgesics and adjuvant analgesics are generally required. It can be described by a variety of terms, depending on the nerve affected (eg, hot, cold, sharp, shooting, stabbing, itching).

Somatic pain Somatic pain is produced by activation of peripheral nociceptors found in skin, bone, joints and muscles. Typically described as aching or throbbing, the pain is generally localised and constant. It usually responds well to conventional analgesics, although occasionally adjuvant analgesics are required (eg, bisphosphonates for bone pain).

Visceral pain Visceral pain is produced by stimulation of nociceptors within internal organs. It is often poorly localised and can be referred to non-visceral areas. Visceral pain can be described as constant and sharp. It usually responds well to conventional analgesics, although occasionally adjuvant analgesics are required (eg, hyoscine butylbromide for bowel colic). Nausea can accompany visceral pain.

Breakthrough pain Also called episodic pain, breakthrough pain is a term used to describe a transient exacerbation of pain that occurs spontaneously or in relation to a trigger that can be either predictable (eg, movement) or unpredictable (eg, cough) despite relatively stable and adequately controlled background pain.

the UK as Panadol tablets. Paracetamol's analgesic and antipyretic activity is similar to that of aspirin, but it has no anti-inflammatory action. Many health care professionals and patients dismiss paracetamol as a useful analgesic because it is so widely available, but it remains useful in treating mild to moderate pain. Despite having been available for so long, its mechanism of action remains elusive, although recent research suggests that serotonin modulation pathways may be involved. Adverse effects are rare, although skin reactions and blood disorders (including a proposed interaction with warfarin) have been reported.

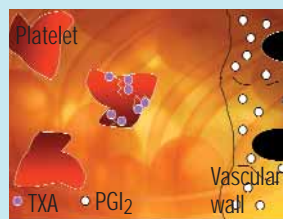
The catastrophic effects of paracetamol overdose are well-documented. Case reports suggest that patients co-prescribed enzyme-inducing drugs, such as carbamazepine or phenytoin, may be at greater risk of developing unexpected paracetamol toxicity. People with chronic alcoholism and binge drinkers may also be at a greater risk of toxicity. Paracetamol has been tenuously linked to renal damage and hypertension in women with long-term use, although further evidence is needed before widespread changes to practice occur.

NSAIDs NSAIDs are a heterogeneous group of analgesics ranging from aspirin (the oldest), through to lumiracoxib (the newest; Prexige) and represent the most common group of analgesics prescribed worldwide. They are useful in treating mild to moderate pain mediated by prostaglandins, which serve to sensitise nociceptors. While radiotherapy remains the treatment of choice, NSAIDs have traditionally been used in the palliation of metastatic bone pain, in spite of insufficient data.⁴ There is undoubtedly an element of inflammation in bone pain, but sole use of NSAIDs may not provide sufficient analgesia and additional drugs, as described by the analgesic ladder, may be required.

Analgesia is produced through the inhibition of one or both of the isoenzymes of cyclo-oxygenase: COX-1 and COX-2. Non-specific COX inhibitors, such as aspirin, ibuprofen, diclofenac and naproxen, inhibit both isoenzymes to produce analgesia. Unfortunately, this also causes adverse effects, most notably gastrointestinal and renal toxicity. Minor adverse effects include dyspepsia, nausea and vomiting.

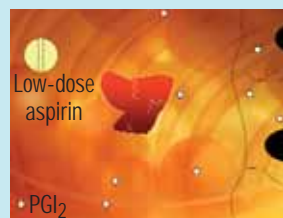
Contrary to popular belief, dyspepsia does not necessarily indicate impending peptic ulceration; symptoms are poor predictors of gastroduodenal damage and are not a reliable means of determining whether or not a patient is developing serious complications.⁵ The deleterious effects of the NSAIDs were thought to be due to inhibition of COX-1 and it was hoped that by selectively inhibiting COX-2, a drug could be developed with the analgesic benefits of the traditional NSAIDs, but without their adverse effects. COX-2 selective NSAIDs, such as etodolac and meloxicam, were initially developed, quickly followed by the COX-2 inhibitors.

Panel 3: NSAID effects on the cardiovascular system



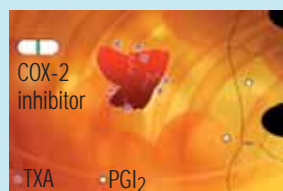
Blood clotting and vasodilation

A damaged platelet secretes thromboxane A₂ (TXA) in response to injury. This is mediated by COX-1. If this were to go unopposed, a clot would begin to form. To balance the production of TXA, cells lining the vascular wall secrete prostacyclin (PGI₂), mediated by COX-2. PGI₂ has antiplatelet and vasodilatory properties.



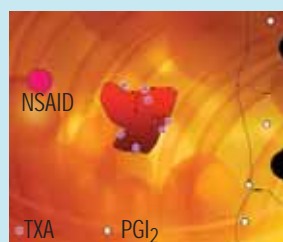
The antiplatelet effect of low dose aspirin

At low doses (<150mg/day) aspirin binds irreversibly to both COX-1 and COX-2. The cells within the vascular wall are able to synthesise new COX-2 enzyme, so the production of PGI₂ continues, if slightly reduced. The platelet, however, cannot synthesise further COX-1, so TXA production halts.



COX-2 inhibitors

COX-2 inhibitors have no effect on the COX-1 mediated synthesis of TXA by the platelet. They do, however, reduce the COX-2 mediated synthesis of PGI₂ by cells within the vascular wall. This is an oversimplification, but the net effect is a potentially pro-thrombotic state.



Non-selective NSAIDs

A non-selective NSAID binds to both COX-1 in the platelet and COX-2 in cells within the vascular bed. Most of these drugs have no clinically significant antiplatelet effect; TXA production by the platelet continues. It is believed that there will be a reduction of PGI₂ synthesis; the clinical significance is as yet unknown, but there is a similarity between this situation and that of the COX-2 inhibitors.

The early trials with rofecoxib and celecoxib did indeed show a reduced incidence of gastrointestinal toxicity, but adverse renal effects, similar to the non-selective NSAIDs, were detected. It soon became evident that the initial picture was too simplistic; COX-2 appeared to have important homeostatic functions. It is now accepted that all the NSAIDs can cause deterioration of renal function and can precipitate hypertension in patients on anti-hypertensive therapy. Although the analgesic action of the NSAIDs has been elucidated, the pharmacology of the adverse effects remains uncertain.

The entire class of NSAIDs has been under close scrutiny since the worldwide withdrawal of rofecoxib in September 2004. This was a consequence of high rates of cardiovascular adverse effects in a trial examining the use rofecoxib in the prevention of cancerous polyps.⁶ The withdrawal of valdecoxib followed in 2005, although for a completely different reason — a perceived unacceptable risk of Stevens-Johnson syndrome. The cardiovascular effects of the COX-2 inhibitors were certainly unexpected. Recent work suggests that this may not simply be a COX-2 inhibitor effect, but the entire NSAID class may be affected.⁷ Panel 3 contains a proposed explanation of the cardiovascular effects.

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Panel 4: Guide to NSAID selection in palliative care

Risk factors	No or low NSAID gastrointestinal risk factors*	NSAID gastrointestinal risk factors*
No CVD [†]	Non-selective NSAID ± [‡] PPI [§]	COX-2 inhibitor ± PPI or Non-selective NSAID + PPI
CVD	Consider alternative analgesia first (eg, paracetamol ± tramadol) then a non-selective NSAID ± PPI (cautiously)	Consider alternative analgesia first (eg, paracetamol ± tramadol) then non-selective NSAID + PPI (cautiously)

* Risk factors include age over 65 years, previous history of peptic ulcer, concurrent medication (eg, aspirin, warfarin, corticosteroid, selective serotonin reuptake inhibitors)

[†] CVD = cardiovascular disease; [‡] ± = with or without; [§] PPI = proton pump inhibitor

Panel 5: Commonly encountered adjuvant analgesics

Indication	Drugs
Neuropathic pain	Amitriptyline, carbamazepine, clonazepam, dexamethasone, gabapentin, pregabalin, tramadol*
Musculoskeletal pain	Dexamethasone, diazepam, disodium pamidronate, tramadol
Bowel colic	Dexamethasone, hyoscine butylbromide

* Although not strictly an adjuvant analgesic, tramadol (a weak opioid) can be introduced to the treatment regimen of a patient already taking a strong opioid

Currently, the remaining COX-2 inhibitors are contraindicated for use in patients with pre-existing ischaemic heart disease, peripheral vascular disease or cerebrovascular disease. Non-selective NSAIDs and COX-2 selective NSAIDs should be used with caution in these patients. However, two things do remain clear: the COX-2 inhibitors are less toxic to the gastrointestinal tract than non-selective NSAIDs⁶ and the toxicity of NSAIDs is related to dose and duration of therapy.⁹

The choice of NSAID before September 2004 was fairly simple and was related to gastrointestinal risk factors alone, since all NSAIDs appeared to have similar renal effects. What followed can only be described as a debacle as conflicting information continually appeared. Nearly two years later, the situation is only a little clearer. A treatment strategy based on current information is shown in Panel 4.¹⁰

It is worth noting that aspirin should never be used as an analgesic in palliative care due to the increased risk of adverse effects (particularly haemorrhage).

Adjuvant analgesics Drugs that have analgesic properties but have a primary indication other than alleviating pain, are termed adjuvant analgesics. Panel 5 lists common adjuvant analgesics. The choice of adjuvant is a difficult one; there is little evidence from clinical trials that have involved palliative care patients and selection of an adjuvant is as much an art as it is a science.

The choice of a category of drug, or specific drug, depends on a number of factors, including type of pain (ie, nociceptive or neu-

ropathic), co-existing morbidity and current medication. In some cases the type of pain may suggest one adjuvant over another and in other situations, a co-existing condition may determine the adjuvant to be used. For example, a patient with a history of epilepsy may benefit from an antiepileptic, an anxious patient unable to sleep may benefit from clonazepam or pregabalin and a depressed patient may benefit from an antidepressant.

It is quite common to see low starting doses of adjuvants for neuropathic pain in cancer patients, especially if a patient is taking a strong opioid. For example, gabapentin may be started at 100mg at night, rather than the recommended 300mg. There are two reasons for this. First, most clinical trials have studied patients with a non-malignant cause of neuropathic pain. Such patients are unlikely to have been on strong opioids, or have the same level of co-morbidity as cancer patients. Second, there is the potential for a synergistic interaction between the adjuvant and strong opioid. If usual starting doses were used, the patient would be likely to display signs of toxicity, such as drowsiness or dizziness. Adjuvants can have opioid-sparing effects and the dose of the opioid should be carefully reviewed as the adjuvant is titrated.

Opioid analgesics The use of opioid analgesics in palliative care will be discussed in an article to be published on 23 June.

Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Read the summary of product characteristics for Prexige (lumiracoxib). Does it offer benefits over older NSAIDs? Discuss with a colleague.
2. List three counselling points for Tramacet. Can additional paracetamol be taken?
3. Investigate local policies or guidelines for the use of NSAIDs in palliative care.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions:

- What have you learnt?
How has it added value to your practice? (Have you applied this learning or had any feedback?)
What will you do now and how will this be achieved?

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