Palliative care has traditionally been associated with the model of care introduced for cancer patients by hospices within the U.K. 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 recognizes 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. It is now recognized that pain perception is governed by a multitude of factors that have been described as the neuromatrix theory of pain. 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 (i.e., 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 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 (e.g., transcutaneous electrical nerve stimulation) will also be of value. It is not surprising...
Pain persisting or increasing

Step 1
Non opioid ± adjuvant

Step 2
Opioid for mild to moderate pain
+ non opioid ± adjuvant

Step 3
Opioid for moderate to severe pain
+ non opioid ± adjuvant

* ± = with or without

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 analgesics 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 patients 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). An 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 prescribing 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, N-SAD1 plus tramadol, opioid plus N-SAD1) 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...
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 sensitize 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. 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 cyclo-oxygenases, COX-1 and COX-2. Non-selective 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. 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.

Andrew Dickman, MSc, MRPharms, is a senior clinical pharmacist at the Marie Curie Palliative Care Institute and The Cardiothoracic Centre, both in Liverpool.

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 of rofecoxib in the prevention of cancerous polyps. 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.
Panel 4: Guide to NSAID selection in palliative care

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>NSAID gastrointestinal risk factors*</th>
<th>NSAID gastrointestinal risk factors*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CVD†</td>
<td>Non-selective NSAID ± PPI</td>
<td>COX-2 inhibitor ± PPI or</td>
</tr>
<tr>
<td></td>
<td>(cautiously)</td>
<td>Non-selective NSAID + PPI</td>
</tr>
<tr>
<td>CVD</td>
<td>Consider alternative analgesia first</td>
<td>Consider alternative analgesia first</td>
</tr>
<tr>
<td></td>
<td>(eg, paracetamol ± tramadol then)</td>
<td>(eg, paracetamol ± tramadol) then</td>
</tr>
<tr>
<td></td>
<td>a non-selective NSAID ± PPI</td>
<td>non-selective NSAID + PPI (cautiously)</td>
</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic pain</td>
<td>Amitriptyline, carbamazepine, clonazepam, dexamethasone, gabapentin, pregabalin, tramadol*</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>Dexamethasone, diazepam, disodium pamidronate, tramadol</td>
</tr>
<tr>
<td>Bowel colic</td>
<td>Dexamethasone, hyoscine butylbromide</td>
</tr>
</tbody>
</table>

* 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 NSAIDs and the toxicity of NSAIDs is related to dose and duration of therapy.

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. By early two years later, the situation is only a little clearer. A treatment strategy based on current information is shown in Panel 4.

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 neuropathic), 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.

References