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The principles of cancer pain management

Marie Fallon MD FRCP(Glas) FRCP(Ed) MRCPGP, Reader in Palliative Medicine, *University of Edinburgh, Edinburgh Cancer Centre, Western General Hospital, Edinburgh*

Sandra McConnell MB ChB MRCP, Specialist Registrar in Palliative Medicine, *Western General Hospital, Edinburgh*

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Pain occurs in up to 70% of patients with advanced cancer and in about 65% of patients dying from non-malignant disease. Pain can be controlled in most (about 80%) using a simple, stepwise approach and a limited number of analgesics as set out in the World Health Organization (WHO) analgesic ladder (Fig 1).¹ The severity of the pain dictates the strength of analgesic and the pathophysiology dictates the adjuvant analgesic to be prescribed.

About 10% of patients will require more complex, sometimes invasive,

management to control their pain, leaving another 10% with cancer pain that is difficult to control.

Assessment of pain

The keystone to successful management is assessment which should reveal:

- patient characteristics, including mood
- pain characteristics
- drug responsiveness.

Patient characteristics

Characteristics relating to the patient are:

- previous problems with analgesia
- fear of opioids
- deranged biochemistry, and
- mood.

Assessment of mood in a patient with uncontrolled cancer pain should be made with an open mind. If depressed, patients

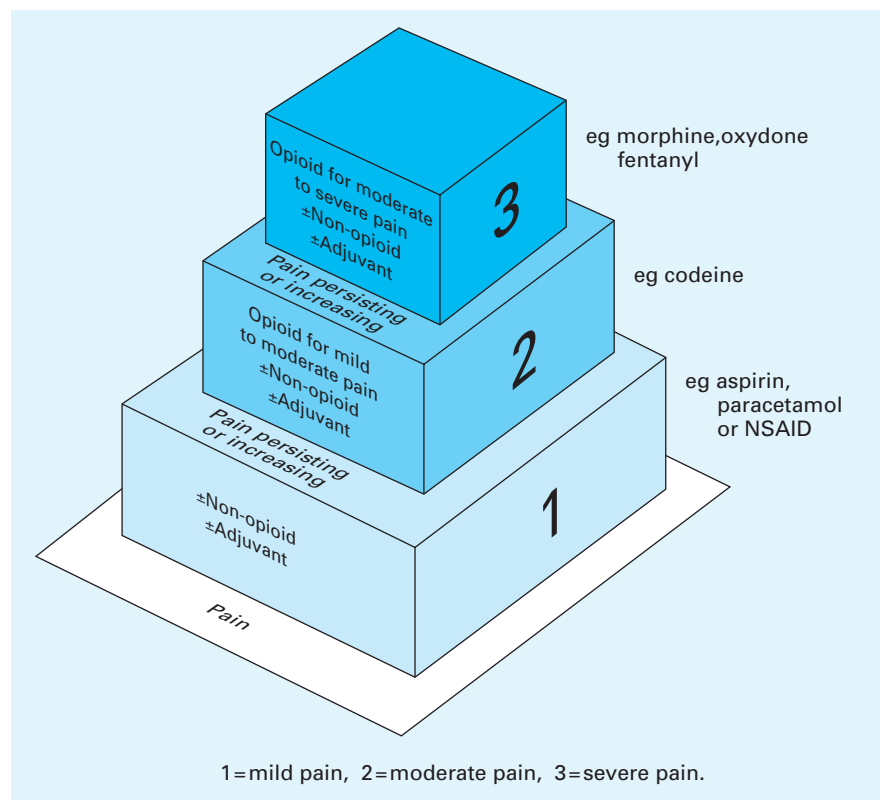


Fig 1. World Health Organization three-step analgesic ladder. NSAID = non-steroidal anti-inflammatory drug.¹

will often state that this results from severe pain affecting many aspects of quality of life. Many patients will have improved mood with adequate pain control but some will require an antidepressant. This is particularly likely in established, severe depression.

Pain characteristics

Characteristics relating to the patient's pain are:

- *cancer-pain related*: this may have characteristics of a classical cancer pain syndrome such as liver capsule pain, lumbosacral plexopathy, brachial plexopathy, coeliac plexus infiltration, raised intracranial pressure
- *treatment-related*: for example, platinum-induced neuropathy, radiotherapy-induced oesophagitis, radiotherapy-induced plexopathies
- *non-cancer pain*: for example, osteoarthritis.

Drug responsiveness

Drug responsiveness may relate to previous analgesics tried, current analgesia and, if exposed to an opioid,

degree of opioid responsiveness – one of the most important prognostic factors in pain control.²

Total pain

One of the central tenets of modern palliative care was Dame Cicely Saunders' concept of 'total pain', first described in the 1960s.³ This concept is now understood in terms of the sophisticated interaction in the nervous system of physical and emotional aspects which make up the subjective feeling of pain. The non-nociceptive factors are integrated with the nociceptive factors and can magnify the subjective pain sensation experienced (Fig 2).

The World Health Organization analgesic ladder (Fig 1)

The three-step WHO analgesic ladder remains the mainstay of the approach to analgesia. However, non-pharmacological treatments, together with appropriate interventions such as surgery, radiotherapy, bisphosphonates, chemotherapy and other tumoricidal treatments, should be integrated with this analgesic approach, as appropriate.⁴

Adjuvant analgesics (Table 1)

NSAIDs and steroids

Non-steroidal anti-inflammatory drugs (NSAIDs) can be helpful in cancer pain, particularly pain associated with bone metastases, soft tissue infiltration and inflammation. Steroids are also effective in relieving pain caused by inflammation and oedema. However, side effects often limit their usefulness, especially in the longer term.

Tricyclic antidepressants and anticonvulsants

Tricyclic antidepressants are effective in relieving neuropathic pain. There are no significant differences in efficacy between the different tricyclic antidepressants (number needed to treat (NNT) = 3). Unfortunately, side effects often limit their use.

There is a lack of high-level evidence of efficacy of selective serotonin reuptake inhibitors for treating neuropathic pain.

The anticonvulsants carbamazepine, phenytoin, sodium valproate, gabapentin and pregabalin are effective in treating neuropathic pain (NNT = 3). Gabapentin and pregabalin are licensed for treatment

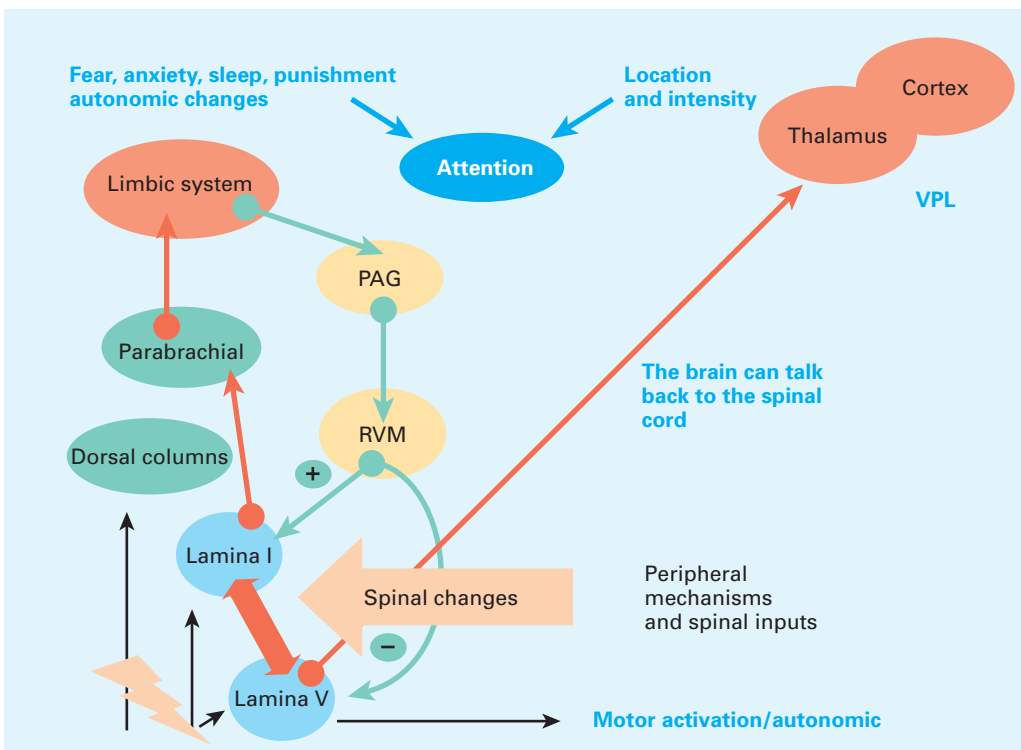


Fig 2. The components contributing to the subjective sensation of pain. PAG = periaqueductal gray; RVM = rostroventromedial medulla; VPL = thalamic nucleus ventroposterior lateralis.

of neuropathic pain. Benefit is independent of pain characteristics.

There is no measurable difference in the analgesic benefit of the two drug classes in neuropathic pain or in the NNT before a minor or major adverse event occurs. Gabapentin and pregabalin seem to have a more favourable side effect profile in many patients, but systematic examination of this in relation to other adjuvants is awaited in patients with cancer pain.⁵

Antidepressants and anticonvulsants may occasionally be prescribed simultaneously but it is good clinical practice to introduce only one drug at a time. Bisphosphonates have been shown to delay the onset of symptomatic bone metastases and their use for acute bone pain is currently being investigated.

Opioids

Opioid analgesics for moderate and severe pain

Morphine is the most commonly used opioid in this group. When possible, it should be given by mouth, the dose tailored to each patient with doses repeated at regular intervals to prevent the

pain from returning. There is no arbitrary upper limit, but negative attitudes to using morphine still exist. The skilled use of morphine will confer benefit rather than harm, but many patients express fears, which should be discussed.

Dose titration. A normal release formulation of morphine (either elixir or tablet), with a rapid onset and short duration of action, is preferred for dose titration. The simplest method is to prescribe a regular, four-hourly dose but to allow extra doses of the same amount for 'breakthrough pain' as often as necessary. The daily requirements may be reassessed after 24–48 hours and the regular dose adjusted as necessary. This process is continued until satisfactory pain relief is achieved.

By this method, the many factors that contribute to the variability in dose are taken into account, including:

- the severity of pain
- the type of pain
- the affective component of pain, and
- variation in pharmacokinetic parameters.

The regular four-hourly dose may range from 5–10 mg to 250 mg or more

(or the equivalent in controlled-release (CR) tablets). The dose is titrated against effect, but very few patients need high doses with most requiring less than 200 mg a day.

Maintenance of pain relief. Once pain is relieved, maintenance will be with a CR morphine preparation, available as a once-daily preparation that remains effective for 24 hours or a twice daily preparation with effects that last 12 hours.

Which opioid for cancer pain?

Comparative trials of opioids in cancer pain are extremely difficult to perform and do not always answer our questions because of the complexity of the populations studied.

There is no strong evidence for the superiority of one opioid over another. However, a number of factors play different roles in the balance between analgesia and side effects including pharmacokinetic profile, route of administration and genetic variability in opioid responses. The transdermal route with TTS-fentanyl (transdermal therapeutic system) or transdermal buprenorphine can be useful in patients with swallowing

Table 1. Adjuvant analgesics.*

Drug	Dosage	Indications	Side effects**
NSAIDs eg diclofenac	50 mg oral 8-hourly (SR 75 mg 12-hourly) 100 mg per rectum once a day	Bone metastases, soft tissue infiltration, liver pain, inflammatory pain	Gastric irritation and bleeding, fluid retention, headache Caution in renal impairment
Steroids eg dexamethasone	8–16 mg per day; use morning; titrate down to lowest dose which controls pain	Raised intracranial pressure, nerve compression, soft tissue infiltration, liver pain	Gastric irritation if used together with NSAID, fluid retention, confusion, Cushingoid appearance, candidiasis, hyperglycaemia
Gabapentin	100–300 mg nocte (starting dose) (titrate to 600 mg 8-hourly; may need higher dose)	Nerve pain of any aetiology	Mild sedation, tremor, confusion
Amitriptyline (evidence for all tricyclics)	25 mg nocte (starting dose) 10 mg nocte (elderly)	Nerve pain of any aetiology	Sedation, dizziness, confusion, dry mouth, constipation, urinary retention Avoid in cardiac disease
Carbamazepine (evidence for all anticonvulsants)	100–200 mg nocte (starting dose)	Nerve pain of any aetiology	Vertigo, sedation, constipation, rash
Bisphosphonates	Various regimens	Malignant bone pain	Hypocalcaemia, 'flu-like' symptoms

* Drugs with a primary indication other than pain, but analgesic when used as above.

** In the elderly all drugs can cause confusion.

NSAID = non-steroidal anti-inflammatory drug; SR = slow release.

difficulties as the drug is released into the skin at a constant rate depending on the dose of patch chosen.⁶ Oxycodone or hydromorphone may provide an alternative to morphine if hallucinations or disturbed sleep are troublesome.

Any opioid can accumulate in renal dysfunction. The various metabolites from the different opioids are not fully understood and care should always be taken in this situation. Opioid doses are usually smaller, with increased dosing intervals or even administered on an 'as required' basis. It is usually acceptable to consider drugs such as fentanyl, alfentanil, hydromorphone and buprenorphine in renal dysfunction.⁷

Tolerance, addiction and physical dependence

Tolerance to opioids is rarely seen in the clinical practice of managing cancer pain. Requirements for increasing doses of morphine can usually be explained by progressive disease rather than by pharmacological tolerance. Psychological dependence or addiction is not a problem except in patients with pre-existing addiction. If alternative methods of pain control are used (such as nerve blocks), it is usually possible to reduce the dose of the analgesic or even withdraw it without adverse psychological effects. Physical dependence can occur; this physiological response can manifest itself as a flu-like illness in some patients if an opioid is discontinued suddenly.

Opioid toxicity

There is wide variation over time in the dose of opioid which can be tolerated, both between and within individuals. The ability to tolerate a particular dose depends on the degree of responsiveness of the pain to opioid analgesia, prior exposure to opioids, rate of titration of the dose, concomitant medication and renal function. Toxicity can be a frightening and life-threatening experience but it is usually reversible if diagnosed early.

Opioid toxicity may present as subtle agitation, seeing shadows at the periphery of the visual field, vivid dreams, visual and auditory hallucina-

Key Points

Pain affects 70% of patients with advanced cancer

Successful management depends on full assessment of patient and pain characteristics and drug responsiveness

Most patients' pain can be controlled by applying the three-step WHO analgesic ladder

Non-pharmacological treatments together with appropriate interventions should be integrated with drug treatment as necessary

Opioid dose should be titrated using short-acting normal release opioid

Opioid toxicity should be monitored actively and treated promptly

KEY WORDS: adjuvants, cancer pain, opioids, total pain, toxicity, World Health Organization

tions, confusion and myoclonic jerks. Agitated confusion may be interpreted as uncontrolled pain and further opioids given. A vicious cycle then follows in which the patient is given sedation and may become dehydrated, resulting in the accumulation of opioid metabolites and further toxicity.

Management of opioid toxicity includes reducing the dose of opioid, ensuring adequate hydration and treating the agitation with haloperidol (1.5–3 mg orally or subcutaneously, repeated hourly as needed). If toxicity is severe and opioid analgesia is still needed, a switch in opioid usually leads to a faster recovery.

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