

Opioid analgesics in palliative care

In a second article on the treatment of pain in palliative care, Andrew Dickman discusses the use of opioids

The discovery of the opioid receptors began in the 1970s and three (μ , δ and κ) are now recognised. Most current opioid analgesics interact preferentially with μ receptors, although some have actions at δ and κ receptors. The revelation that opioid receptors are present on peripheral sensory neurones and immune system cells,^{1,2} has led to the realisation that the opioid system is involved in a host of actions, including the central and peripheral modulation of pain transmission and the regulation of immune and neuroendocrine processes.

Opioid pharmacology has become even more complex with the recent suggestion of multiple receptor subtypes (eg, μ_1 and μ_2). The predominant subtype can have a profound effect on analgesic response. In addition, the existence of subtypes may partially explain incomplete cross-tolerance to μ receptor opioids and the need to reduce the equianalgesic dose by 25–30 per cent when switching between them. The effects mediated by each receptor type are shown in Panel 1.

Mild to moderate pain

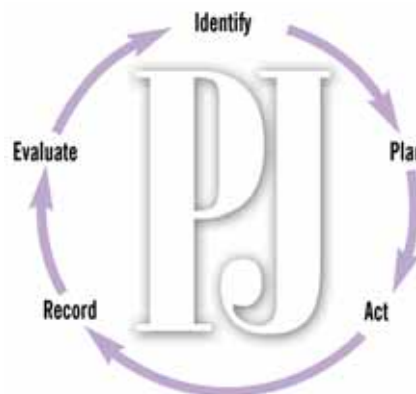
Codeine is the opioid typically encountered at step 2 of the World Health Organization analgesic ladder (see *PJ*, 9 June, pp679–82). Its analgesic effect is largely due to its metabolism to morphine by cytochrome CYP2D6. However, about 10 per cent of Caucasians lack the active enzyme and so derive little benefit from codeine.³ Similarly, patients taking CYP2D6 inhibitors (eg, paroxetine, haloperidol and levomepromazine) may also derive reduced benefit from codeine.

Codeine is considered one 10th as potent as morphine. As a general rule, products containing less than 30mg of codeine per dose are not suitable step 2 analgesics. Despite being a weak opioid, codeine causes typical opioid side effects, such as nausea, vomiting, sedation and constipation. Laxatives should be considered with regular codeine use.

Unlike morphine, weak opioids have a “ceiling dose”, above which any increase in analgesia is outweighed by progressively more adverse effects. For codeine, this is typically 240mg over 24 hours. When the ceiling dose has been reached, step 3 treatment should be introduced — there is no point switching to another step 2 opioid.



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Identify knowledge gaps

1. What proportion of Caucasians do not respond to codeine or tramadol?
2. How should breakthrough pain be managed?
3. What are the alternatives to morphine?

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”).

Although it is traditionally considered a step 2 analgesic, tramadol is unlike conventional opioids in that it has a dual and synergistic mechanism of action involving weak opioid activity and monoaminergic reuptake inhibition. This may explain its effectiveness for pain traditionally considered to be poorly responsive to opioids, such as neuropathic pain.⁴ Commercial tramadol is a racemic mixture of two enantiomers. (+)-Tramadol displays weak opioid activity and mediates serotonin reuptake inhibition whereas (–)-tramadol mediates noradrenaline reuptake inhibition. Tramadol is preferentially metabolised by CYP2D6 to the only active metabolite, (+)-O-desmethylntramadol ([+]-M1). The contribution of (–)-M1 to analgesia is minimal. Tramadol is additionally metabolised by CYP3A4, which explains the reduced analgesia that occurs when carbamazepine (a CYP3A4 inducer) is co-prescribed. Patients lacking CYP2D6 activity cannot produce (+)-M1 so the analgesic profile is altered — the opioid effect is reduced and the monoaminergic effect enhanced. Like codeine, analgesia derived from tramadol can also be affected by CYP2D6 inhibitors. The genetic variability of the μ -opioid receptor and CYP2D6, coupled with the complex pharmacology, helps to explain the wide variation in both effect of, and tolerability to, tramadol.

For musculoskeletal pain, tramadol offers a less toxic alternative to non-steroidal anti-

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Panel 1: Effects mediated by opioid receptors

Receptor	Response
μ_1	Supraspinal analgesia, physical dependence
μ_2	Spinal analgesia, respiratory depression, miosis, euphoria, reduced gastrointestinal motility, physical dependence
δ	Analgesia, euphoria, physical dependence
κ	Spinal analgesia, sedation, miosis, dysphoria

inflammatory drugs. The commonest adverse effects of tramadol are nausea, vomiting and dizziness, but with slow titration, tolerability can be improved.² Modified release formulations are generally preferred for long-term therapy.

There is a potential risk of serotonin syndrome if other serotonergic drugs, such as selective serotonin reuptake inhibitors, are taken and such combinations require caution. At therapeutic doses, withdrawal symptoms have been rarely reported. Nonetheless, tramadol should be withdrawn gradually rather than stopped abruptly.

A combination product containing paracetamol 325mg and tramadol 37.5mg is available (Tramacet) and although its place in therapy is unclear, it offers advantages for elderly patients who are less able to tolerate the standard 50mg dose of tramadol. Despite the low doses of both drugs, this combination has been shown to work synergistically.

Moderate to severe pain

For most patients, morphine remains the oral opioid of choice to treat moderate to severe pain. It is metabolised to two principal forms: morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M6G is believed to be a more potent analgesic than morphine itself while the pharmacology of M3G remains unclear. Both metabolites are renally excreted so patients with renal failure are at a greater risk of opioid toxicity (see section on end of life issues).

The starting dose of morphine depends on whether or not the patient has used opioids before and his or her previous dose. For an opioid-naïve patient, initially an immediate release formulation (eg, Oramorph or Sevredol) is prescribed and the dose of morphine titrated according to response. Typically, 5–10mg every four hours is prescribed, with provision for “rescue doses” if pain occurs within the four-hour interval (note this should not be referred to as breakthrough pain — see below). The rescue dose is one sixth of the total daily morphine dose. When pain control has been achieved (evaluated through the use of pain scores) and the 24-hour dose of morphine has been established, a modified release formulation (eg, MXL *od* or MST/Zomorph *bd*) can be introduced. To avoid confusion, it is recommended that the prescriber specifies a brand. Provision must again be made for rescue doses, based on one sixth of the total daily morphine dose.

Patients should be advised to expect some sedation during the titration phase. Although tolerance to this effect will develop, tasks such as driving should be avoided until a stable dose has been achieved. Nausea and vomiting is another common adverse effect of opioid therapy. Anti-emetics should be prescribed regularly for the first week of treatment then on an as-required basis when the patient develops tolerance to this adverse effect. Tolerance to constipation does not occur and regular laxative use will be required for as long as the patient receives the opioid.

Panel 2: Opioid potencies

Equianalgesic doses are difficult to ascertain due to wide interpatient variations. Initial dose conversions should be conservative; it is preferable to under-dose the patient and use rescue medication for any shortfalls.

Commonly used opioid analgesics, listed in order of least to most potent are as follows:

Codeine (oral)	0.1
Tramadol (oral)*	
Oxycodone (oral)	1.5–2.0
Hydromorphone (oral)	7.5
Fentanyl (transdermal)†	

The opioid dose can be multiplied by the conversion factor (in italics above) to give the equivalent oral morphine dose. Although these figures represent equianalgesic values, practitioners must individualise treatment — in some circumstances, equianalgesic doses may need to be reduced by up to 50 per cent when opioids are switched.

*Tramadol is unsuitable to convert, given its complex pharmacology and risk of withdrawal symptoms due to its monoaminergic reuptake inhibition
† See manufacturer’s guidelines for conversion calculation

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Respiratory depression and opioid addiction are often major concerns for patients and health care professionals but, in practice, neither should be used as grounds to avoid prescribing morphine. Respiratory depression does not appear to occur in patients with cancer pain, which seems to act as a respiratory stimulus. A patient requiring morphine 600mg twice daily should not be denied a rescue dose of 200mg simply because it is a large dose. It is only when additional doses, above those needed to control pain, are given that respiratory depression can occur. Psychological dependence to morphine is unlikely in patients with cancer.^{6,7} Physical dependence can occur, but this is rarely a problem in palliative care because opioid therapy is unlikely to be stopped abruptly.

Alternatives to morphine

There are various alternatives to oral morphine, such as oxycodone and hydromorphone. Oxycodone is available as immediate release (OxyNorm) and modified release oral formulations (OxyContin), in addition to a recently introduced injectable product. Oxycodone is metabolised mainly to an inactive form, which is unlikely to cause problems in renal failure; the parent drug however, does accumulate in renal failure so an empirical dose reduction may be necessary. Oral oxycodone is considered to be one and a half to two times more potent than oral morphine (see Panel 2). Its adverse effect profile is similar to morphine, but it is often better tolerated.

Hydromorphone is available in immediate release capsules (Palladone) and modified release capsules (Palladone SR). Despite offering some benefits to patients unable to tolerate morphine, immediate release hydromorphone is only available in two strengths: 1.3mg and 2.6mg. This, together with an equianalgesic ratio of hydromorphone to morphine of 1:7.5 (which complicates calculations), makes the drug a less attractive alternative.

Fentanyl is a strong opioid that forms non-toxic inactive metabolites, so it is relatively safe to use in renal failure. It is available as a transdermal patch and immediate release lozenge. Lozenges are only used to treat breakthrough pain. The patch is applied for 72 hours and a reservoir of fentanyl is formed in the fatty tissue under the skin. Analgesia is not achieved for at least 12 hours after the first patch is applied and steady state may not be achieved for up to 48 hours so analgesic benefit should not be assessed until three days after the first patch is applied. Once steady state is attained, the plasma half life can be up to 25 hours. Transdermal fentanyl does not cause the same level of constipation as morphine (or oxycodone) and, more often than not, the laxative dose has to be reduced when switching to fentanyl.

Three transdermal products are available: two matrix patches (Durogesic D-Trans and Matrifen) and a reservoir patch (Tilofyl). Matrix patches can be cut to size if necessary (unlicensed use) but the reservoir patch must

never be cut. Given such differences, the prescriber should specify a brand. In all cases, patches must only be prescribed for patients who are already stabilised on a strong opioid and have stable pain (ie, opioid requirements remain unchanged).

Transdermal fentanyl can be considered as the first-line modified release opioid for patients with renal failure, severe constipation, dysphagia or in anticipation of future complications, such as bowel obstruction.

Patients should be advised to avoid heat sources, such as prolonged hot baths or showers, heating pads, hot water bottles, electric blankets, heat lamps and saunas because of the potential for an increase in the delivery rate of the drug. An increased delivery rate can also occur in patients with fever.

Methadone is occasionally used in palliative care. It is used in patients typically displaying pain that is refractory to conventional treatment — invariably an element of neuropathic pain is evident. Due to its complicated pharmacokinetics it must only be initiated by a specialist.

Buprenorphine is available as a weekly (BuTrans) and 96-hour (Transtec) transdermal patch. Its pharmacology is complex but the transdermal formulation acts as a simple μ agonist when used according to its marketing authorisation. Sublingual buprenorphine should be avoided due to the risk of adverse effects, notably nausea and vomiting.

Breakthrough pain

Breakthrough or episodic pain is a transient exacerbation of pain that occurs despite relatively stable and adequately controlled background pain. Pain that occurs as a result of inadequate background analgesia (ie, at any time during the titration phase or towards the end of a dose as analgesic levels decline) is incorrectly referred to as breakthrough pain.

There are two types of breakthrough pain:

- Incident pain: predictable pain caused by voluntary (eg, walking, wound dressing) or involuntary (eg, cough) events
- Spontaneous pain: unexpected pain with no apparent cause

The choice and dose of drug for breakthrough pain should be based on pain characteristics (eg, temporal profile), drug characteristics (eg, pharmacokinetic profile) and the individual's response. For example, there is no point administering immediate release oral morphine, which has an onset of action of approximately 30 minutes and a duration of action of four hours, to a patient whose breakthrough pain lasts 10 minutes. In many cases, the pain will have eased before the dose has had time to work and the effect of the drug will persist long after the pain has passed with possible adverse effects, such as sedation (see Figure 1). However, if breakthrough pain that persists for several hours after the trigger can be anticipated, a rescue dose of oral morphine given 30 minutes before the trigger will ensure optimal treatment.

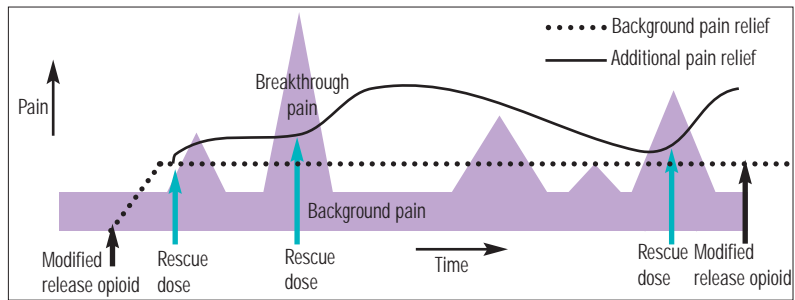


Figure 1: Current treatment of short-duration breakthrough pain (eg, caused by movement). Traditional rescue doses do not act quickly enough and lead to accumulation of opioid.

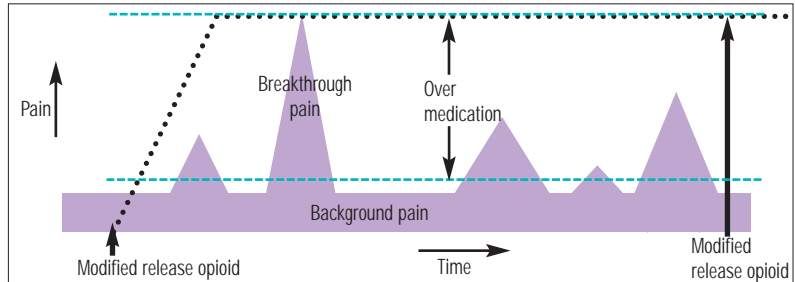


Figure 2: Titration of the round-the-clock dose by using rescue doses of opioids administered for short-duration breakthrough pain can lead to over-medication and opioid toxicity

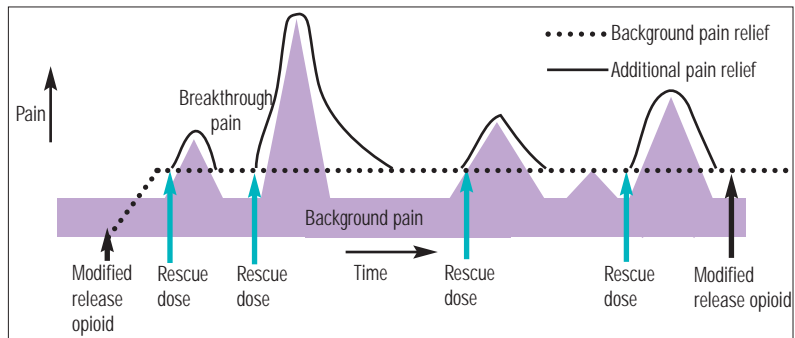


Figure 3: Ideal treatment of short-duration breakthrough pain: a rapid acting opioid of relatively short duration. No accumulation of opioid

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. Familiarise yourself with local formulary products for cancer pain.
2. Discuss breakthrough pain with your local hospice pharmacist.
3. Discuss the treatment of neuropathic pain caused by cancer with your peers.

In addition, a patient with breakthrough pain caused by movement and who needs successive rescue doses of morphine should not have his or her background dose of analgesia increased as per titration — higher than necessary background doses of morphine rapidly lead to opioid toxicity (see Figure 2).

Oral transmucosal fentanyl citrate (OTFC; Actiq lozenges) has been shown to be effective in the management of breakthrough pain. Alfentanil nasal or buccal spray (available as a special from Torbay Hospital, Devon) has also been used successfully. Both formulations are quick acting, producing a faster onset and shorter duration of action than immediate release morphine (see Figure 3). OTFC and alfentanil offer excellent means of treating short duration breakthrough pain but their dose titration is fairly complicated and the initial dose has no bearing on the background 24 hourly opioid dose.

In some cases, successful treatment of neuropathic breakthrough pain may require the introduction of adjuvant analgesia or use of anaesthetic interventions, such as an epidural. In addition, patients should be en-

Panel 3: Converting oral to subcutaneous doses

Dose conversion from oral morphine to subcutaneous morphine

- Calculate the total daily dose of oral morphine
- Divide the total daily dose of oral morphine by 2 to give the equivalent daily dose of subcutaneous morphine
- Infuse the total daily subcutaneous morphine dose by syringe driver
- Ensure that subcutaneous rescue doses of morphine, equivalent to one sixth of the total daily dose, are prescribed

For example Zomorph or MST 60mg twice daily
= 120mg morphine orally in 24 hours
= 60mg morphine subcutaneously over 24 hours

Dose conversion from oral oxycodone to subcutaneous oxycodone

Napp recommends dividing the oral dose of oxycodone by 2 to arrive at the subcutaneous equivalent but, in practice, an early increase in dose may be required.

Panel 4: Examples of rescue doses to be used for patients on fentanyl patches

Fentanyl patch for background pain	Morphine subcutaneous rescue dose	Oxycodone subcutaneous rescue dose *
25µg/h	5mg	5mg
50µg/h	10mg	10mg
75 µg/h	15mg	15mg
100µg/h	20mg	20mg

* Based on a conversion of 1:1 between subcutaneous morphine and oxycodone

couraged to use non-drug measures such as heat packs.

End of life issues

As patients approach the end of their lives they invariably become unable to take medicines orally and continuous subcutaneous infusions (CSCIs) will be needed to ensure continued analgesia. Until recently, diamorphine was the opioid of choice for CSCIs due to its high solubility; 1g of diamorphine dissolves in 1.6ml water, compared with 21ml for an equivalent weight of morphine sulphate.

Unfortunately, since December 2004, the supply of diamorphine has been sporadic. Morphine is currently the opioid most commonly used for CSCIs, although CSCI of oxycodone provides the straightforward route for continued analgesia in patients who have been maintained on oral oxycodone. Dose conversions from oral to subcutaneous routes are shown in Panel 3.

The deteriorating renal function that can occur at the end of life can precipitate signs of opioid toxicity in patients receiving CSCIs of morphine or oxycodone. These include agitation, delirium, restlessness and, paradoxically, worsening pain. While simple dose reductions may help, it is often easier to convert to a CSCI of alfentanil. This drug is relatively safe in renal failure and is considered to be approximately 15 times more potent than subcutaneous morphine or oxycodone and 10 times as potent as diamorphine.

Patients receiving either transdermal fentanyl or buprenorphine should be maintained on these. At this stage, it is often difficult to separate breakthrough pain from inadequate

background analgesia or, indeed, agitation. Nonetheless, continuing analgesic requirements are determined by the use of rescue doses of subcutaneous morphine or oxycodone administered for inadequate background analgesia (see Panel 4). After 24 hours, the number of rescue doses is assessed and the total dose given as rescue doses for inadequate background pain should be delivered by a CSCI in addition to the patch.

Continuation of treatment for neuropathic pain can pose problems since most recognised adjuvants are not available in parenteral formulations. Some of the adjuvants, such as the tricyclic antidepressants, have long half-lives, so their effects can persist for several days after discontinuation. Clonazepam and ketamine are two adjuvants that can be administered via CSCI, although this should be under specialist supervision.

Bone pain, especially that caused by movement, can be a problem in palliative care but this is less problematic during the dying phase because the patient is generally immobile and, at rest, bone pain responds well to opioids. Nonetheless, there may be occasions when an NSAID is required. Under specialist supervision, ketorolac can be given via a CSCI.⁹

The future of analgesia

The current accepted practices in pain management are set to change dramatically. The future promises to revolutionise pain management through the development of highly specific drugs and, potentially, genetically determined, individualised therapy. In the case of the opioids, it may soon be possible to genetically determine a patient's predominant opioid subtype and metabolic genotype, thus allowing the selection of the most suitable drug. Research on endogenous opioid peptides and the molecular biology of pain will lead to an increase in both drugs and pharmacological targets. The management of pain will undoubtedly become more complicated, but with the tantalising prospect of optimal analgesia with minimal adverse effects.

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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?