Pain control in palliative care

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Abstract
Pain is one of the most feared symptoms of advanced, progressive disease and dying. It is a common but not universal experience in both advanced malignant and non-malignant conditions. A patient-centred approach involving systematic and thorough assessment, management and regular review can provide pain relief for most people. Even in advanced disease, it is important to identify the underlying cause of the pain. Pharmacological management should be structured around the analgesic ladder. Particular emphasis is given to the safe and effective use of strong opioids, including the person's information needs and the management of unwanted effects. A range of adjuvant drugs is also available, as are interventional techniques and non-pharmacological interventions. Guidance is provided on the reassessment of pain that has not responded adequately to the usual measures, and on indications for specialist referral.

Keywords
Analgesic ladder; bone pain; cancer; morphine; neuropathic pain; nociceptive pain; opioid analgesics; pain assessment; pain management; palliative care

Key points
•A comprehensive holistic assessment is key to successful pain management
•The pharmacological management of pain should be systematic, based on the analgesic ladder, and include frequent patient review
•The benefits and burdens of any intervention must be considered in the context of the individual patient
•A thorough explanation of the management plan should be provided and must address how to take any medication, management of adverse effects and implications for driving. Where strong opioids are prescribed, barriers including addiction, tolerance and association with imminent death should also be discussed
•Specialist referral is indicated if adequate pain control is not rapidly achieved

Introduction
Pain is 'an unpleasant sensory and emotional experience'.[1] It usually results from an underlying physical pathology causing nerve stimulation or injury.[2] Pain is a common symptom, experienced by more than half of patients with many advanced and progressive diseases. It can adversely affect quality of life.[1] Pain perception is modified by psychological, social and spiritual factors. The principles described here refer to pain management in advanced and progressive disease. They should not be assumed to be transferable to other clinical contexts such as chronic pain, particularly with respect to the prescribing of strong opioids and corticosteroids.

Approach to the consultation
This should be patient focused. It is important to understand the patient's ideas, concerns and expectations, particularly in the palliative setting where the pain experience is affected by beliefs, fear of the cause of the pain and the meaning of the pain to the patient. In addition, the association of commonly used analgesics with death and addiction[3] influences the acceptability of and concordance with the management plan if such issues are left unaddressed.

Assessment

This must be thorough and directed towards identifying the type (Table 1) and underlying cause of the pain. Where possible, addressing the cause may treat the pain most effectively, even in very advanced disease. This is exemplified by abdominal pain caused by constipation: treating the constipation will relieve the pain whereas many analgesics will worsen it.

History and examination

Information must be sought on the patient's underlying condition, its management and any co-morbidities. Particular consideration should be given to the previous treatment history of the underlying condition. The pain must be explored in detail (Table 1), and the examination should be focused and thorough.

Investigations

The potential benefit of any investigations, particularly whether and to what extent the findings might influence the management plan, should be weighed against the potential burden to the patient in terms of time, inconvenience, energy expenditure and discomfort.

Management

Goals

It is important to negotiate and agree goals for management. Although there has been limited research on what patients want from their pain management, the ability to perform activities and maintain relationships is probably important. Approaches to shared decision-making can be enabled by asking the patient what matters most to them. Relief of moderate to severe pain can be achieved for most cancer patients,[2] but it may not be a realistic goal for them to be pain-free all of the time. Conversations relating to goal-setting can incorporate realistic expectations through a considered use of vocabulary, for example avoiding terms such as 'pain control' and 'pain free'.

Frequent review is essential, particularly when disease is progressing or the patient's condition is rapidly changing.

Treatment of the underlying cause

Examples include fixation of a pathological fracture, radiotherapy of a painful bony metastasis or antimicrobial therapy for bladder pain caused by infection. As the patient's frailty and dependency increase, positioning and regular pressure area care become increasingly important.

Pharmacological management

The analgesic ladder: the World Health Organization analgesic ladder (Figure 1) is the established structure for managing cancer pain. Its application to non-malignant conditions in the palliative care setting is also practiced, although this has not been thoroughly researched. The underlying principles are that analgesia is administered:

- regularly
- by mouth
- with progression up the ladder if adequate analgesia is not achieved.[2]

The role of adjuvants, which can be added in on any step of the ladder, is discussed in more detail below.

Step 1 – non-opioids – *paracetamol* (1 g 4–6 hourly, maximum 4 g/day) is generally well tolerated, although a decrease in dosage is necessary if the patient has a reduced body weight (<50 kg) or risk factors for hepatotoxicity.

Non-steroidal anti-inflammatory drugs are mainly used for pain associated with inflammation, a common element of cancer pain.[4] This type of pain can also predominate in some non-malignant conditions. Relative contraindications including renal impairment, and potential risks including gastrointestinal, renal and cardiovascular toxicity, must be individually balanced against the anticipated benefits.[4]

Step 2 – weak opioids – weak opioids such as codeine (30–60 mg 4-hourly to a maximum of 240 mg daily) or tramadol (50–100 mg not more than every 4 hours to a maximum of 400 mg daily) are added if adequate pain relief has not been achieved. Adverse effects should be managed as for step 3 (below). Step 2 should not delay progression to step 3 if the pain is severe: if adequate pain relief is not achieved at step 2, progression should be up the ladder and not to another drug within the step 2 class. In countries where morphine is readily available, step 2 is increasingly omitted and progression is directly from step 1 to step 3 (below).[4]

Step 3 – strong opioids – the National Institute for Health and Care Excellence (NICE) has published guidance on the initiation of opioids in palliative care.[3]

Oral morphine is the recommended first-line strong opioid. This recommendation is based on cost, availability and clinician familiarity. Other strong opioids are equally as effective. Treatment with morphine can be initiated with either regular sustained-release or immediate-release preparations depending on the patient's preference. For example, 10–15 mg sustained-release morphine 12-hourly is a typical starting dose for a person with normal hepatic or renal function. Oral immediate-release morphine 5 mg should be available as required as a rescue medication to treat pain occurring between doses of regular analgesia (Table 2).[4] Such pain is often referred to as 'breakthrough pain'.

Regular review and dosage adjustment are necessary, taking account of the additional rescue medication the patient has required when calculating the new dosage of slow-release opioid (Table 2). Titration should occur until 'a good balance exists between acceptable pain control and adverse effects'.[4] There is no maximum dosage of strong opioids. However, continued upward titration should be avoided in the absence of analgesic benefit. Table 3 outlines guidance should the response to analgesia be inadequate.

Clear explanation supported by written guidance must be provided on:

•how to take the medication, including rescue medication and medication to control unwanted effects
•arrangements for review and interim contact information
•how to obtain further prescriptions.

Communication: the NICE guidance highlights barriers to successful opioid treatment, which should be acknowledged and addressed:[3]

•Tolerance and addiction – these are not a practical problem in the vast majority of cancer patients.[4]
•Association with imminent death – it should be explained that the strong opioid is being offered for its analgesic efficacy and not to hasten the patient's death. Patients should be reassured that strong opioids do not cause death when used appropriately. Exploring the patient's fears and beliefs, including from a cultural and religious perspective, can also enable conversations around the patient's understanding of their illness, prognosis, priorities and preferences and enable a shared decision-making approach.

Unwanted effects:

Constipation – this is an almost ubiquitous adverse effect and requires proactive management. Regular laxatives should be prescribed and their regular use emphasized. Review is essential.

Nausea – this is common, particularly when starting treatment, and is likely to be transient and improve after 5–7 days.[4] This should be explained to the patient. If nausea persists despite treatment with antiemetics, other causes of the symptom should be considered.[4]

Drowsiness – this can occur when treatment is started or doses are increased. Guidance on driving must be provided (Table 4).

Central nervous system effects – unwanted effects can present as persistent drowsiness, twitching or hallucinations.[3] Patients should be advised to report these features, which can often be managed by reducing the opioid dosage.

Life-threatening toxicity from respiratory depression is unusual when strong opioids are carefully titrated but can occur if, for example, the patient develops renal impairment.

In addition to supportive measures such as the administration of oxygen, naloxone (100–200 micrograms intravenously) may be required. Naloxone should be used with caution to avoid precipitating severe pain, distress and an acute withdrawal syndrome when the opioid analgesic is reversed.

Use of paracetamol and non-steroidal anti-inflammatory drugs in step 3: an individualized and pragmatic approach (Table 2) is needed that weighs the analgesic benefit conferred against issues such as tablet burden and unwanted effects.[4]

Indications for alternative strong opioids: for the reasons outlined above, morphine is the first-line strong opioid in palliative care. In the UK, several alternative strong opioids with different opioid receptor affinities are commonly used, including buprenorphine, diamorphine, fentanyl and oxycodone (see below).[3]

Care must be taken if converting between strong opioids, and specialist advice should be routinely sought.[3] Opioid conversion ratios are only an approximate guide, and conversions can result in life-threatening toxicity, particularly in individuals requiring high dosages of strong opioids. A dosage reduction of 25–50% is recommended.[4]

Renal impairment – fentanyl is often used in this context. Specialist advice should be sought on titration of the drug in its transdermal form when the patient's pain is unstable. Owing to the complex conversion ratio and lack of clinician familiarity, specialist advice should also be sought if the drug is to be administered subcutaneously.[3]

When oral opioids are not suitable – if the patient's analgesic requirements are stable, transdermal patches of buprenorphine or fentanyl can be considered. If the pain and analgesic requirements are unstable or are at risk of becoming so (e.g. during the dying phase), the subcutaneous administration of opioids such as morphine can allow rapid pain control and dose flexibility. Some opioids such as fentanyl can be administered transmucosally for breakthrough or incident pain.

Dose titration can be complex, and it is advisable to obtain specialist advice. The choice of opioid when oral opioids are not suitable should take into consideration availability, health professional familiarity, cost and renal function.

To minimize adverse effects – for gastrointestinal adverse effects, the treatments outlined above should be used first. If these are unsuccessful, an alternative opioid such as transdermal fentanyl should be considered if constipation is problematic.[4] For central nervous system adverse effects, a dosage reduction should be considered if the pain is stable. If this is not possible or proves unsuccessful, consider an alternative opioid.[3]

To optimize analgesia – morphine has been shown to be effective for most cancer patients.[2] However, an opioid switch can, if needed, improve analgesia. Before considering this, review why treatment might have failed (Table 3) and consider seeking specialist advice.

Adjuvant drugs: these are 'drugs whose effect on pain is circumstance specific'.[4] The detailed history can identify whether they might be beneficial. Their continuing use must be informed by the balance of experienced benefit, unwanted effects and tablet burden.

Neuropathic agents – NICE has produced guidance on the management of neuropathic pain, recommending the initial use of a tricyclic antidepressant (e.g. amitriptyline at a starting dose of 10 mg at night) or an anticonvulsant (e.g. gabapentin at a starting dose of 300 mg three times a day titrated over 3 days).[1] A drug from the class not initially prescribed can be added if adequate benefit is not obtained after careful titration.[1]

Careful and regular assessment of the patient is needed to prevent continued use if the drugs are unhelpful or the unwanted effect burden is too high. Drug misuse in society can be an issue for some neuropathic agents, as can be the case with opioids. For this reason gabapentin was reclassified as a class C controlled substance in the UK in 2019.

Topical capsaicin cream is an option for patients with localized peripheral neuropathic pain if they are unable to or prefer not to use oral neuropathic agents.[1]

Bisphosphonates – these are never used as first-line therapy but can help in the treatment of malignant bone pain.

Muscle relaxants – smooth muscle spasm, for example of the bowel, can be treated with anticholinergic medications such as hyoscine butylbromide 20 mg four times a day. Skeletal muscle spasm can be treated with, for example, diazepam at a starting dose of 5 mg daily, or baclofen at a starting dose of 5 mg three times daily.

Corticosteroids – the potent anti-inflammatory effects of some corticosteroids, for example dexamethasone 8 mg once daily, can provide analgesia when there is obstruction or pressure, as in liver capsule pain. These drugs sometimes also confer other benefits, for example improving appetite and well-being in advanced cancer, although these beneficial effects diminish with time.

Prolonged use causes many adverse effects, which can be amplified by the concurrent use of other drugs, such as non-steroidal anti-inflammatories. Important interactions can occur, for example with anticonvulsants such as phenytoin, which increases the metabolism of dexamethasone. Dexamethasone can increase or reduce serum phenytoin concentrations.[4]

Cannabis-based products for medicinal use

The place of cannabis-based products for medicinal use in the treatment of cancer pain cancer is uncertain.[5] They are not recommended in treatment of chronic pain.[5] Some patients use products containing cannabidiol that are legally sold in the UK as oils or food products or use cannabis illicitly. Exploring the patient's experience of the impact of all cannabis-based products and non-prescribed medication is important within the assessment (Table 1), in order to inform the continuing plan of care.

Interventional procedures

Interventional procedures, usually performed by anaesthetists, can benefit carefully selected patients. Specialist referral should be considered when pain is not responding to conventional management (Table 3).

Non-pharmacological measures

Patients often identify techniques that they find helpful, such as heat pads. There is a lack of evidence on the use of interventions such as transcutaneous electrical nerve stimulation and acupuncture. It is important to assess and address psychological, social and spiritual factors, for example by referral to psychiatry, psychology, physiotherapy, social care services or chaplaincy teams.

Pain control when patients are dying

Uncontrolled pain in a dying patient requires prompt and careful assessment, following the principles described above.

Taking medication by mouth often becomes difficult as patients deteriorate during the last days and hours of their lives. When patients with no previous regular analgesic requirements are dying and unable to take medication orally, it is usual to prescribe a small 'as-required' dose of a strong opioid for subcutaneous administration (e.g. morphine 1.25–2.5 mg subcutaneously at a maximum frequency of hourly) so analgesia can be administered rapidly if indicated. Such anticipatory prescribing must be discussed with the patient and those important to them.

Those who have required regular oral analgesia should be provided with analgesia via another route. After discussion with patients and those important to them, strong opioids can be administered via a continuous subcutaneous infusion. Conversion of the total 24-hour dose of oral to subcutaneous morphine is 2:1 (see pages xx-xx of this issue).[4] Guidance should be sought regarding other conversion ratios. It may also be possible to include in the subcutaneous infusion drugs previously prescribed orally to control other symptoms. Subcutaneous 'as-required' rescue medication should also be prescribed.

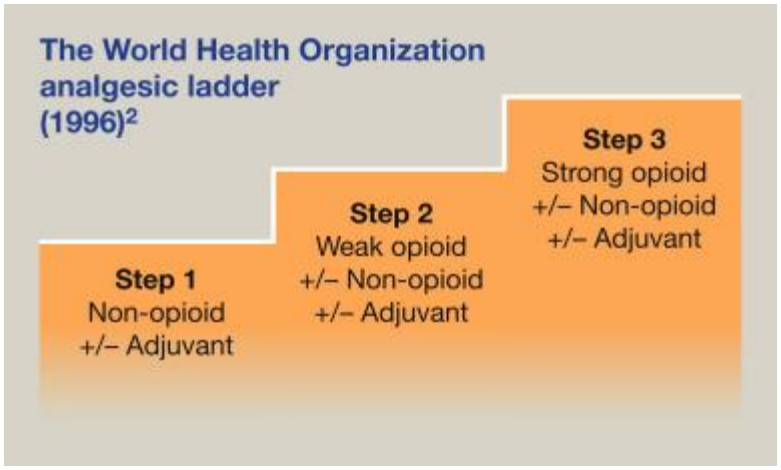
Analgesic patches should be continued if a patient is established on these before their deterioration, together with subcutaneous 'as-required' rescue medication. The patch should not be uptitrated if an increase in background analgesia is required. Instead the additional requirement should be administered via a continuous subcutaneous infusion of an appropriate strong opioid.

Elderly care medicine

A thorough and holistic pain assessment remains important, particularly with multiple coexisting conditions. A systematic management approach should include an assessment of:

- the response to any intervention to avoid unnecessary tablet burden
- unwanted effects from age-related alterations of drug metabolism
- unwanted effects from drug interactions.

Advanced dementia presents a particular challenge, especially if communication is impaired. Pain can manifest as a change in behaviour such as irritability or aggression. Observation-based tools are recommended to screen for pain and monitor the response to interventions. Research is examining many aspects of pain in dementia including pain perception and management strategies. Systematic assessment and review including ruling out causes such as urinary retention, constipation and considering the impact of the environment in which the patient is being given their care is essential.


The World Health Organization analgesic ladder (1996)[2]
Step 1
Non-opioid
+/– Adjuvant
Step 2
Weak opioid
+/– Non-opioid
+/– Adjuvant
Step 3
Strong opioid
+/– Non-opioid
+/– Adjuvant
Figure 1

The pain history

	Question to ask	Notes
	‘Tell me about the pain’	Always start with open questions
Site	‘Where is the pain?’	Nociceptive pain (pain caused by stimulation of nerve endings) is typically localized Ask if there is more than one pain
Onset	‘When/how did it start and how has it changed?’	Progressive back pain (particularly thoracic) should raise a suspicion of spinal cord compression
Character	‘What is it like?’	Aching/throbbing/gnawing pain is typical of nociceptive pain Shooting/burning pain is typical of neuropathic pain (pain caused by nerve damage or infiltration) Cancer pain is often a combination of both
Radiation	‘Does it go anywhere else?’	Neuropathic pain can follow a nerve or dermatomal distribution Pancreatic pain radiates to the back because of coeliac plexus involvement
Associated symptoms	e.g. ‘Does the pain interfere with your sleep?’	If there is a concern about spinal cord compression, always ask about bowel and bladder function and limb weakness and numbness
Temporal factors	‘Is it there all the time or does it come and go?’	Pain that arises shortly before the next dose of slow-release morphine is due suggests that the dose of slow-release morphine may need to be increased
Exacerbating and relieving factors	‘What makes it better and what makes it worse?’	Explore the response of the pain to analgesics and other interventions, including those previously tried Ask about unwanted effects of analgesics Clarify the dose of current analgesics and whether the analgesics are being taken as prescribed and whether they are being used regularly or as required Explore all interventions the patient uses including recreational or online purchased or over-the-counter medications
Severity	‘How bad is it?’, ‘Does it stop you doing anything?’	Ask the patient to give a score out of 10 at the time of assessment, when the pain is at its worst, when it is at its best and after analgesia Explore the impact of the pain on the patient’s activities of daily living and lifestyle, goals and priorities. Does the pain trigger any thoughts or feelings. Explore these with the patient

Table 1

Prescribing example

A 70-year-old lady with a history of metastatic breast cancer is experiencing pain from disease recurrence on her left chest wall. She is currently on step 2 of the analgesic ladder. She is taking:
•co-codamol 30/500 two tablets four times daily. This has provided some but incomplete benefit

After thorough reassessment and discussion, it is agreed that she needs to step up the analgesic ladder. The following changes are made:
•Co-codamol is stopped
•Sustained-release morphine 15 mg 12-hourly is prescribed, with immediate-release morphine 5 mg as required as rescue medication
•She is continuing on paracetamol 1 g four times daily as she felt this was helpful when it was first started
•She is referred to her oncologist for consideration of palliative radiotherapy

Two days later, she is reviewed. Her pain is well controlled on the analgesic regimen and no changes are made

You see her again some months later. Her dose of sustained-release morphine has been titrated to 30 mg 12-hourly, and she is taking at least two breakthrough doses of immediate-release morphine 10 mg in every 24-hour period

Thorough reassessment reveals the following:
•Palliative radiotherapy provided some initial benefit but unfortunately the disease has continued to progress
•She dislikes having to take so many tablets and no longer feels the paracetamol confers any benefit
•The pain used to resolve completely after she took the rescue medication. However, she is increasingly noticing some ‘burning’ residual pain, especially at night

After discussion the following is agreed:
•Stop the paracetamol
•Increase the dose of sustained-release oral morphine to 40 mg 12-hourly and increase the rescue dose of immediate-release morphine to 12.5 mg as required
•Add the neuropathic adjuvant amitriptyline 10 mg at bedtime
•Make a review appointment for 3 days time

Table 2.

Inadequate pain relief think list. Is this … ?

Breakthrough pain – pain occurring between doses of regular analgesia. This is usually caused by an inadequate regular dose of strong opioid	•Ensure rescue medication is available (usually one-sixth of the total daily dose of strong opioid) •Recalculate the regular dose based on the requirement for rescue medication
Incident pain – predictable pain with an identifiable trigger	•An anticipatory dose of immediate-release analgesia may help •Newer transmucosal opioid preparations can have a role •Specialist referral is advised
Non-adherence to the analgesic regimen	•Explore whether and why this could be the case •Revisit communication and consider different formulations, e.g. patches, which could be more acceptable
Pain that is only partially opioid responsive – many pains respond to opioids but incompletely	•Revisit the pain history •Consider whether adjuvants are indicated and consider interventional techniques, e.g. nerve blocks
Total pain – an overwhelming pain experience resulting from social, psychological and/or spiritual distress. This can present as frequent use of rescue medication with no apparent benefit when background analgesia is increased	•Explore this with the patient •Specialist referral is advised

In all cases of inadequately controlled pain, consider specialist referral

Table 3.

Driving guidance

It is an offence to drive if the concentrations of some drugs, including strong opioids, are above certain levels

Patients taking medication in accordance with advice may drive as long as their driving is not impaired. If, however, their driving is impaired, they are breaking the law

Patients should be made aware of the law, and clinicians should document the advice they have given

Advice to patients should include:
•to keep taking the medicines as prescribed
•to refer to the leaflet that comes with the medicines about how they can affect ability to drive
•not to drive until they know how any change in the medication is affecting them
•not to drive if they are experiencing adverse effects, such as drowsiness, which could affect their ability to drive

Adapted from UK Government. Drugs and driving: the law. https://www.gov.uk/drug-driving-law (accessed 10 Apr 2022).

Table 4.

KEY REFERENCES

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 50-year-old man presented with abdominal pain. This was caused by a nodal mass from advanced bowel cancer. Oncological treatment options were being addressed. He was using cannabis oil purchased via the internet to treat his pain. He was not taking any other medication for analgesia.

What is the most appropriate next step?

A. Start pain management using the principles of the analgesic ladder
B. Explore his rationale for taking the cannabis oil and any benefits and adverse effects he has experienced from it
C. Explain that there is a risk the cannabis oil could interact with other medications and that the doctor is unable to help him while he is continuing to take it
D. Offer him only analgesics that are not addictive, such as paracetamol and non-steroidal anti-inflammatory drugs
E. Explain there is currently no need for analgesia as the forthcoming oncological treatment options will address the pain

Correct answer: B. Exploration will enable a fuller understanding of his perspective and the impact of the cannabis oil, which is essential to inform the continuing plan of care and must take place before any other option. The analgesic ladder (A) may subsequently be appropriate. Although interactions (C) occur this does not preclude helping the patient. An offer of non-addictive analgesics (D) is based on assumptions about the patient that may well be incorrect and should be fully explored. Patient comfort is a priority and there is likely to be a delay before any oncological treatment option is commenced (E) as well as uncertainty over its impact on the pain.

Question 2

A 35-year-old woman presented with significant nausea. This began after starting morphine 15 mg modified-release (MR) capsules, one capsule every 12 hours for pain in the chest wall arising from a lung tumour. Her experience of pain had improved since commencing morphine. She had required one dose of immediate-release (IR) morphine 5 mg in the previous 36 hours. She was not currently taking an anti-emetic.

What is the most appropriate next step in managing the nausea?

A Stop the MR and IR morphine and record morphine as an allergy
B Stop the MR and IR morphine and seek specialist palliative care advice to guide a switch to an alternative strong opioid.
C Continue the MR and IR morphine. Advise the patient that nausea is transient for many people and subsides after the first few days of starting morphine. Advise a short-term antiemetic
D Continue the MR and IR morphine. Advise a long-term antiemetic
E Continue the MR and IR morphine and explain that the nausea is unavoidable

Correct answer: C. Use of an anti-emetic short term reflects the NICE guidance that nausea is transient for many people when starting strong opioid treatment or during a dose increase. A plan for review and advice needs to be provided should the nausea persist. Nausea is an adverse effect of morphine, not an allergy (so A is incorrect). The patient's pain appears to be responding to morphine, so an opioid switch (B) might compromise her pain without any assurance that the nausea will improve. It is likely the adverse effect will resolve (so D is incorrect). The patient's comfort is a priority and she is unlikely to continue the analgesic medication if she is experiencing significant adverse effects (therefore E is incorrect).

Question 3

An 85-year-old man with end-stage dementia was likely to be in the dying phase. He had a history of osteoarthritis. He had a buprenorphine 10 microgram/hour transdermal patch, which was changed every 7 days. He was unable to swallow oral medication and had required four injections of morphine 2.5 mg subcutaneously over the preceding 24 hours in response to pain. Use of an observation-based tool indicated that the pain was responsive to each injection of morphine, but the pain recurred within

4–6 hours. After a holistic assessment, causes such as urinary retention and constipation had been ruled out.

What is the most appropriate next step?
A Continue the buprenorphine transdermal patch and administer morphine 2.5 mg subcutaneously as required
B Increase the dose of the buprenorphine transdermal patch and administer morphine 2.5 mg subcutaneously as required
C Continue the buprenorphine transdermal patch and commence continuous subcutaneous infusion over 24 hours of morphine at a dose to reflect the additional morphine requirements in previous 24 hours
D Remove the buprenorphine transdermal patch and start a continuous subcutaneous infusion of morphine over 24 hours at a dose reflecting the additional morphine requirements of the previous 24 hours
E Remove the buprenorphine transdermal patch and commence a continuous subcutaneous infusion of morphine over 24 hours at a dose equivalent to the buprenorphine 10 microgram/hour transdermal patch every 7 days and the additional morphine requirements in the previous 24 hours

Correct answer: C. Commencing a subcutaneous infusion to reflect the additional morphine requirements will promote a more steady and continuous approach to symptom management, rather than waiting for the pain to recur. The continuation of the same dose of the buprenorphine patch and as-required subcutaneous morphine will mean the patient is likely to continue to experience breakthrough pain (therefore A is incorrect). As the time to peak plasma concentrations for transdermal buprenorphine is 3 days, a dying patient is unlikely to experience improved pain control quickly enough (so B is incorrect). Transdermal buprenorphine has a plasma half-life of 13–35 hours. The wide range of this half-life cannot be predicted on an individual basis, and after stopping the patch the morphine dose is almost impossible to predict. This increases the risk of medicine errors and uncontrolled pain (therefore D and E are incorrect).