Pain occurs in up to 70% of patients with advanced cancer and about 65% of patients dying of non-malignant disease.[1] Much can be done medically to make their last few weeks or months relatively pain-free. Patients frequently express the desire to have open and honest dialogue about pain and the patient should be the prime assessor of their pain. Pain is a complex subjective phenomenon and is affected by the emotional context in which it is endured. [2]

<table>
<thead>
<tr>
<th>Pain tolerance is lowered by:</th>
<th>Pain tolerance is raised by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discomfort</td>
<td>Relief of symptoms</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Sleep</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Rest or physiotherapy</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Relaxation therapy</td>
</tr>
<tr>
<td>Fear</td>
<td>Explanation/support</td>
</tr>
<tr>
<td>Anger</td>
<td>Understanding/empathy</td>
</tr>
<tr>
<td>Boredom</td>
<td>Diversion</td>
</tr>
<tr>
<td>Sadness</td>
<td>Listening</td>
</tr>
<tr>
<td>Depression</td>
<td>Elevation of mood</td>
</tr>
<tr>
<td>Introversion</td>
<td>Finding meaning and significance</td>
</tr>
<tr>
<td>Social abandonment</td>
<td>Social inclusion</td>
</tr>
<tr>
<td>Mental isolation</td>
<td>Support to express emotions</td>
</tr>
</tbody>
</table>

Adequate psychological support is critical, as removing the fear of pain in itself will help to optimise pain control. Non-drug measures to help psychological or spiritual distress may be as important as medication in relieving pain and suffering.

**Assessing pain**

Always try to diagnose the cause of any pain prior to treatment, by making a detailed assessment including:

- Physical effects or manifestations.
- Functional impact of pain.
- Psychosocial factors.
- Spiritual aspects.

Regular monitoring (at least daily) with visual analogue, numerical or verbal rating scales allows treatment to be modified promptly where pain is inadequately controlled. Self-assessment should be used wherever possible, including in patients with cognitive impairment, only substituting with observational pain rating scales when a patient cannot complete self-assessment.[2]

**Principles of pain control in end of life care**

Over 80% of cancer pain can be controlled with inexpensive oral drugs, given a good assessment of pain and systematic choices of analgesics.[3] See the British National Formulary (BNF) for further information regarding drug doses and equivalent doses when converting from one drug to another.[4]

- Provide information and instruction about the pain, agree on treatment goals and encourage the patient to take an active role in their pain management.
Use the World Health Organization (WHO) analgesic ladder to guide systematic pain relief but remember other treatments (surgery, nerve blocks, radiotherapy, etc) and non-drug treatments may also have a role.

### WHO analgesic ladder

<table>
<thead>
<tr>
<th><strong>Step 1</strong> (pain &lt;3/10)</th>
<th>Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 2</strong> (pain 3-6/10)</td>
<td>Weak opioid for mild-to-moderate pain + paracetamol and NSAIDs +/- adjuvant analgesic.</td>
</tr>
<tr>
<td><strong>Step 3</strong> (pain &gt;6/10)</td>
<td>Strong opioid for moderate-to-severe pain + paracetamol and NSAIDs +/- adjuvant analgesic.</td>
</tr>
<tr>
<td><strong>Objective:</strong> freedom from pain.</td>
<td></td>
</tr>
</tbody>
</table>

Base the choice of drug on the severity of pain and not the stage of disease. Commence at an appropriate step dependent on severity of pain (remembering that Step 1 paracetamol and NSAIDs should be applied at any step). All patients with moderate-to-severe cancer pain should receive a trial of opioid analgesia.[2] Step up to strong opioids when Step 1 and Step 2 analgesics have failed for less severe pain.

- Do not prescribe another analgesic of the same potency if pain relief has failed at a particular step.
- Prescribing should always be adjusted if pain severity alters.
- Adjuvant analgesics may be usefully added at any stage, the response usually observed in 1-2 days.[5]

### Adjuvant analgesics for cancer pain

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Indications</th>
</tr>
</thead>
</table>
| Non-steroidal anti-inflammatory drugs (NSAIDs) | - Bone pain  
- Soft tissue infiltration  
- Hepatomegaly |
| Corticosteroids | - Raised intracranial pressure  
- Soft tissue infiltration  
- Nerve compression  
- Hepatomegaly |
| Antidepressants and anticonvulsants | - Nerve compression or infiltration  
- Paraneoplastic neuropathies |
| Bisphosphonates | - Bone pain |
| Ketamine (specialist use only) | - Refractory pain  
- Neuropathic pain  
- Ischaemic limb pain |

Where pain is continuous, analgesia needs to be prescribed on a regular not 'as-required' basis. Explain that pain is easier to prevent than it is to relieve and drugs should be prescribed on a prophylactic basis with no other consideration than maintaining quality of life.
Prescribe also for breakthrough or incident/episodic pain that occurs with everyday activities such as walking. Explain that additional medication should be taken before a potentially pain-provoking activity. The aim is to keep the patient pain-free both when sitting at home and also when undertaking normal daily activities.

Keep the treatment as simple as possible. Aim to use the minimum number of drugs in the most acceptable form and dose intervals possible. Provide written guidance on the drug regimen for the patient and family.

Regular review is essential to ensure that treatment goals are being met and side-effects avoided.

Use anticipatory prescribing to avoid delay in response to a symptom which may predictably occur due to disease progression. Availability of equipment and adequate quantities of drugs needs to be assured, particularly out of hours, so always anticipate changes with patients, district nursing teams, community pharmacists, etc to avoid delays and unnecessary suffering.

A 'just in case' box containing drugs which might be needed, including injectable pain relief, antiemetics and sedatives is recommended.

Nerve blocks or regional anaesthesia (eg, epidural or intrathecal catheters) may be considered when pain is localised to a specific area. \[4\]

**Analgesia**

**Non-opioids**

- Paracetamol is a weak analgesic with very few side effects. It has a dose-sparing effect with codeine. \[6\]
- NSAIDs are particularly useful for bone pain that is often poorly controlled by opioids. Their main side-effect is gastrointestinal bleeding - a proton pump inhibitor (standard dose), \(H_2\)-receptor antagonist (double dose) or misoprostol may be co-prescribed to counter this risk. \[7\]

**Weak opioids**

These are used when non-opioids are ineffective. These include codeine phosphate, dihydrocodeine and tramadol, which are often used in combination with paracetamol, for its dose-sparing effect.

**Strong opioids**

**Oral morphine**

This forms the backbone of first-line therapy. Patients and family may be concerned regarding the use of morphine. It is important to explain that it is a very effective analgesic, conferring overall benefit and not implying imminent death.

- It is not normally addictive.
- Respiratory depression is not usually a problem. Morphine is also used for symptomatic relief of dyspnoea.
- Significant tolerance to morphine does not usually develop. Patients may well be maintained for several weeks on a constant dose and this is only increased because of advancing disease.
- Morphine should not be stupefying. At the correct dose, patients can continue with normal activities. Always warn patients that initial sedation may occur but that it usually settles within 48 hours. It may affect their ability to drive.

**Dose titration** \[8\]

- Initially give 4-hourly immediate-release morphine tablets or elixir or 12-hourly oral sustained-release morphine, depending on patient preference.
- Prescribe extra doses of immediate-release for ‘breakthrough pain’ as required during the titration phase.
- A typical daily starting dose for opioid-naïve patients is 20-30 mg oral morphine:
  - Regular 4-hourly 5-10 mg immediate-release oral morphine; or
  - Regular 12-hourly 10-15 mg sustained-release oral morphine.
- After 24 hours, total the previous day's intake and divide by 6 to provide 4-hourly doses, or by 2 to provide 12-hourly doses, thus adjusting the regular dose upwards if needed.
- Patients who have already been using weak opioids should not be considered opioid-naïve - convert on the basis of relative potencies shown below.
Seek specialist advice for patients with moderate-to-severe renal or hepatic impairment.

### Oral to oral route conversions

<table>
<thead>
<tr>
<th>Converting from: (current opioid)</th>
<th>Converting to: (new opioid)</th>
<th>Divide 24-hour dose of current opioid by figure below to calculate initial 24-hour dose of new opioid.</th>
</tr>
</thead>
<tbody>
<tr>
<td>oral codeine</td>
<td>oral morphine</td>
<td>Divide by 10</td>
</tr>
<tr>
<td>oral tramadol</td>
<td>oral morphine</td>
<td>Divide by 5</td>
</tr>
<tr>
<td>oral morphine</td>
<td>oral oxycodone</td>
<td>Divide by 2</td>
</tr>
<tr>
<td>oral morphine</td>
<td>oral hydromorphone</td>
<td>Divide by 7.5</td>
</tr>
</tbody>
</table>

### Maintenance dose

- The National Institute for Health and Care Excellence (NICE) recommends that oral sustained-release morphine, not transdermal formulations, is first-line for maintenance treatment.
- Any breakthrough pain, not associated with unusual activity, should be treated with immediate-release morphine at 1/6 total daily dose. Review the daily dose of sustained-release morphine and increase as required. The aim is preventing pain from occurring rather than relieving it.
- NICE also recommends that incident or episodic pain, such as unusual activity or dressing changes, should also be treated with immediate-release morphine. However, buccal or intranasal fentanyl may be useful, as it is swiftly absorbed, providing a more rapid onset of pain relief, compared with oral morphine.\(^8\)
- If pain remains inadequately controlled despite optimising first-line maintenance treatment, review analgesic strategy and consider seeking specialist advice.

### Common problems of opiates

- Constipation - so common that laxatives should be prescribed prophylactically.\(^6\)
  - There is no good-quality evidence to guide prescribers on the choice of laxative in palliative care patients. What evidence there is suggests that they are all of similar effectiveness.\(^{10}\)
  - A combination of drugs with different modes of action is likely to be more effective in resistant constipation.
  - There is some evidence that constipation is less with transdermal fentanyl.\(^{11}\)
- Sedation - usually subsides within a few days.
- Nausea and vomiting - occurs in up to 40% of opioid-naïve patients. May settle within a few days but an antiemetic such as metoclopramide 10 mg tds or haloperidol 1.5 mg nocte should be used.\(^6\)
- Dry mouth - advise good mouth care: frequent sips of iced drinks, dental floss, eating pineapple chunks, saliva replacements or stimulants. See also separate Dry Mouth (Xerostomia) article.
- Histamine release:
  - Pruritus - try oral antihistamine to control itch.
  - Bronchoconstriction - use IV/IM antihistamine and bronchodilators and switch to a pharmacologically distinct opioid such as methadone.
- Toxicity - appears as agitation, hallucinations, confusion, vivid dreams and myoclonic jerks:
  - Worsening renal or hepatic function will alter the metabolism of morphine and may cause accumulation and toxicity.
  - In agitation, consider opioid toxicity rather than uncontrolled pain before giving further opioids.
Morphine intolerance - may be affected by:
- Responsiveness of the pain to opioids. NB: pain may appear to be morphine-resistant if under-dosed (eg, insufficient dose, immediate-release form not taken by the clock, etc).
- Previous exposure to opioids.
- Rate of dose titration - start with a low initial dose and titrate upwards slowly.
- Additional medication.
- Concomitant disease.
- Genetic factors.
- Renal and hepatic function.

If problems persist, consider other cause of pain and switching to an alternative strong opioid. Alternatives include hydromorphone, methadone and oxycodone. Consult local guidelines and seek advice from palliative care teams. Methadone in particular is difficult to use safely due to a long and variable elimination half-life and should be initiated by specialists.

In patients with poor or worsening kidney function, to prevent or manage opioid toxicity:
- Consider dose reduction and/or increased dose interval.
- Change from a sustained-release to an immediate-release oral formulation.
- Consider switching to alfentanil, buprenorphine or fentanyl, which are the opioids of choice where eGFR is <30 ml/minute.
- Ensure frequent monitoring and review.
- Seek specialist advice.

Parenteral routes

Subcutaneous delivery
Subcutaneous opioids may be initiated for first-line treatment if oral opioids are not suitable and analgesic requirements are unstable.

Syringe drivers

- If vomiting, dysphagia or increasing debility prevent patients from taking oral morphine then usual practice is to convert to a subcutaneous infusion of opioid via a device such as a syringe driver. Injection site should be changed every 2-3 days.
- Diamorphine is approximately three times as powerful as oral morphine as an analgesic. Subcutaneous morphine can be used in its place when diamorphine is not available; it has twice the potency of oral morphine. Daily doses for the syringe driver, when moving from tablets to subcutaneous infusion, are simple to calculate.

Examples of equivalent doses:

<table>
<thead>
<tr>
<th>Daily dose oral morphine (mg)</th>
<th>Daily dose SC diamorphine (mg)</th>
<th>Daily dose SC morphine (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>300</td>
<td>100</td>
<td>150</td>
</tr>
</tbody>
</table>

Many other drugs can be mixed with diamorphine in the syringe driver, to help with nausea and vomiting, restlessness, etc. However, check compatibility first. Drug solutions for SC infusion should be diluted as much as possible to reduce risk of drug incompatibility and irritation at the infusion site. See separate Prescribing in Palliative Care article for more details.

Transdermal opioids
Transdermal opioids are an alternative to both oral morphine and SC diamorphine in patients with stable pain (the dose cannot be changed quickly), who cannot tolerate oral morphine or have intractable constipation or subacute obstruction. Caution must be used when calculating opioid equivalence.
Transdermal fentanyl is 100-150x more potent than oral morphine. It diffuses across the skin to provide a continuous level of analgesia without tablets or needles. It is, however, comparatively expensive.

- Patches are worn for 72 hours.
- Steady state of fentanyl is achieved after a variable time due to large individual differences; ensure availability of immediate-release morphine during switch. Review the fentanyl patch dose after 72 hours.
- When converting from oral morphine to transdermal fentanyl, consult the manufacturer’s information, as there is significant variation in conversion ratios. If in doubt, seek advice.
- A transdermal fentanyl 12 micrograms patch equates to approximately 45 mg oral morphine daily. [8]
- If taking immediate-release oral morphine preparations, continue for 12 hours after the first patch is applied or, if on sustained-release oral morphine preparations, take the last dose as the first patch is applied. Modified withdrawal symptoms may occur, so ensure immediate-release oral morphine doses are available during titration.
- If effective analgesia lasts less than three days, increase the patch strength rather than the frequency of patch changes.
- After removing a patch, elimination plasma half-life is almost 24 hours, so care should be taken not to overdose. [15]

Transdermal buprenorphine is approximately 75x more potent than morphine.

- Patches are available as 4- and 7-day patches. Seek specialist palliative care advice if converting from oral morphine to transdermal buprenorphine.
- A transdermal buprenorphine 20 micrograms patch equates to approximately 30 mg oral morphine daily. [8]
- Time to reach steady-state plasma concentration is slow and there is a half-life of approximately 30 hours, so that elimination may also take some time after patches are stopped.
- Its role in the palliative care formulary remains to be clarified but expert consensus supports its efficacy as well as good safety and tolerability profile. [16]

Common problems

About 10% of patients at the end of life have ‘difficult pain’. [1] Pain that is difficult to control is often:

- Pain that is poorly responsive to opioids.
- Episodic and breakthrough despite background opioid analgesia.
- Caused or aggravated by non-physical factors, such as psychological or social distress.

Doctors find the care of patients with resistant pain at the end of life particularly stressful. Where pain control proves difficult, seek help. Possible sources of advice include: [17]

- Specialist palliative care teams (hospital- or hospice-based).
- Macmillan teams.
- GPs with special interest in palliative care.

Neuropathic pain [1]

See also separate Neuropathic Pain and its Management article.

- Described as aching, burning, shooting or stabbing in quality. May be associated with abnormal sensation and allodynia (normal touch felt as painful).
- Caused by nerve damage due to tumour invasion or compression, as well as surgery, chemotherapy and radiotherapy.
- Often poorly responsive to opioids.
- Consider an adjuvant analgesic early: tricyclic antidepressants (eg, amitriptyline 10-75 mg nocte) and anticonvulsants (eg, carbamazepine 100-200 mg nocte, gabapentin 100 mg nocte titrating up to 600 mg tds) are commonly used - normal number to treat (NNT) = 3 for both categories.
- Little evidence for combining adjuvants. Often a second is added if the first has been titrated to an upper limit and pain has only partially responded. Adding a second usually means reducing the dose of the first.
- There is no evidence for a specific drug for different neuropathic pains.
Other options include:
- Psychological techniques - eg, cognitive behavioural therapy, simple relaxation, hypnosis.
- Capsaicin cream.
- Local nerve blocks and epidurals.
- Acupuncture.
- Transcutaneous electrical nerve stimulation (TENS).

Episodic/incident pain
Bony pain due to metastases in the spine, pelvis or femora, exacerbated by walking or weight-bearing can be particularly problematic.

- Opioids plus NSAIDs are the mainstay; however, doses sufficient to control pain on movement cause sedation when the patient is at rest.
- Advise prn doses of immediate-release opioid in anticipation of movement.
- Other options:
  - Radiotherapy.
  - Surgical stabilisation of pathological fractures - eg, vertebroplasty (for malignant vertebral collapse) or percutaneous cementoplasty.
  - Bisphosphonates.
  - Epidurals.
  - Appropriate appliances and aids.

'Total pain'
Pain can be a physical expression of compound psychological/spiritual and social distress and requires an holistic approach.\[18\] Consider:

- Counselling.
- Access to spiritual advisors.
- Antidepressants or anxiolytics.

Whilst pain relief is vital, good palliative care encompasses far more. Within primary healthcare teams, improving the quality of palliative care can be facilitated by the Gold Standards Framework.\[19\] Good communication within and between teams is vital (eg, between primary and secondary care and between usual daytime GP and out-of-hours provision) to avoid unnecessary problems during this period\[20, 17\]

Further reading & references

- Palliativedrugs.com

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20. Care of dying adults in the last days of life; NICE guidance (Dec 2015)

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