# Pain Control in Palliative Care

See also separate articles End of life care and Palliative care.

Pain occurs in up to 70% of patients with advanced cancer and about 65% of patients dying of non-malignant disease.[1] Much can now 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 with medical carers about pain. The patient should be the prime assessor of their pain and be encouraged to take an active role in their pain management. A doctor must be able to get alongside the patient and their family and to spend time presenting options, answering questions and quelling fears. Pain is a complex subjective phenomenon and is affected by the emotional context in which it is endured:[2]

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

Adequate psychological support is critical, as removing the fear of pain in itself will help to optimise pain control. Nondrug 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 the pain prior to treatment. Take a detailed history of the pain(s) and make a full assessment including:

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

Given the subjective nature of pain, the patient is central to pain assessment. Regular monitoring (at least daily) with visual analogue, numerical or verbal rating scales can allow treatment to be modified promptly where pain is inadequately controlled. Self-assessment should be used wherever possible, including in patients with cognitive impairment. Only substitute 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 nondrug treatments may also have a role.

| WHO analgesic ladder | |
|---|---|
| **Step 1** (pain <3/10) | **Non-opioid +/-adjuvant** |
| *Pain persisting or increasing?* | |
| **Step 2** (pain 3-6/10) | **Opioid for mild-to-moderate pain +/-non-opioid +/-adjuvant** |
| *Pain persisting or increasing?* | |
| **Step 3** (pain >6/10) | **Opioid for moderate-to-severe pain +/-non-opioid +/-adjuvant** |
| *Objective: freedom from pain* | |

- 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 non-opioids+/- adjuvants 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 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.

| Adjuvant analgesics for cancer pain [3] | |
|---|---|
| **Drugs** | **Indications** |
| Non-steroidal anti-inflammatory drugs (NSAIDs) | • Bone pain<br>• Soft tissue infiltration<br>• Hepatomegaly |
| Corticosteroids | • Raised intracranial pressure<br>• Soft tissue infiltration<br>• Nerve compression<br>• Hepatomegaly |
| Antidepressants and anticonvulsants | • Nerve compression or infiltration<br>• Paraneoplastic neuropathies |
| Bisphosphonates | • Bone pain |
| Ketamine (specialist use only) | • Refractory pain<br>• Neuropathic pain<br>• Ischaemic limb pain |

- Where pain is continuous, analgesia needs to be prescribed on a regular not 'as required' basis and patients should be educated that taking medication regularly will gain best results. 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 pain that occurs with everyday activities such as walking. Explain that additional medication should be taken before undertaking 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 for the patient and family to reinforce the drug regimen.
- 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. Ensure adequate prn medications. Availability of equipment and 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. Some PCTs have instituted a 'just in case box' containing drugs which might be needed, including injectable pain relief, anti-emetics and sedatives.
  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.
- NSAIDs are particularly useful for bone pain that is often poorly controlled by opioids. Their main side effect is gastrointestinal bleeding and a proton pump inhibitor (standard dose), $H_2$-receptor antagonist (double dose) or misoprostol may be co-prescribed to counter this risk.

### National Institute for Health and Clinical Excellence guidance for use of opioids in palliative care [5]

- Starting strong opioids:
  - When starting treatment with strong opioids, offer patients with advanced and progressive disease regular oral sustained-release or oral immediate-release morphine (depending on patient preference), with rescue doses of oral immediate-release morphine for breakthrough pain.
  - For patients with no renal or hepatic comorbidities, offer a typical total daily starting dose schedule of 20-30 mg of oral morphine plus 5 mg oral immediate-release morphine for rescue doses during the titration phase.
  - Adjust the dose until a good balance exists between acceptable pain control and side-effects. If this balance is not reached after a few dose adjustments, seek specialist advice. Offer patients frequent review, particularly in the titration phase.
  - Seek specialist advice before prescribing strong opioids for patients with moderate-to-severe renal or hepatic impairment.

- First-line maintenance treatment:
  - Do not routinely offer transdermal patch formulations as first-line maintenance treatment to patients in whom oral opioids are suitable.
  - If pain remains inadequately controlled despite optimising first-line maintenance treatment, review analgesic strategy and consider seeking specialist advice.

- First-line treatment if oral opioids are not suitable - transdermal patches:
  - Consider initiating transdermal patches with the lowest cost for patients in whom oral opioids are not suitable and analgesic requirements are stable, supported by specialist advice where needed.
  - Use caution when calculating opioid equivalence for transdermal patches:
  - A transdermal fentanyl 12 microgram patch equates to approximately 45 mg oral morphine daily.
  - A transdermal buprenorphine 20 microgram patch equates to approximately 30 mg oral morphine daily.

- First-line treatment if oral opioids are not suitable - subcutaneous delivery:
    - Consider initiating subcutaneous opioids with the lowest acquisition cost for patients in whom oral opioids are not suitable and analgesic requirements are unstable, supported by specialist advice where needed.

- First-line treatment for breakthrough pain in patients who can take oral opioids:
    - Offer oral immediate-release morphine for the first-line rescue medication of breakthrough pain in patients on maintenance oral morphine treatment.
    - Do not offer fast-acting fentanyl as first-line rescue medication.
    - If pain remains inadequately controlled despite optimising treatment, consider seeking specialist advice.

### Weak opioids

These are used when non-opioids are ineffective. These include codeine phosphate and dihydrocodeine tartrate and are often used in combination with paracetamol.

### Strong opioids

### Oral morphine

This forms the backbone of first-line therapy. Patients and family are commonly concerned at the outset and it needs to be explained that morphine is an effective analgesic, conferring overall benefit and does not imply imminent death. Other common myths and misunderstandings include:

- It is *not* normally addictive. Patients commonly reduce their dose if other measures counter the cause of the pain.
- Respiratory depression is *not* usually a problem. Pain tends to counteract this effect even in those with respiratory disease. Morphine is also used for symptomatic relief of dyspnoea.
- Significant tolerance to morphine does *not* usually develop. Patients are normally maintained for several weeks on a constant dose and this is only increased because of advancing disease.
- Morphine is *not* 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.

#### Dose titration

- Initially give 4-hourly as normal-release morphine tablets or elixir.
- Allow extra doses of the same size for 'breakthrough pain' as required.
- After 24 hours, total the previous day's intake and divide by 6 to provide 4-hourly doses, thus adjusting the regular dose upwards if needed.
- A regular 4-hourly starting dose for opioid-naive patients is usually 5-10 mg morphine.
- Patients who have already been using weak opioids should not be considered opioid-naive - convert on the basis of relative potencies shown below.

**Oral to oral route conversions** [2]

| Converting from: (current opioid) | Converting to: (new opioid) | Divide 24-hour dose of current opioid by figure below to calculate initial 24-hour dose of new opioid |
|---|---|---|
| oral codeine | oral morphine | Divide by 10 |
| oral tramadol | oral morphine | Divide by 5 |
| oral morphine | oral oxycodone | Divide by 2 |
| oral morphine | oral hydromorphone | Divide by 7.5 |

#### Maintenance dose

- Once pain relief is at a satisfactory and stable level, sustained-release preparations can be substituted to allow od or bd dosing (oral oxycodone or hydromorphone require bd modified-release preparation dosing).
- Any breakthrough pain not associated with unusual activity should be treated with morphine elixir or ordinary tablets at 1/6 total daily dose. Review the daily dose of sustained-release morphine and increase by anything from 30% to 100%. Remember that the aim is preventing pain from occurring rather than relieving it.

## Common side-effects

Use the lowest necessary dose for full analgesic effect to minimise side-effects.

- Sedation - usually subsides within a few days.
- Nausea and vomiting - common in opioid-naive patients. Usually settles within a few days but can be prevented by access to an anti-emetic, eg metoclopramide 10 mg tds or haloperidol 1.5 mg nocte.
- Constipation - very common and laxatives should be prescribed prophylactically.
- Dry mouth - advise good mouth care: frequent sips of iced drinks, dental floss, saliva replacements or stimulants.
- Pruritus - related to histamine release. Try oral antihistamine to control itch.
- Bronchoconstriction - again related to histamine release. 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 patients with poor or worsening kidney function, to prevent or manage opioid toxicity:

- Consider dose reduction and/or increased dose interval.
- Change from a modified-release to an immediate-release oral formulation.
- Consider switching to alfentanil, buprenorphine or fentanyl, which are the opioids of choice where eGFR <30ml/minute.
- Ensure frequent monitoring and review.
- Seek specialist advice.

## Parenteral routes

**Syringe drivers**:

- If vomiting, dysphagia or increasing weakness 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, and is twice the potency of oral morphine. Daily doses for the syringe driver, when moving from tablets to subcutaneous infusion, are simple to calculate.[6]

Examples of equivalent doses:

| Daily dose oral morphine (mg) | Daily dose subcut diamorphine (mg) | Daily dose subcut morphine (mg) |
|---|---|---|
| 180 | 60 | 90 |
| 300 | 100 | 150 |

Many other drugs can be mixed with diamorphine in the syringe driver, to help with nausea and vomiting, restlessness, etc. but check compatibility first. Drug solutions for subcutaneous infusion should be diluted as much as possible to reduce risk of drug incompatibility and irritation at the infusion site.

**Transdermal opioids**:

An alternative to both oral morphine and subcutaneous diamorphine in patients with stable pain is transdermal fentanyl or buprenorphine patches. They can be useful in ambulatory patients where the following exist:

- Problems with the oral route.
- Intractable constipation or subacute obstruction.

- Morphine intolerance.

Fentanyl is a very powerful synthetic opioid (150x potency of oral morphine). It diffuses across the skin to provide a continuous level of analgesia without tablets or needles. It is, however, comparatively expensive.[7]

- Patches are worn for 72 hours.
- Time for the drug to take effect or to clear from the body needs to be allowed. Steady state of fentanyl is achieved after 36-48 hours and minimal effective plasma concentration from 3-23 hours (note large individual differences). Analgesic effect should not be evaluated until the patch has been worn for 24 hours.
- When converting from oral morphine to transdermal fentanyl, consult the manufacturer's information, as there is significant variation in conversion ratios between 100:1 to 150:1. If on 4-hourly oral morphine preparations, continue for 12 hours after the first patch is applied or if on 12-hourly 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.
- Only use with patients whose pain is stable, because of the long time needed to titrate the dose upwards.
- If effective analgesia lasts less than 3 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.[8]

Buprenorphine patches are available as 4- and 7-day patches. Seek specialist palliative care advice if converting from oral morphine to transdermal buprenorphine. Time to reach steady-state plasma concentration is slower 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.[9]

# Common problems

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

- Poorly responsive to opioids.
- Episodic and breaks through despite background opioid analgesia.
- Caused or aggravated by non-physical factors.

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[10] include:

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

Do not forget non-pharmacological interventions for analgesia - colleagues in oncology, pain relief and orthopaedics may be able to assist with difficult-to-control pain, particularly where there is significant locally advanced disease, neuropathic pain or marked movement-related pain.

### Morphine intolerance

Factors affecting the ability to tolerate opioids include:

- Responsiveness of the pain to opioids.
- Previous exposure to opioids.
- Rate of dose titration.
- Additional medication.
- Concomitant disease.
- Genetic factors.
- Renal and hepatic function.

Strategies for improving tolerance include the following:

- Start with a low initial dose of opioid and titrate slowly upwards. Avoid inducing tolerance or toxicity unnecessarily.
- Use short-acting preparations until dose is stabilised.
- Pain may appear to be morphine-resistant if underdosing (insufficient dose, not taken by the clock, taken prn).
- Consider if agitated confusion is due to opioid toxicity rather than uncontrolled pain before giving further opioids.
- Consider switching to an alternative strong opioid. Alternatives include hydromorphone, methadone and oxycodone.[11] 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.
- Manage side-effects with additional medication.
- Consider changing the route of administration - eg where gastrointestinal absorption is poor, consider switching to skin patches.
- Consider other causes of pain.

### Neuropathic pain

See also separate article Neuropathic pain and its management.

- 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.
- Try an adjuvant analgesic: 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.
- 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.
- 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 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, but doses sufficient to control pain on movement cause sedation when the patient is at rest.
- Advise prn doses of normal-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.[10] Consider:

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

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. [12] Similarly, good practice is outlined in the Liverpool Care Pathway for the Dying, [13] which provides an important resource for those caring for those at the end of life. 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.

# Further reading & references

- The National End of Life Care Programme, Dept of Health, 2009
- Palliativedrugs.com; online palliative care formulary


1. Colvin L, Forbes K, Fallon M; Difficult pain. BMJ. 2006 May 6;332(7549):1081-3.
2. Control of pain in adults with cancer; Scottish Intercollegiate Guidelines Network - SIGN (November 2008)
3. Fallon M, Hanks G, Cherny N; Principles of control of cancer pain. BMJ. 2006 Apr 29;332(7548):1022-4.
4. British National Formulary; 63rd Edition (Mar 2012) British Medical Association and Royal Pharmaceutical Society of Great Britain, London
5. Opioids in palliative care; NICE Clinical Guideline (May 2012)
6. Opioid Potency Ratios; Palliative Medicine Handbook (online)
7. Clark AJ, Ahmedzai SH, Allan LG, et al ; Efficacy and safety of transdermal fentanyl and sustained-release oral morphine in patients with cancer and chronic non-cancer pain. Curr Med Res Opin. 2004 Sep;20(9):1419-28.
8. Symptom Management in advanced cancer by R. Twycross and A. Wilcock (3rd edition) 2001. Radcliffe Medical Press ISBN 1857755103
9. Pergolizzi JV, Mercadante S, Echaburu AV, et al ; The role of transdermal buprenorphine in the treatment of cancer pain: an expert panel consensus. Curr Med Res Opin. 2009 May 11.
10. Supportive and palliative care; NICE (2004)
11. Riley J, Eisenberg E, Muller-Schwefe G, et al; Oxycodone: a review of its use in the management of pain. Curr Med Res Opin. 2008 Jan;24(1):175-92.
12. Gold Standards Framework: Improving Community Care
13. Liverpool Care Pathway for the Dying Patient (LCP), The Marie Curie Palliative Care Institute, Liverpool





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