

Palliative care 1 - pain control

This bulletin and the accompanying issue, on symptom control in palliative care, focus on the care of cancer patients. It is recognised that many terminally ill patients cared for by general practitioners suffer with other conditions, such as heart failure, but many of the management strategies discussed here will be relevant to those patients.

Pain is the most common symptom in patients with malignant disease. Unrelieved pain can be psychologically devastating for patients and their families. The goal of therapy is to ensure that no patient lives or dies in pain.

In order to treat pain appropriately, it is necessary to identify the type of pain (for example, visceral, or bone pain). Pain from separate causes may be experienced simultaneously and pain may be worsened by factors such as hypercalcaemia. Emotional, social, and spiritual issues may also contribute to a person's distress or "total pain". The following information relates to the pharmacological management of physical pain, recognising that this may be just one aspect of treatment for a patient's pain.

Summary

- ◆ Pain should be controlled with oral therapy whenever possible. Subcutaneous or transdermal administration is used if the patient cannot swallow or absorb oral medications.
- ◆ Constant pain requires regular therapy.
- ◆ The choice of pain relief is dependent on severity of pain and previous analgesia, not on the stage of disease.
- ◆ Morphine is the strong opioid of choice; other opioids are used only if there are specific indications.
- ◆ Patients should be titrated with normal-release morphine which then can be converted to a modified-release preparation. Normal-release morphine preparations should be made available for breakthrough pain.
- ◆ Adverse effects of opioids, such as constipation, and nausea and vomiting, should be anticipated and treated.
- ◆ Some pain, such as bone pain and neuropathic pain, may be less responsive to opioids and require other therapy.

The accompanying WeMeReC Bulletin contains information on **symptom control** in palliative care, including the management of adverse effects associated with opioid use.

World Health Organisation (WHO) analgesic ladder

WHO guidelines for the treatment of cancer pain emphasise the need for regular therapy, which should be given orally whenever possible. The 1982 WHO guidelines essentially comprise a three-step analgesic ladder (figure 1). When followed correctly, this method of management controls cancer pain in 80-90% of patients.[†]

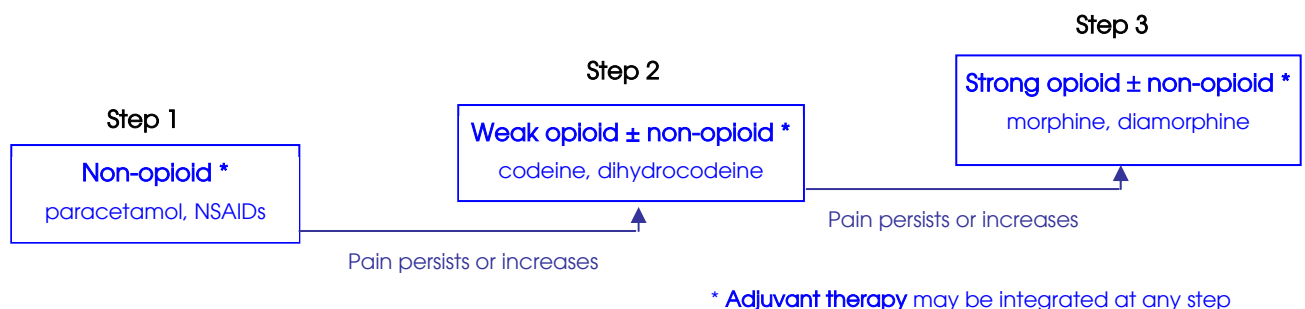


Figure 1: WHO analgesic ladder † www.who.int/cancer/palliative/painladder/en

Step 1: non-opioid analgesics

Non-opioids, such as **paracetamol** taken regularly and non-steroidal anti-inflammatory drugs (**NSAIDs**), are often highly effective. If there is an

inflammatory component to the pain, such as with bone or pleuritic pain, an NSAID can be used at any stage as adjuvant therapy.

Step 2: weak opioids

If Step 1 medicines do not relieve pain, an adequate dose of a weak opioid, such as **codeine**, can be added. Products that contain just one active agent offer flexibility. If combination products are used, they should contain an adequate dose of opioid (e.g. 30 mg codeine) and care should be taken not to exceed the maximum dose of the second constituent (e.g. paracetamol). **Tramadol** may be used, but advantages over other analgesics in this group are

negligible. Because opioids cause constipation, prophylactic laxatives (stimulants with softeners or osmotic agents) need to be co-prescribed.

If a weak opioid used correctly (e.g. co-codamol 30/500, 8 tablets in 24 hours; with adjuvant therapy if appropriate) becomes ineffective, move to Step 3. Changing between weak opioids should not prevent or delay an appropriate increase to Step 3 analgesia.

Step 3: strong opioids

Morphine is the strong opioid of choice because of its ease of administration and titration, and its well understood pharmacokinetics. When initiating morphine, a normal-release formulation (such as *Oramorph*[®] oral solution or *Sevredol*[®] tablets) should ideally be used. These preparations have relatively rapid onsets and short times to peak effect; thus, titration to optimum doses can be achieved quickly. Morphine, given every 4 hours, should be started at a dose of: 2.5 mg if the patient is elderly or frail or has renal impairment; 5 mg if Step 2 of the analgesic ladder has been omitted (i.e. if the patient is opioid naïve); or 10 mg. For breakthrough pain, the **same** morphine dose needs to be available to be given between regular doses.

The dose of morphine should be titrated against the patient's pain until relief is satisfactory. The regular dose should be reviewed daily and adjusted according to how many rescue doses have been given. Adjustments should be by increments of 30-50% as needed and not by a fixed amount. Stable plasma concentrations are reached within 24 hours of the start of treatment and each dose adjustment. There is no maximum dose, as long as increasing doses continue to provide improved pain relief. (The analgesic requirements of some patients will fall as their condition deteriorates.)

The adverse effects of opioids must be anticipated. When starting treatment, some sedation is common, and nausea may be a problem. These symptoms usually wear off after a few days, but anti-emetic therapy may be required in the meantime. Constipation does not diminish and prophylactic laxatives (see above) are essential. Dry mouth may also be troublesome. These effects are discussed in the accompanying bulletin on symptom control.

Historically, opioids have been underused because of fears of tolerance, addiction, and respiratory depression. Tolerance and dependence are rarely a problem in palliative care. Respiratory rate is a sensitive indicator of toxicity. Other signs of toxicity to be watchful for include twitching and pinpoint pupils.

When the dose of morphine is relatively stable, modified-release (MR) preparations can be used for maintenance therapy. These medicines have the advantage of only needing to be administered every 12 hours (or 24 hours for *MXL*[®]; *Morcap*[®] SR capsules can be given every 12 or 24 hours). If switching between different preparations, pain control may need to be reassessed. (In some cases, therapy may be initiated with MR preparations but prescribers should be mindful of the longer times for onset and peak effects that these have.)

To convert from normal-release to MR morphine, the total morphine dose given over the previous 24 hours should be divided by 2. This gives the dose of MR morphine that should be taken every 12 hours. This should be started when the next regular dose of normal-release morphine was due.

For capsules given 24-hourly, the previous daily dose does not need to be halved.

Example: In the past 24 hours the patient received:
six doses of morphine 20 mg
+ two breakthrough doses of 20 mg
= 160 mg in 24 hours
∴ MR morphine dose = 80 mg every 12 hours

Normal-release morphine should be available and given as often as necessary for breakthrough pain at

the equivalent 4-hourly dose (i.e. the 24-hour dose divided by 6).

Example: The patient is receiving MR morphine
120 mg every 12 hours
= 240 mg in 24 hours
∴ 4-hourly equivalent dose of normal-release
morphine for breakthrough pain = 40 mg

Modified-release morphine is unsuitable for breakthrough pain. If breakthrough pain becomes a regular feature then the dose of MR morphine needs to be increased accordingly. The new breakthrough dose of normal-release morphine then also needs to be increased to the new 4-hourly equivalent. As the morphine dose increases the dose of laxative may also need to be increased.

Bear in mind that it is necessary to assess the effectiveness of any breakthrough medication. If the pain is not opioid-sensitive then increasing opioid doses will not be helpful. Pain may need to be re-evaluated.

Subcutaneous morphine is being used more commonly because the availability of parenteral diamorphine has been limited by supply. The 24-hour dose of morphine for use by the subcutaneous route should be half the 24-hour dose of oral morphine.

Example: In the past 24 hours the patient received:
two doses of MR morphine 150 mg
= 300 mg in 24 hours
∴ subcutaneous morphine dose = 150 mg over
24 hours

Fentanyl is a strong opioid that is available in transdermal patches. Fentanyl patches can be used when there is dysphagia, intractable nausea and vomiting, or persistent adverse effects with morphine (e.g. severe constipation, nausea, or drowsiness). Fentanyl patches are suitable for pain that is stable but **not** for pain that is changing rapidly – they are not appropriate for breakthrough pain.

Fentanyl is available in patches that release approximately 25, 50, 75, or 100 micrograms/hour for 72 hours. (*Durogesic® DTrans®* is also available in a “12” patch; generic reservoir patches cannot be cut to deliver this dose). Some fentanyl patch formulations have no distinguishing features on them, so it is important that patients and their carers are aware of the dose being used in case referral to secondary care is required and/or the patient becomes unconscious.

Fentanyl patches have a slow onset of action; therefore, if a patient is being switched from morphine, this should be phased out gradually. Normal-release morphine should be continued for 6-12 hours, or the first fentanyl patch should be applied at the same time as the last dose of MR morphine. Appropriate starting doses of fentanyl are given in the *Prescribing in palliative care* section of the BNF, the manufacturers’ Summaries of Product Characteristics, and specialist references. Conversion guidelines use approximate doses and patients must be monitored while doses are titrated. Effectiveness can only be evaluated when patches have been worn for 24 hours. Note that the absorption of fentanyl can be affected by the application site, and absorption can be decreased with sweating and increased with fever.

Morphine withdrawal symptoms such as shivering, diarrhoea, and flu-like symptoms may occur when switching to fentanyl patches; these can be treated with normal-release morphine. Patients on fentanyl patches may also require normal-release morphine for breakthrough pain (the 4-hourly equivalent dose). When stopping fentanyl patches, it can take up to 25 hours for plasma concentrations of fentanyl to drop by 50%. The replacement opioid should be started at a low dose and increased gradually.

When used in the last days of life, a fentanyl patch may remain in place, being changed every 72 hours as previously, with subcutaneous doses of diamorphine or morphine being given as required. If pain becomes more problematic and is opioid-sensitive, it may be easier to achieve effective control by continuing the patch as above, but adding a subcutaneous infusion of opioids, starting at low doses and titrating up as needed. The local palliative care team can provide further advice. In the event of referral, it is vital that the secondary care team is informed of the reasons for use of both transdermal and subcutaneous therapy so that pain control can be maintained.

Diamorphine is highly soluble in water and is, therefore, the opioid of choice if parenteral therapy is required. Subcutaneous diamorphine is three times as potent as oral morphine. The equivalent 24-hour dose of diamorphine is one third of the total dose of oral morphine given over the preceding 24 hours.

Example: In the past 24 hours the patient received:
two doses of MR morphine 150 mg
= 300 mg in 24 hours
∴ subcutaneous diamorphine dose = 100 mg over
24 hours

Oxycodone is an alternative strong opioid available orally in normal-release *OxyNorm*[®] formulations and modified-release *OxyContin*[®] tablets. For patients who gain effective pain relief with morphine, but who experience unacceptable adverse effects (the elderly and patients with impaired renal function are at particular risk), a switch to oxycodone may be suitable. To convert to oral oxycodone, the 24-hour morphine dose should be halved. Advice should be sought if the subcutaneous route is needed.

Opioids via syringe drivers

Syringe drivers are used to administer continuous subcutaneous infusions of medicines. They are used for patients with persistent nausea and vomiting, intestinal obstruction, swallowing difficulties, those who are semi-comatose or comatose, or who are suffering severe weakness before death. The syringe driver is an alternative route for delivery of medicines and is **not** a method of pain relief itself.

Diamorphine can be mixed with several other medications in syringe drivers; however, care is needed, especially at high concentrations. When mixing medicines for a syringe driver, there is a need to check that the mixture does not precipitate, crystallise, or discolour, and that there is no pain or inflammation at the injection site. Some drugs are too irritant for subcutaneous delivery; these include diazepam, chlorpromazine, and prochlorperazine. Advice on mixing medicines in syringe drivers should be sought from the local hospice, palliative care team, or medicines information department.

Some points to note:

- ◆ In the community setting, control of pain should first be tried using the WHO analgesic ladder. Failing this, advice should be sought from the palliative care team. Specialists do sometimes use hydromorphone, methadone, and ketamine.
- ◆ *Cyclimorph*[®] (morphine and cyclizine) injection is generally inappropriate as it is not possible to increase the dose of morphine without increasing the dose of cyclizine.
- ◆ Buprenorphine, a partial agonist (*BuTrans*[®] and *Transtec*[®] patches), may alter the action of other opioids.
- ◆ Pethidine is unsuitable as it has a short plasma half-life and a toxic metabolite that accumulates with regular use.

Pain poorly-responsive to opioids

Some pain, such as bone pain and neuropathic pain, may be only partially responsive to opioids. An opioid should be used at the maximum tolerated dose and adjuvant treatment initiated.

Radiotherapy is the treatment of choice for bone pain with an onset of action ranging from a few days to four weeks. Opioid requirements might decrease as radiotherapy takes effect. Bone pain can also be treated with **NSAIDs**. Advice on the use of **bisphosphonates** for bone pain should be sought from an oncologist or palliative care team.

For neuropathic pain, such as burning and stabbing pain, **tricyclic antidepressants** such as amitriptyline can be useful. The starting dose of amitriptyline should be 25 mg at night (10 mg in the elderly). Dose increases depend on the pain but, in general, the final dose is usually lower than that for depression. Be aware of potential antimuscarinic adverse effects.

If an element of pain remains then **anticonvulsants**, such as sodium valproate, carbamazepine or gabapentin may be added or substituted. These should give relief within a few days but care should be taken with dosing, especially in the elderly. Gabapentin is started at 300 mg given once on day 1, twice on day 2, and three times from day 3 onwards; increasing by 100 mg/dose (300 mg/day) as required.

For pain caused or exacerbated by the effects of inflammatory oedema, **corticosteroids** can be helpful (see the accompanying bulletin on symptom control).

Information sources:

www.pallcare.info

- links to the *Palliative Medicine Handbook*, the Welsh Care Pathway, and to information on syringe drivers.

www.palliativedrugs.com

- provides medicines information and a discussion forum.

- ◆ Watson M, Lucas C, Hoy A, Back I. *Oxford handbook of palliative care*. Oxford: Oxford University Press, 2005.
- ◆ Twycross R, Wilcock A, Charlesworth S, Dickman A. *Palliative care formulary*, 2nd ed. Abingdon: Radcliffe Medical Press, 2002.
- ◆ Fallon M, Hanks G. *ABC of palliative care*, 2nd ed. Blackwell BMJ Books, 2006.

Some of the recommendations for medicines discussed here are for **non-licensed indications and routes**. It is important for prescribing doctors to recognise the responsibility that such prescribing entails. Summaries of Product Characteristics should be consulted for full prescribing information.