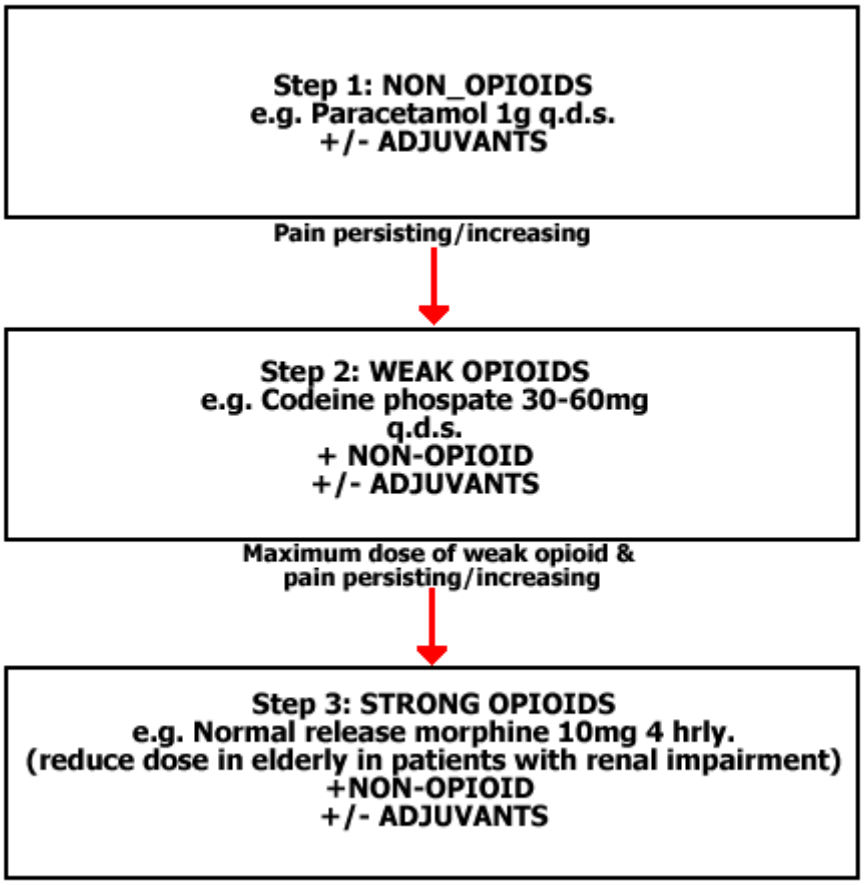
Analgesia

The World Health Organisation (WHO, 1990) has devised a model to assist health care professionals in the management of cancer pain. The recommendations include managing pain,

- 'by the mouth' - oral route to be used wherever possible
- 'by the clock' - analgesia to be taken regularly
- 'by the ladder' - 3 step approach in prescribing

If after optimising the dose, a drug fails to give adequate relief, move up the ladder; do not move sideways in the same efficacy group. The flow chart below demonstrates this process.



Step 1 Non-opioid analgesia

Paracetamol

This is widely used in palliative care. It has antipyretic and analgesic effects but no anti-

inflammatory action. Paracetamol does not damage the gastric mucosa and can be used in conjunction with NSAIDs. Indicated for mild to moderate pain. Maximum dose 4g/24 hours.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs are widely used in palliative care particularly for soft tissue pain and bone metastases. They have analgesic and anti-inflammatory effects. Use lowest effective dose and increase according to need. Assess analgesic response after regular use of one week (effect may be noted in 2-3 days for ibuprofen and diclofenac). Some NSAIDs are useful in the short term treatment of intractable pain when other oral NSAIDs have failed or the oral route is no longer available e.g. ketorolac 60 -120 mg/ 24hours via continuous subcutaneous infusion (short term use only) **Please seek specialist palliative care advice** .

Patients at risk of NSAID induced gastroduodenal ulceration and those taking both steroids and NSAIDs together or anticoagulation therapy should receive a gastro protective drug suc as a proton pump inhibitor (PPI).

Asthma, fluid retention and renal function may all be worsened by NSAID.

Cyclo-oxygenase-2 inhibitors and cardiovascular events

The selective inhibitors of cyclo-oxygenase-2, e.g. etoricoxib, celecoxib are as effective as non-selective NSAIDs such as diclofenac and naproxen. Short-term data indicate that the risk of serious upper gastro-intestinal events is lower with selective inhibitors compared to non-selective NSAIDs; this advantage may be lost in patients who require concomitant low-dose aspirin. There are concerns about the cardiovascular safety of cox-2 selective inhibitors. In the light of emerging concerns about cardiovascular safety, cox-2 selective inhibitors should be used in preference to non-selective NSAIDs only when specifically indicated (i.e. for patients who are at a particularly high risk of developing gastroduodenal ulcer, perforation, or bleeding) and after an assessment of cardiovascular risk. Furthermore, the CSM has advised (August 2005) that patients who have ischaemic heart disease or cerebrovascular disease should not receive a cox-2 selective inhibitor (BNF 51).

Step 2 Weak-opioid analgesia

Weak opioids have low potency and a ceiling effect (maximum therapeutic dose) but can a useful second step for patients with moderate pain.

Compound preparations of paracetamol and weak opioids may be useful.

Commonly used weak opioids are listed below.

Drug	Strength	Dose
Codeine Phosphate	**25mg/ 5ml syrup** **15mg, 30mg and 60mg tablets**	**30-60mg 4-hrly Max.240mg/ 24hrs**
Co-codamol 8/500	**8mg codeine/500mg paracetamol tablet and dispersible tablets**	**1 or 2 tablets 4-6 hrly. Max. 8tablets/ 24hrs**
Co-codamol 30/500	**30mg codeine/500mg paracetamol tablet and effervescent tables**	**1 or 2 tablets 4-6hrly Max. 8 tablets/ 24hrs**
Dihydrocodeine	**30mg tablets**	**30mg 4-6 hrly 60-120mg 12 hrly Max.**

	10mg/5ml solution **60, 90, 120 mg M/R (modified-release) tablets**	**240mg/ 24hrs**
Tramadol	**50mg and 100mg capsules** **M/R capsules also available (see BNF)**	**50-100mg q.d.s. Max. 400mg/ 24hrs**

Patients should be informed of the possibility of constipation, and the prescribing of laxatives considered.

Step 3 Strong-opioid analgesia: morphine

Morphine is the strong opioid of choice for moderate to severe pain in palliative care. Some patients associate its use with advancing disease or may fear addiction, thus support and explanation is required.

Commencing morphine

There is neither standard dose nor ceiling dose, although dosage may be limited by side effects .

- If pain remains uncontrolled after optimising the dose of weak opioid, start short-acting morphine as morphine elixir 5-10mg 4 hourly regularly
  - Or morphine modified release tablets or capsules as 15-30mg 12 hourly (e.g. Zomorph, MST)
  - Or morphine modified release tablets or capsules as 30-60mg 24 hourly (e.g. MXL, Morcap)
- Always prescribe short-acting morphine PRN. To calculate appropriate dose:
  - Take total daily dose of morphine and divide it by 6 e.g.

MST 60mg b.d. = 120mg morphine daily
PRN dose = 20mg short-acting morphine

- If taking modified release morphine and pain relief is not effective, then increase dose by 30% - 50%

MST 30mg b.d. --> 45mg b.d. --> 60mg b.d.

- If taking short-acting morphine and pain relief is not lasting 4 hours or is not effective, then increase dose by 30% - 50%
- e.g. 10mg -> 15mg -> 20mg -> 30mg -> 45mg -> 60mg morphine 4hourly
- Once dose requirements established on short-acting morphine, convert to a modified release preparation.
- If PRN doses required regularly, calculate the total required in 24 hours and increase the dose of modified release preparation accordingly.
- It may be helpful to request the patient/ carer to keep a record of the number of PRN.
- Anticipate potential side-effects, particularly constipation and nausea. Regular laxative are usually always required, together with an antiemetic.
- A key component of safety and efficacy is to ensure patients and their carers understand the use of opioids prescribed and that they undergo regular review.
- If further pain develops or pain uncontrolled reassess cause of pain and treat appropriately. See pain assessment

Side effects of opioids

Side-effect	Management
Constipation must be anticipated and prevented in all patients on weak or strong opioids. Start laxatives concurrently with opioids	**Laxatives (softener & stimulant) e.g. Senna & docusate sodium or Co-danthramer or co-danthrusate**
Nausea/ vomiting (usually settles after a few days)	**Antiemetic – haloperidol 1.5–3mg nocte or metoclopramide 10mg t.d.s.**
Drowsiness (exclude other causes, e.g. renal failure, hypercalcaemia, etc.)	**Warn patients that drowsiness may occur at start of therapy and when dose increased, but should lessen after a few days. If persistent, consider switching to alternative opioid**
Confusion	**May indicate opioid toxicity. Consider reducing dose or switching to alternative opioid and managing symptoms e.g. haloperidol 3-5mg nocte**
Hallucinations	**As for confusion**
Dry mouth	**Local measures**
Myoclonus – muscle spasms (exclude other causes, e.g. renal failure)	**May indicate opioid toxicity. Consider reducing dose or switching to alternative opioid and managing symptoms e.g. clonazepam or midazolam (seek specialist advice)**

Respiratory depression is rarely a problem when opioid doses are increased by appropriate increments.

Morphine preparations

Name	Preparation	Frequency
MST	**Tablets - 5, 10, 15, 30, 60, 100, 200mg Suspension available in sachets - 20, 30, 60, 100, 200mg. Can be administered via PEG tube**	**b.d.**
Zomorph capsules	**10, 30, 60, 100, 200mg Swallow whole or open capsule and sprinkle contents onto soft food**	**b.d.**
Morcap S/R capsules	**20, 50, 100mg Swallow whole or open capsule and sprinkle contents onto soft food**	**o.d.**
MXL capsules	**30, 60, 90, 120, 150, 200mg Swallow whole or open capsule and sprinkle contents onto soft food**	**o.d.**
Morphine solution	**10mg/5ml, 20mg/1ml**	**2 –4 hourly PRN**
Morphine unit dose vials (oramorph)	**10mg/5ml, 30mg/5ml, 100mg/5ml**	**2 –4 hourly PRN**
Sevredol tablets	**10, 20, 50mg**	**2 –4 hourly PRN**
Morphine suppositories	**10, 15, 20, 30mg**	**4 hourly**
Diamorphine injection	**10, 30, 100, 500mg ampoules**	**2 –4 hourly PRN**

Parenteral use

Diamorphine is used subcutaneoulsy, being significantly more soluble than morphine. It can be administered as PRN injection or via a continuous infusion in a syringe driver. To convert from oral morphine to s/c diamorphine divide by 3 e.g.

MST 90mg b.d. = Diamorphine 60mg s/c over 24hours = Diamorphine 10mg s/c 4 hourly

Alternative strong opioids

Alternative strong opioids can be used when there are intolerable side-effects from morphine Switching to an alternative may significantly reduce such side-effects. There are a number o alternative opioids available, including fentanyl, hydromorphone, oxycodone, methadone an buprenorphine. Pethidine is not recommended in palliative care due to its short duration of action. **Specialist palliative care advice is usually required when switching from one strong opioid to another.**

Fentanyl Transdermal (Durogesic DTrans)

It is licensed for chronic intractable pain. It is contraindicated for patients who require rapid titration of their medication. It can be used when,

- Patient is intolerant of morphine or experiencing unacceptable level of side-effects with other strong opioids
- Oral route is inappropriate, e.g. dysphagia, vomiting
- Where use may improve compliance
- Presence of renal failure
- May cause less constipation than other strong opioids
- Patient is unwilling to take morphine

Dosing

- Available as as Durogesic DTrans 12, 25, 50, 75, 100 micrograms/ hour
- Should be replaced every 72 hours (rarely every 48 hours)
- Takes 12-24 hours to reach therapeutic blood levels and on discontinuing fentanyl, levels decrease by about 50% in 17 hours.
- Patients who have not previously received a strong opioid analgesic, initial dose, one '25 micrograms/hour' patch replaced after 72 hours; patients who have received a strong opioid analgesic, initial dose based on previous 24-hour opioid requirement (ora morphine sulphate 90 mg over 24 hours is approximately equivalent to one '25 micrograms/hour' patch, consult product literature for details) See drug conversion tables
- Dose adjustment - When starting, evaluation of the analgesic effect should not be made before the system has been worn for 24 hours (to allow for the gradual increase in plasma-fentanyl concentration)—previous analgesic therapy should be phased out gradually from time of first patch application; if necessary dose should be adjusted at 72-hour intervals in steps of 12–25 micrograms/hour.

To convert from oral morphine to Fentanyl Transdermal (Durogesic DTrans):-

- From four hourly opioid - apply Durogesic DTrans and continue to give regular 4 hourly doses for 12 hours.
- From twice daily controlled release tablets/capsules – give the last dose of 12 hourly opioid at the same time as applying the Durogesic DTrans.
- From once daily controlled release capsules - take the last dose of opioid, wait 12 hours then apply the first Durogesic DTrans.
- Continue PRN dose of short-acting strong opioid. Fentanyl lozenge on a stick (Actiq) is available as an alternative (seek specialist advice) .
- After 48-72 hours, if a patient requires 2 or more PRN doses of fast acting morphine

then the Durogesic DTrans should be increased accordingly
- A reduction in laxatives may be necessary.
- A small proportion of patients may experience morphine withdrawal after switching to fentanyl, with symptoms of shivering, restlessness and bowel cramps. These symptom can be managed with PRN short-acting morphine.

For a guide to dosage conversion see drug conversion tables

Management of patients in the terminal phase, receiving fentanyl (see guidelines in ICP document).

It is recommended practice to leave the fentanyl Transdermal in place. Diamorphine (where tolerated) can be given to treat breakthrough pain. The ‘rule of 5' can be used as a guide to calculate the PRN dose of diamorphine:-

$$\frac{\text{Fentanyl Transdermal rate in micrograms/hour}}{5} = \text{Dose of s/c diamorphine in milligrams}$$

$$\text{e.g., } \frac{\text{25 micrograms/hour}}{5} = \text{5mg s/c diamorphine p.r.n.}$$

The total number of PRN doses given in a 24 hour period can be calculated and started in a 24 hour s/c infusion. If PRN diamorphine is not feasible eg in the home, 2-3 PRN doses could be introduced in a 24 hour s/c infusion via a syringe driver.

Information for patients

- Matrix should be applied to dry, non inflamed, non-irradiated and hairless (if possible) skin on the upper arm, chest or upper back.
- Matrix should be checked daily.
- Patient may shower but not soak in the bath.

Oral transmucosal fentanyl citrate lozenges (OTFC) - (Actiq)

- Indicated for the management of breakthrough pain in patients already receiving maintenance opioid therapy for chronic pain.
- The optimal dose of OTFC cannot be predicted from the patients background opioid requirements.
- Close monitoring of patients by healthcare professionals is required during the titration process.
- Dose titration should be initiated with a 200 microgram lozenge.
- The patient should consume the lozenge by sucking. If adequate analgesia is not obtained within 15 minutes after complete consumption of one lozenge, a second unit of the same strength may be consumed.
- If treatment of several consecutive breakthrough pain episodes require more than one dose unit per episode, an increase to the next higher unit dose should be made.
- Once an adequate dose has been identified, consumption should be maximised to fou dose units daily.
- Alternative breakthrough analgesia should also be prescribed to cover breakthrough pain un relieved by OTFC. **Seek specialist palliative care advice for further information.**

Oxycodone

It is licensed for moderate to severe pain in cancer. It can be used when,

- Patient is intolerant of morphine or experiencing unacceptable level of side effects with oral morphine.
- Can be used as breakthrough medication for patients using fentanyl patches but intolerant of morphine
- It may cause less vomiting and pruritus.

Dosing

- Analgesic potency ratio of oral morphine to oral oxycodone is approximately 2:1.
- Available in short-acting or modified release (over 12 hours) formulations,
- Instant release OxyNorm capsules - 5, 10, 20mg
- OxyNorm liquid - 5mg/5ml
- OxyNorm concentrate - 10mg/ml
- Modified release OxyContin tablets - 5, 10, 20, 40, 80mg
- Injection OxyNorm injection - 10mg/ml (seek specialist advice)
- In opioid naïve patients, start 5mg every 4-6 hours or m/r 10mg bd – titrate to achieve pain control.
- Elderly and patients with renal impairment may require lower doses.

Hydromorphone (Palladone)

It is licensed for the relief of severe pain in cancer. It can be used when,

- Patient is intolerant of morphine or experiencing unacceptable level of side effects with oral morphine, particularly sedation / hallucinations.
- Can be used as breakthrough medication for patients using fentanyl patches but intolerant of morphine,
- Patients having difficulty swallowing as the capsules can be opened and sprinkled onto soft foods (not suitable to be emptied down a PEG or NG tube).

Dosing

- Analgesic potency ratio of oral morphine to oral hydromorphone is 7.5:1 e.g. 10mg oral morphine = 1.3mg oral hydromorphone
- Available in short-acting or modified release (over 12 hours) formulations,
- Short-acting - 1.3, 2.6mg capsules
- Modified release - 2, 4, 8, 16, 24mg capsules
- Capsules may be swallowed whole or opened and sprinkled onto soft food (not suitable to be emptied down PEG or NG tubes).
- In opioid naïve patients, 1.3mg every 4 hours or m/r 2mg bd– titrate to achieve pain control.
- Elderly and patients with renal impairment may require lower doses.

Methadone

It is licensed for the relief of severe pain. It can be used when,

- Patient requires increasing doses of opioids with no improvement in pain (morphine tolerance)
- Patient has renal failure (when morphine metabolites accumulate)
- Pain is only partially responsive to morphine, e.g., ischaemic or neuropathic pain

Pharmacology of methadone is complex and its use should be under specialist supervision, preferably as an inpatient (seek specialist advice).

Buprenorphine Patch (Transtec)

Indicated for moderate to severe pain and not recommended for rapid titration for severe, uncontrolled pain.

Dosing

- Buprenorphine transdermal (Transtec) is approximately half as potent as transdermal fentanyl. e.g. fentanyl 25mcg/hr equivalent to 52.5 mcg/hr buprenorphine patches
- Available in 3 strengths of patches - 35, 52.5, 70mcg/hr patches
- Transtec patches have a duration of action of up to 96 hours. Therefore can be changed on the same two days every week e.g. Monday and Thursday.
- In opioid naïve patients, start 35mcg/hr patch
- Prescribe breakthrough medication equivalent to 1/6 th morphine 24 hour dose (see dose conversion chart) .
- To switch from or to other opioid, seek specialist advice .