Palliative Care
Guidelines for the use of drugs in symptom control

COVID-19 Version
This is the free 2020 version to help during the Covid-19 outbreak
Guidelines for the use of drugs in symptom control

These guidelines are not meant to replace the many available texts on the subject of palliative care. They are a summary of the current practice of specialists working in palliative care in the West Midlands Region.

These guidelines can be used for patients who are receiving care at home, or in hospitals, and should meet the needs of most patients. The medical and nursing staff of your local Specialist Palliative Care Team are available if further advice is required.

Some of the management strategies describe the use of drugs outside their licensed indications. They are, however, established and accepted good practice.

The drug information in this guideline is not exhaustive. Please refer to the current BNF for guidance.

The production of these guidelines remains independent, funded by the sales of previous editions. No external funding has been received. The guidelines have the approval of the West Midlands Palliative Care Physicians.
Patient & Family / Carer

- Specialist palliative care / hospice day care
- Primary Health Care team
- Multi-Professional specialist home care support and advice
- Multi-professional hospital support teams
- Bereavement care and counselling
- Nursing homes
- Nursing services, Marie Curie and sitters
- Specialist palliative care / hospice inpatient care
## Pain

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Pain

This chapter will guide you through assessing what may be the cause of your patient’s pain, and what measures and medication you may need to provide to help with pain relief.
Pain Assessment

• The assessment of pain is part of the holistic care of the patient.
• 30% of people with cancer have no pain and those with pain often have several types.
• Cancer pain may also be related to debility e.g. pressure ulcers.
• A patient who feels cared for may feel less pain and a patient free from pain is better placed to face his/her illness.
• 95% of pain in cancer can be well controlled.
• Patient and carer understanding of the use of their medication is vitally important in achieving good pain control.

Four types of cancer related pain

Visceral/soft tissue pain
- Opioid sensitive.
- Use the “ladder” see section: Analgesic Medication.

Bone pain
- Maybe NSAID sensitive.
- Partly opioid sensitive.
- Radiotherapy may help.

Nerve related
- Partly opioid sensitive.
- Adjuvant analgesics may often be needed.

Incident pain
This is a specific type of breakthrough pain related to a particular activity, e.g. micturition, wound dressing changes or movement.

Other considerations
Many pains are not cancer related but may be:
- Treatment related e.g. constipation, post radiotherapy.
- Coincident illness or condition e.g. arthritis, migraine.

Many factors influence the perception of pain. e.g. fear, loneliness, boredom.
If the patient’s pain appears not to respond, consider alternative causes of pain (spiritual, social or psychological factors).
1. By the clock

Cancer pain is continuous – Use regular analgesia with appropriate dose intervals – not just P.R.N.

2. By the ‘Ladder’

STEP 1
Non Opioid
    e.g. Paracetamol

STEP 2
Weak Opioid
    e.g. Codeine for mild to moderate pain + non opioid.

STEP 3
Strong Opioid
    e.g. Morphine for moderate to severe pain + non opioid.

Plus adjuvant analgesia if required e.g. NSAID / anticonvulsant / antidepressant (See Adjuvant Analgesia)

The ‘ladder’ has no ‘top rung’ as there is no maximum dose for strong opioids.

If pain is still a problem with high doses of strong opioid, e.g. greater than 300mg PO morphine equivalent /24hrs, or severe side effects, reconsider the cause of the pain, and/or seek specialist palliative care advice.

3. By the Mouth

The oral route is preferred for all steps of the analgesic ‘ladder’ unless there is a clinical reason why absorption of drugs given orally will not be effective.
Step 1: Paracetamol & NSAIDs

Paracetamol

**Therapeutic effects**
Analgesic | anti-pyretic

**Dose:** 500mg - 1g, 4–6 hourly. Max dose 4g in 24 hours

**Preparations:** Tablets/caplets/capsules: 500mg, 1g

**Dispersible tablets:** 500mg

**Oral suspension:** 120mg/5ml, 250mg/5ml, 500mg/5ml

**Suppositories:** 60mg, 125mg, 250mg, 500mg

**Injection for IV infusion:** 10mg/ml, 50ml (500mg) and 100ml (1g) vials

*Reduce dose if severe liver disease, alcohol dependence, malnutrition, low weight (<50kg), frail elderly.*

*Dose interval should be ≥ 6h if severe renal impairment.*

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Non-steroidal anti-inflammatory agents - NSAIDs

**Therapeutic effects**
Anti-inflammatory | Anti-pyretic | Analgesic

**Indications:** for analgesia in palliative care, including action as adjuvant analgesic
Bone pain | Soft tissue pain due to malignant infiltration | Arthritis | Possible role in early management of neuropathic pain.

Assess analgesic response after regular use for one week.

Patients considered to be at risk of NSAID induced gastroduodenal ulceration (age over 65 years, past history of peptic ulcer disease, concomitant oral steroids or anticoagulants, serious comorbidity) should receive a gastro-protective drug such as a proton pump inhibitor.

Use with extreme caution in renal failure. Fluid retention and renal function may all be worsened by NSAIDs. There is little evidence to suggest that any particular NSAID is safer than another in respect of renal toxicity.

NSAIDs may be considered for asthmatic patients unless they have a history of sensitivity.
Ibuprofen

Usually first line NSAID

**Adult Dose**
**Oral:** 200mg-400mg TDS

**Dosage Forms**
- **Tablet:** 200mg, 400mg, 600mg
- **MR tablet:** 800mg OD
- **MR capsule:** 300mg BD
- **Suspension:** 100mg/5ml
- **Granules:** 600mg sachet
- **Gel:** for topical use 5% and 10%

**Additional Information**
Current evidence suggests an increased risk of cardiovascular thrombotic events with NSAIDs. For those at risk consider naproxen or low dose ibuprofen (1200mg or less/24h).

Nabumetone

**Adult Dose**
**Oral:** 500mg – 1g BD

**Dosage Forms**
- **Tablet:** 500mg
- **Suspension:** 500mg/ml

**Additional Information**
It appears to be associated with a lower incidence of GI side effects.

In patients who are terminally ill the increased risk of renal, cardiovascular and GI toxicity associated with NSAIDs must be weighed against the potential for improved pain control.
**Diclofenac**

**Adult Dose**
Up to 150mg in 24 hours. Can be given via CSCI but not compatible with other drugs. **Injection can cause skin necrosis**

**Dosage Forms**
- **Tablet:** 25mg, 50mg
- **Modified Release tablets and capsules:** 75mg, 100mg
- **Dispersible tablets:** 50mg
- **Suppositories:** 12.5mg, 25mg, 50mg, 100mg
- **Injection:** 25mg/ml
- **Gel:** For topical use

**Additional Information**
Low GI Risk  |  Higher cardiac risk

For further guidance on the use of NSAIDs (including alternative parenteral agents) consult your local Specialist Palliative Care Team.
These opioids have low potency but can be a useful second step for patients with moderate pain.

It is seldom useful to change from one weak opioid preparation to another (unless to alter side effects). If regular doses do not provide adequate analgesia, move up the ladder to step 3.

Compound preparations of paracetamol and weak opioids may be useful.

Only preparations with higher doses of opioids (codeine 30mg, dihydrocodeine 20mg-30mg) should be used, as the lower strength preparations produce opioid side effects with little analgesia.

## Codeine

### Adult Dose

30mg–60mg 4 hourly  |  Max 240mg in 24 hours

### Dosage Forms

- **Tablets:** 15mg, 30mg, 60mg
- **Syrup:** 25mg/5ml, 15mg/5ml linctus, 25mg/5ml oral solution
- **Injection:** 60mg/ml (CD)

### Additional Information

*Caution in renal impairment / Can cause constipation*
Co-codamol 30/500
(Codeine 30mg with Paracetamol 500mg)

**Adult Dose**
2 tablets 4–6 hourly  |  Max 8 in 24 hours
*(cautions for paracetamol dose apply)*

**Dosage Forms**
- Tablets, capsules, effervescent tablets and granules: 30/500
- Granules: 60/1000 – max 4 sachets daily

**Additional Information**
*Caution in renal impairment / Can cause constipation*

Dihydrocodeine

**Adult Dose**
30mg–40mg 4 hourly  |  Max 240mg in 24 hours
*(higher dose may be associated with more side effects)*

**Dosage Forms**
- Tablets: 30mg, 40mg
- MR tablets: 60mg
- Oral solution: 10mg in 5ml
- Injection: 50mg/ml (CD)

**Additional Information**
*Caution in renal impairment / Can cause constipation*
**Step 2: Weak Opioids (continued)**

### Dihydrocodeine 20mg with Paracetamol 500mg

**Adult Dose**
2 tablets every 4–6 hours | Max 8 in 24 hours
*(cautions for paracetamol dose apply)*

**Dosage Forms**
- **Tablets**: 20/500

**Additional Information** *Caution in renal impairment / Can cause constipation*

### Dihydrocodeine 30mg with Paracetamol 500mg

**Adult Dose**
2 tablets every 4–6 hours | Max 8 in 24 hours
*(cautions for paracetamol dose apply)*

**Dosage Forms**
- **Tablets**: 30/500

**Additional Information** *Caution in renal impairment / Can cause constipation*

### Tramadol

**Adult Dose**
50mg–100mg 4 hourly | Max 400mg in 24 hours

**Dosage Forms**
- **Capsules**: 50mg (CD)
- **Soluble tablets**: 50mg (CD)
- **Orodispersible tablets**: 50mg (Zamadol Melt®) (CD)
  - MR 12 hourly tablets: 50mg, 100mg, 150mg, 200mg (CD)
  - MR 24 hourly tablets: 150mg, 200mg, 300mg, 400mg (CD)
  - **Injection**: 50mg/ml (CD)

**Additional Information** *Caution in renal impairment / Can cause constipation*
Step 3: Strong Opioids

First line: Morphine remains the drug of choice

1. Gain control of pain
   • ‘Immediate’ release morphine (oral solution or tablets) gives greatest flexibility for dose titration.
   • Starting dose 2.5mg–10mg four-hourly. In the opioid naïve, elderly or those with renal impairment use smaller doses e.g. 2.5mg four-hourly, with close monitoring.
   • Additional P.R.N. doses at the same starting dose may be prescribed up to hourly.
   • Review the total daily dose of morphine every 24 hours. Titrate the dose to achieve pain relief by increasing in 30–50% increments per day.

   In patients with less severe pain, or where circumstances dictate, morphine may be initiated as a modified release preparation at the appropriate dose.

   Use conversion table later in this section to determine the appropriate starting dose.

2. Reassess pain regularly

   A ‘log’ of treatment kept by patients and carers is helpful in titration. There is no ‘maximum’ dose if pain is morphine responsive.
   Specialist palliative care advice should be sought in the following circumstances:
   • Rapidly escalating dose of morphine
   • Morphine exceeds 300mg po in 24 hours
   • If the patient develops adverse effects e.g. opioid toxicity (signs are respiratory depression, increasing drowsiness, confusion, myoclonic jerks and hallucination)
   • If alternative opioid being considered because of toxicity
      
      See conversion table later in this section.

   Always prescribe a laxative when initiating opioid and continue to review bowel habit.
3. Maintenance

Once pain is controlled there is a choice of options for maintenance:

- Continue regular immediate release Morphine.
- Change to 12 hourly modified release Morphine.

To change from immediate release morphine to modified release Morphine, add up the amount of Morphine used in 24h and divide the 24h total dose of Morphine by 2.

E.g. Patient on 10mg immediate release Morphine 6 times in 24 hours: Total daily dose = 60mg/24h

Therefore Morphine Sulfate modified release would be: \( \frac{60}{2} = 30 \text{mg} \) 12 hourly.

- Patients on modified release opioids should always have available immediate release opioid prescribed p.r.n. for episodes of breakthrough pain.
- The recommended dose of immediate release opioid (usually Morphine) prescribed p.r.n. for breakthrough pain is the equivalent of up to 1/6th of the total 24-hour opioid dose.

A patient should never be prescribed more than one modified release opioid at a time.

For example:
A patient taking Morphine Sulfate MR 30mg BD, the breakthrough dose of Morphine Sulfate IR is:
30mg + 30mg = 60mg  |  60mg ÷ 6 = 10mg

Therefore the breakthrough pain dose of Morphine Sulfate immediate release is 10mg P.R.N.
- If the regular dose of opioid is increased, ensure that the p.r.n. breakthrough dose is increased appropriately so that it remains 1/6th of the total daily dose of regular opioid.
- Incident pain (e.g. exacerbations of pain on movement) may require faster acting analgesia.
- Ensure patients and their carers understand the use of the opioids they are taking and that doses are reviewed regularly.
4. If further pain develops

Reassess cause of pain and treat appropriately (see Pain Assessment).

If there is consistent need for frequent breakthrough analgesia, and the pain is opioid sensitive, increase the total daily opioid dose by 30–50% and reassess.

If the proposed dose increase is greater than 30–50% seek advice from specialist palliative care.

5. Incident pain

First line choice of analgesia for predictable breakthrough pain related to particular event e.g. pain related to movement with a pathological fracture where there is no fixation option, should be an immediate release opioid used in anticipation of the pain, usually the same opioid as that they have prescribed as a modified release preparation. Immediate release preparations are available as described previously.

They should be used in advance of the expected pain and it maybe that increasing the background analgesia may not improve pain control. Seek specialist palliative care advice if needed.

Morphine preparations

Immediate release oral preparations

<table>
<thead>
<tr>
<th>Morphine Sulfate tablets</th>
<th>Sevredol® tablets: 10mg (blue), 20mg (pink), 50mg (pale green) (56 tablet pack)</th>
</tr>
</thead>
</table>
| Morphine Sulfate solution | **Oramorph® oral solution:** 10mg in 5ml, (100ml, 300ml & 500ml)  
**Oramorph® concentrated oral solution:** 100mg in 5ml (30ml & 120ml both sugar-free and alcohol-free with calibrated dropper) |
| Morphine Sulfate suppositories | **Suppositories:** 10mg, 15mg, 20mg, 30mg (12 suppository pack) |
### 12-hourly Morphine Modified Release oral preparations

<table>
<thead>
<tr>
<th>Product</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zomorph® Capsule*</td>
<td>10mg (yellow/clear), 30mg (pink/clear), 60mg (orange/clear), 100mg (white/clear), 200mg (clear) (60 capsule pack)</td>
</tr>
<tr>
<td>Morphgesic® SR tablets</td>
<td>10mg (buff), 30mg (violet), 60mg (orange), 100mg (grey) (60 tablet pack)</td>
</tr>
<tr>
<td>MST Continus® Tablets</td>
<td>5mg (white), 10mg (brown), 15mg (green), 30mg (purple), 60mg (orange), 100mg (grey), 200mg (green) (60 tablet pack)</td>
</tr>
<tr>
<td>MST Continus® Suspension</td>
<td>20mg, 30mg, 60mg, 100mg, 200mg (30 sachet pack) (sachets of granules to mix with water)</td>
</tr>
</tbody>
</table>

### 24-hour Morphine Modified Release oral preparations

<table>
<thead>
<tr>
<th>Product</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>MXL® Capsules*</td>
<td>30mg (light blue), 60mg (brown), 90mg (pink), 120mg (green), 150mg (blue), 200mg (red-brown) (28 capsule pack) RARELY USED</td>
</tr>
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</table>

### Morphine Injection

<table>
<thead>
<tr>
<th>Product</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine Sulfate</td>
<td>10mg/ml <strong>1ml ampoules</strong>, 15mg/ml <strong>1ml ampoules</strong>, 20mg/ml 1ml ampoules, 30mg/ml (in 1ml and 2ml ampoules) (5 ampoule pack)</td>
</tr>
</tbody>
</table>

*Capsules containing slow release pellets can be opened and sprinkled onto soft food*
Side Effects of Opioids

Certain side effects are common to all opioids. These are readily managed by appropriate dosing and concomitant use of other agents such as laxatives and anti-emetics. True allergic reactions are rare.

Constipation

Must be anticipated and prevented in all patients on weak or strong opioids. Constipation may be less severe in some patients with transdermal Fentanyl.

Regular stimulant laxatives must be commenced at the same time as weak or strong opioids. The dose of laxative required may increase as the dose of opioid increases (See Constipation chapter).

Nausea

Is a common problem (for around 30%) during the first few days of treatment. If it occurs, haloperidol or metoclopramide are suitable anti-emetics. (See Nausea and Vomiting chapter).

Psychological Addiction

Is rare in patients taking opioids for their analgesic effects.

Tolerance (i.e. to the analgesic effects)

May occur, but an increase in dose requirement often reflects an increase in pain due to advancing disease. For patients who exhibit tolerance to a particular strong opioid, switching to another strong opioid might be helpful. Seek specialist palliative care advice.
Side Effects of Opioids (continued)

Respiratory Depression
Is rarely a risk when doses are increased by appropriate increments and the patient is reviewed accordingly. Pain is a physiological antagonist to the central depressant effects of opioids. If pain is relieved by alternative methods e.g. radiotherapy or nerve block, a reduction in opioid dose will be required.

Other recognised side effects are:

- Dry mouth
- Itching
- Sweating
- Hallucinations
- Myclonic jerks

*The latter two are part of a multifactorial syndrome known as neurotoxicity.*

Neurotoxicity
Causes a spectrum of symptoms, from mild confusion or drowsiness to hallucinations, delirium, and seizures. **Seek specialist advice if opioid induced.**

Sedation
May occur with the first few doses, but then can lessen. Caution this may impair fitness to drive, medical advice is advised regarding this if appropriate. Psychostimulant medications can be prescribed to help with this, seek specialist advice.

Myoclonus
Twitching or clonic spasm of a muscle or group of muscles. It can be seen in any muscle group/limbs, may vary in severity and can be sporadic or continuous. Consider reducing opioid dose and add an adjuvant or switch to different opioid and consider reduce dose of new opioid by 20-30%.
Hallucinations (usually visual)

Reduce opioid dose and add an adjuvant or switch to different opioid and consider reduce dose of new opioid by 20-30%, treat symptomatically with Haloperidol.

Delirium

Confusion / Agitation/ Cognitive impairment
Treat symptomatically with Haloperidol/Levomepromazine or newer atypical anti-psychotic in the short term. Consider reducing opioid dose and add an adjuvant (preferably non-psychoactive adjuvant) or switch to different opioid and consider reduce dose of new opioid by 20-30%.

Hyperalgesia / Allodynia:

• An excessive sensitivity to pain (usually that is already present).
• Allodynia: Ordinary painless (non-noxious) stimulus/sensation is experienced as being painful.

Consider reducing opioid dose and add an adjuvant or switch to different opioid and consider reduce dose of new opioid by 20-30%.

If side-effect profile remains too troublesome, a switch to an alternative second line opioid should be considered.

Seek specialist palliative care advice.
Relative Doses of Opioids

Alternative strong opioids may be used to try to improve compliance or the side-effect profile for patients. Their use must be individually tailored and the following tables should be used as guidance only together with information in the following text.

Specialist palliative care advice is usually needed when changing from one strong opioid to another. Usually convert to a slightly lower equivalent dose and provide appropriate p.r.n. breakthrough analgesia for titration.

Palliative Care: opioid equianalgesic dose conversions

- These are approximate dose conversions, caution is always necessary but particularly when converting at high doses and when there has been a recent rapid escalation of initial opioid; individual titration is necessary in order to optimise pain control after opioid switching.

- A switch to methadone should only be undertaken by practitioners experienced in its use; equianalgesic dose conversions cannot be recommended for this opioid because of the wide inter-individual variation in pharmacokinetics of methadone.

- Conversion ratios between oxycodone and other opioids in particular has some regional variation in clinical practice which is reflected in the table opposite. The table assumes an oxycodone to morphine ratio of 1:1.5.
<table>
<thead>
<tr>
<th>Opioid</th>
<th>Conversion Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Codeine</td>
<td>240 mg per 24 hrs = Oral Morphine 24 mg per 24 hrs</td>
</tr>
<tr>
<td>Oral Tramadol</td>
<td>400 mg per 24 hrs = Oral Morphine 40 mg per 24 hrs</td>
</tr>
<tr>
<td>Transdermal Fentanyl</td>
<td>25 micrograms/hr patch = Oral Morphine 50 mg per 24 hrs</td>
</tr>
<tr>
<td>SC / IV Morphine</td>
<td>7.5 mg = Oral Morphine 15 mg</td>
</tr>
<tr>
<td>SC / IV Diamorphine</td>
<td>5 mg = Oral Morphine 10 mg</td>
</tr>
<tr>
<td>SC Oxycodone</td>
<td>5 mg = Oral Oxycodeone 15 mg</td>
</tr>
<tr>
<td>SC Oxycodeone</td>
<td>10 mg = Oral Hydromorphone 15 mg</td>
</tr>
<tr>
<td>SC Hydromorphone</td>
<td>10 mg = SC Diamorphine 10 mg</td>
</tr>
<tr>
<td>SC Alfentanil</td>
<td>1 mg = SC Diamorphine 10 mg</td>
</tr>
</tbody>
</table>

10 x weaker than Oral Morphine
100 x stronger than Oral Morphine
2 x stronger than Oral Morphine
3 x stronger than Oral Morphine
1.5 x stronger than Oral Morphine
2 x stronger than Oral Oxycodeone
7.5 x stronger than Oral Oxycodeone
10 x stronger than SC Diamorphine
### Quick Check Table

**Current opioid and route**  
*(converting from ...)*

<table>
<thead>
<tr>
<th>Current Opioid</th>
<th>oral Codeine (max daily dose: 240 mg)</th>
<th>oral Tramadol (max daily dose: 400 mg)</th>
<th>oral Morphine</th>
<th>oral Oxycodeone</th>
<th>SC Morphine</th>
<th>SC Oxycodeone</th>
<th>SC Diamorphine</th>
<th>oral Hydromorphone</th>
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<th>SC Alfentanil</th>
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<td>× 1.5</td>
<td>× 1.5</td>
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<td>× 5</td>
<td>× 10</td>
<td>× 10</td>
<td>× 10</td>
<td>SC Diamorphine</td>
</tr>
<tr>
<td>oral Hydromorphone</td>
<td>× 2.5</td>
<td>× 2.5</td>
<td>× 2</td>
<td>× 2</td>
<td>× 4</td>
<td>× 10</td>
<td>× 10</td>
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<td>oral Hydromorphone</td>
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<tr>
<td>SC Hydromorphone</td>
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<td>× 10</td>
<td>× 10</td>
<td>× 10</td>
<td>× 10</td>
<td>SC Hydromorphone</td>
</tr>
<tr>
<td>SC Alfentanil</td>
<td>× 2</td>
<td>× 2</td>
<td>× 2</td>
<td>× 2</td>
<td>× 2</td>
<td>× 10</td>
<td>× 10</td>
<td>× 10</td>
<td>× 10</td>
<td>SC Alfentanil</td>
</tr>
</tbody>
</table>

**NOTE:**

Choose the opioid you are converting from in the columns on the left and the opioid you are converting to in the rows below.

The conversion factor is detailed where the relevant column and row meet.

Transdermal opioid preparations not included in this table.

### New opioid and route  
*(converting to ...)*

- oral Codeine (max daily dose: 240 mg)
- oral Tramadol (max daily dose: 400 mg)
- oral Morphine
- oral Oxycodeone
- SC Morphine
- SC Oxycodeone
- SC Diamorphine
- oral Hydromorphone
- SC Hydromorphone
- SC Alfentanil
Converting between morphine and diamorphine

Approximate equivalent doses of oral morphine and subcutaneous morphine and subcutaneous diamorphine:

3mg oral morphine = 1.5mg SC morphine = 1mg SC diamorphine

These conversion ratios apply to PRN and regular dosing.

Example 1
60mg morphine slow release tablet BD PO
= total daily dose oral morphine 120mg PO
= 60mg SC morphine/24 hrs
= 40mg SC diamorphine/24 hrs

Example 2
30mg Oramorph PO PRN
= 15mg SC morphine PRN
= 10mg SC diamorphine PRN

Converting between morphine and transdermal patches

See section: Transdermal opioids

Diamorphine

1mg SC diamorphine = 3mg oral morphine = 1.5mg SC morphine

Diamorphine was traditionally used as the first line injectable strong opioid as it is more water soluble than morphine. Morphine Sulfate injection is now used in many centres as the first line injectable strong opioid.

Diamorphine preparations:
Injection: 5mg, 10mg, 30mg, 100mg, 500mg in packs of 5 ampoules.
10mg oral oxycodone = 5mg SC oxycodone
10mg oral oxycodone = 15mg–20mg oral morphine = 7.5mg–10mg SC morphine

Oxycodone has good oral bioavailability. The example above illustrates the dose conversion when oxycodone is regarded as being 1.5 – 2 times more potent than oral morphine. Oxycodone is an alternative option if morphine is not tolerated. Care should be taken to ensure clarity when prescribing immediate release capsules or modified release tablets. The modified release tablets also deliver a small dose which is immediate release.

**Oxycodone preparations:**

- **Immediate release (OxyNorm®) capsules, for p.r.n. use:**
  5mg (orange/beige), 10mg (white/beige), 20mg (pink/beige) (packs of 56)
- **Oral solution (OxyNorm®):** 1mg/ml (250ml)
- **Concentrated oral solution (OxyNorm®):** 10mg/ml (120ml)
- **Modified release tablets (OxyContin®) for 12-hourly administration:**
  5mg – light blue, 10mg – white, 15mg – grey, 20mg – pink, 30mg – brown, 40mg – yellow, 60mg – red, 80mg – green, 120mg – purple (packs of 56)
- **Injection (Oxynorm® injection) 10mg/ml:** 1ml, 2ml ampoules. 50mg/ml: 1ml ampoules
- **Targinact®:** The opioid antagonist naloxone is added to counteract opioid induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut.

*Seek advice from specialist palliative care before prescribing (See Constipation chapter).*
1.3mg oral hydromorphone = 0.6mg SC hydromorphone = 10mg oral morphine = 5mg SC morphine

An alternative if morphine is not tolerated because of adverse effects under specialist guidance. Immediate and modified release capsules may be opened and sprinkled onto food.

Hydromorphone preparations (Palladone®):

• Immediate release capsules:
  1.3mg (orange/clear), 2.6mg (red/clear) for p.r.n. use (packs of 56)

• Modified release capsules:
  2mg (yellow/clear), 4mg (pale blue/clear), 8mg (pink/clear), 16mg (brown/clear), 24mg (dark blue/clear) for 12-hourly administration

• Hydromorphone injection (Martindale Products):
  10mg/ml, 20mg/ml, 50mg/ml (unlicensed, available on named patient basis)

1mg SC alfentanil = 10mg SC diamorphine = 30mg oral morphine = 15mg SC morphine

Suitable parenteral opioid for use in advanced renal disease under specialist guidance. Alfentanil has a short duration of action which limits its use for breakthrough analgesia.

**Note very different dose conversions than fentanyl (see below for more info).**

N.B. Alfentanil and fentanyl are different drugs.

Alfentanil preparations:

Injection (Rapifen®) 500 microgram per ml, 2ml, 10ml ampoules

Intensive Care Injection 5mg per ml, 1ml ampoules to be diluted before use.


Relative Doses of Opioids (continued)

Methadone

Always seek specialist advice.

Fentanyl (Injectable) – Seek specialist palliative care advice

150 micrograms SC fentanyl = 10 mg SC diamorphine = morphine 30 mg oral = 15 mg SC morphine

Suitable parenteral opioid for use in advanced renal disease under specialist guidance.

Also available as a transdermal patch see section: Transdermal Fentanyl and as immediate release preparations (buccal, intranasal, sublingual and submucosal formulations) for incident pain see section: Transmucosal Fentanyl Preparations.

Note very different dose conversions than Alfentanil (see above for more information).

N.B. Alfentanil and Fentanyl are different drugs.

Please be aware that when prescribing a syringe driver/pump for fentanyl that the dose is micrograms per 24 hours whilst when administering a transdermal patch the dose is micrograms per hour.

Fentanyl injectable preparations:

Injection (generic) 50 microgram per ml, 2ml and 10 ml ampoules Fentanyl (Sublimaze®) 50 microgram per ml, 10 ml ampoules
A novel analgesic combining mu opioid properties and noradrenaline reuptake inhibition. This can be helpful for pain that is mixed and has an element of nerve/neuropathic pain associated with it. At the time of writing there is limited experience of this in palliative care.

*Seek specialist palliative care advice.*

50mg Tapentadol = 15-20mg oral morphine

**Tapentadol preparations:**

**Immediate release (Palexia®):**
- Tablets, f/c, tapentadol (as hydrochloride) 50mg (white), 75mg (yellow)
- Oral solution, tapentadol (as hydrochloride) 20mg/ml

**Modified Release (Palexia®SR):** Tablets, f/c, 50mg, 100mg, 150mg, 200mg, 250mg

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**Transdermal Opioids**

*Useful in a number of cases*

- Patients have an opioid responsive pain.
- Pain control is stable, and as an alternative to morphine, (i.e. a 2nd line strong opioid).
- Where the patient is unable to tolerate morphine, and/or unable to take oral medication, e.g. dysphagia, vomiting.
- Where drug compliance needs to be improved.

**BUT NOT** in situations where the pain is acute, and rapid dose titration is required.
When using transdermal opioid patches

When applying a new patch consider writing the date (and time) on the patch in order to identify when the next patch is due to be applied. This may be useful as an aide memoir or when the patient is moving between different care settings.

Cautions

- If the patient has not had strong opioids previously.
- In patients previously on doses of oral morphine (or equivalent opioid) less than 60mg/24hr.
- In pyrexial patients where rate of absorption may be unpredictable.
- With poor adherence of patches, e.g. patient with sweats or when applied to the chest wall of patients who are cachectic.
- During the dying phase – seek specialist palliative care advice.

Approximate equivalent doses of transdermal opioids

<table>
<thead>
<tr>
<th>Buprenorphine transdermal patch strength (micrograms per hour)</th>
<th>Approximate* oral morphine dose (mg in 24hrs)</th>
<th>Approximate oral codeine dose (mg in 24hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>12</td>
<td>120</td>
</tr>
<tr>
<td>10</td>
<td>24</td>
<td>240</td>
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<tr>
<td>20</td>
<td>48</td>
<td></td>
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<tr>
<td>35</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>52.5</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>168</td>
<td></td>
</tr>
</tbody>
</table>

*Approximate mid-range oral morphine doses are described here; prescribers should note that manufacturers describe a range of oral morphine doses for each strength of patch.
<table>
<thead>
<tr>
<th>Fentanyl transdermal patch strength (micrograms per hour)</th>
<th>Approximate* oral morphine dose (mg in 24hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>25</td>
<td>60</td>
</tr>
<tr>
<td>50</td>
<td>120</td>
</tr>
<tr>
<td>75</td>
<td>180</td>
</tr>
<tr>
<td>100</td>
<td>240</td>
</tr>
</tbody>
</table>

*Approximate mid-range oral morphine doses are described here; prescribers should note that manufacturers describe a range of oral morphine doses for each strength of patch.
Transdermal Fentanyl

- Fentanyl is a strong opioid, available in a patch applied to the skin, for transdermal administration over 72 hours for chronic cancer pain.
- Both matrix and reservoir patch formulations are available.
- Patches should be prescribed by their brand name or specify ‘matrix’ or ‘reservoir’ to avoid confusion.

Contraindications:
Sensitivity to fentanyl or silicone medical adhesive.

Initial dose
Generally, the transdermal route is not recommended in opioid-naïve patients. Alternative routes of administration (oral, parenteral) should be considered. To prevent overdose it is recommended that opioid-naïve patients receive low doses of immediate-release opioids (eg, morphine, hydromorphone, oxycodone, tramadol, and codeine) that are to be titrated until an analgesic dosage equivalent to transdermal fentanyl with a release rate of 12 micrograms/hour or 25 micrograms/hour is attained. Patients can then switch to Transdermal Fentanyl patches.

In the circumstance in which commencing with oral opioids is not considered possible and transdermal fentanyl is considered to be the only appropriate treatment option for opioid-naïve patients, only the lowest starting dose (i.e. 12 micrograms/hour) should be considered. In such circumstances, the patient must be closely monitored. The potential for serious or life-threatening hypoventilation exists even if the lowest dose of transdermal fentanyl is used in initiating therapy in opioid-naïve patients.

In patients currently taking opioid analgesics, the starting dose of transdermal fentanyl should be based on the daily dose of the prior opioid. To calculate the appropriate starting dose of transdermal fentanyl, convert from the oral opioid dose using the table.
Patch Application

- Patch should be applied to dry, non-hairy, non-irritated, non-irradiated skin on torso or upper arm. Replacement patch should be sited on a different area. Avoid previous area for several days.
- After application of the first patch, plasma levels rise for 24 hours, analgesic levels are reached by 6-12 hours and a steady state is reached by the time of application of the second patch.
- The patch should be replaced every 72 hours.
- When converting doses greater than 100 micrograms per hour fentanyl seek specialist palliative care advice.

Starting fentanyl patches, converting from oral morphine

An immediate release opioid preparation should always be available P.R.N. for breakthrough pain.

<table>
<thead>
<tr>
<th>Original regular oral morphine dosing frequency:</th>
<th>Fentanyl patch to be applied:</th>
<th>Original regular oral morphine dose continued after patch application for:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate release regular morphine (liquid or tablets)</td>
<td>At any convenient time</td>
<td>12 to 24 hours</td>
</tr>
<tr>
<td>12-hourly modified release morphine</td>
<td>At the same time as taking the final 12 hourly morphine dose</td>
<td>No further modified release morphine</td>
</tr>
<tr>
<td>24-hourly modified release morphine</td>
<td>12 hours after taking the final 24-hourly morphine dose</td>
<td>No further modified release morphine</td>
</tr>
</tbody>
</table>
Switching to an alternative opioid from transdermal fentanyl

Before removing an opioid patch and changing to an alternative opioid consider carefully the reasons for doing this.

Carrying out this conversion correctly can be challenging and it is advisable to seek specialist palliative care advice.

On removal of the patch, it takes approximately 17 hours for serum concentration of fentanyl to reduce by 50% and this must be considered when converting. Different methods of conversion are practised. REVIEW the patient regularly during the changeover period.

If converting a patient with renal failure from transdermal fentanyl to an alternative opioid, always seek specialist advice.

Switching to alternative opioid when patient’s pain is controlled:

**EITHER**

Change to oral opioid

- Remove patch and document the time of removal.
- Prescribe a starting dose of oral opioid at the approximate equivalent dose (for that patch) to be commenced 12 hours after the time the patch has been removed.
- Ensure adequate dose of oral immediate release opioid is available p.r.n. for breakthrough pain.

**OR**

Change to subcutaneous opioid e.g. diamorphine or morphine or oxycodone infusion.

- Remove patch and document the time of removal.
- Prescribe a starting dose of subcutaneous opioid over 24 hours at the approximate equivalent dose (for that patch) to be commenced 12 hours after the time the patch has been removed.
- Ensure adequate dose of subcutaneous opioid is available PRN for breakthrough pain.
Discontinuing the patch if the patient’s pain is uncontrolled

Consider why the pain was not responding and address any other issues. Consider seeking specialist palliative care advice.

Administer an immediate release opioid (e.g. p.r.n. oral morphine or SC opioid). Re-titratre new analgesics to the patient’s requirements.

Continuing the patch if the patient’s pain is uncontrolled:

In some areas, it is best practice to continue with fentanyl patch administration, adding an appropriate dose of opioid via the subcutaneous route. Consult local guidelines.

Transdermal fentanyl patch preparations:

It is advised that transdermal opioid patches should be prescribed by their brand name where possible.

For approximate equivalent doses see table on page 33.

Two different transdermal formulations are currently available, reservoir and matrix:

- Reservoir patch e.g. Fentalis® and Tilofyl® fentanyl is contained within a reservoir and the release of fentanyl is controlled by a rate limiting membrane.

- Matrix patch e.g. Durogesic D-Trans® and Matrifien® the fentanyl is easily formulated throughout a drug-in-adhesive matrix and the release of fentanyl is controlled by the physical characteristics of the matrix.
Transdermal Buprenorphine

- Certain side effects are common to all opioids. These are readily managed by appropriate dosing and concomitant use of other agents such as laxatives and anti-emetics.
- True allergic reactions are rare.

Buprenorphine is a partial opioid agonist. The transdermal preparation releases the patch strength in micrograms per hour of buprenorphine over several days.

A transdermal buprenorphine patch formulation containing a lower dose of buprenorphine is available (BuTrans®, releasing between 5 and 20 micrograms per hour of buprenorphine over 7 days). These buprenorphine patches may be of some benefit in patients who have difficulties in taking oral medication and have low analgesic requirements.

The manufacturers recommend changing the Transtec® patch twice weekly. It takes at least 24 hours for full analgesic effect. After removal, plasma concentrations of buprenorphine will be halved after 30 hours.

Transdermal opioid preparations must be prescribed by brand name.

Transdermal buprenorphine patch preparations:

- BuTrans® patches releasing ‘5’, ‘10’ or ‘20’ micrograms of buprenorphine per hour over 7 days.
- Hapoctasin® patches releasing ‘35’, ‘52.5’, or ‘70’ micrograms buprenorphine per hour over 3 days.
- Transtec® patches releasing ‘35’, ‘52.5’, or ‘70’ micrograms buprenorphine per hour over 4 days.

For approximate equivalent doses see table on page 32
Transmucosal Fentanyl Preparations

Transmucosal fentanyl preparations are licensed for breakthrough pain in patients receiving opioid therapy for chronic cancer pain.

Such patients should already be receiving a strong opioid for background pain and should have been receiving oral morphine of at least 60mg /24hours (or equivalent dose of an alternative strong opioid) for the previous week before being commenced on an immediate release fentanyl preparation.

*Seek specialist palliative care advice before prescribing immediate release fentanyl preparations.*

Various transmucosal fentanyl preparations are available with similar onset of action and alternative routes of delivery:

- buccal tablets
- intranasal spray
- sublingual tablets
- lozenges
- buccal films

The most appropriate route of administration will depend on the patient’s preference, their manual dexterity and other clinical circumstances. These medications all require careful individual dose titration according to the product literature and patient response.
Transmucosal fentanyl citrate preparations:

Oro-mucosal products:

**Abstral®:**
100, 200, 300, 400, 600 and 800 microgram sublingual tablets

**Actiq® lozenges with applicator:**
200, 400, 600, 800, 1200, 1600 micrograms buccal lozenges

**Breakyl® film (buccal):**
200, 400, 800 microgram films

**Effentora® buccal/sub-lingual tablets:**
100, 200, 400, 600 and 800 microgram tablets

**Recivit® sub-lingual tablets:**
133, 267, 400, 533, 800 microgram tablets
Adjuvant Analgesia

These medications are usually used in conjunction with classical analgesics.

Bone pain

Options include:

- Non steroidal anti-inflammatories: See NSAID section.
- Steroids: See Steroid section.
- Radiotherapy
- Bisphosphonates/Denosumab

In all cases seek specialist advice if needed.

Raised intracranial pressure

Consider the use of steroids See Steroid section.

Hepatomegaly

Consider the use of Steroids See Steroid section. | See NSAID section.

Enlarging tumours

Consider radiotherapy: Seek specialist advice
Muscle spasm

**Diazepam**

**Oral:** 2mg–10mg daily increase if necessary

**Preparations:**
- **Tablets:** 2mg, 5mg and 10mg
- **Oral solution:** 2mg/5ml

**Contraindicated in:**
- Severe or acute respiratory insufficiency/depression
- Sleep apnoea syndrome
- Severe hepatic insufficiency

**Baclofen**

**Oral:** 5mg TDS after food (gradually increase to a max total daily dose of 30mg if necessary)

**Preparations:**
- **Tablets:** 10mg
- **Sugar free oral solution:** 5mg/5ml

Cautioned use in epilepsy and psychotic disorders, schizophrenia depressive or manic disorders, confusional states or Parkinson’s disease may be exacerbated by treatment with baclofen.
Smooth muscle spasm / colic

Hyoscine butylbromide

**Dose SC:** 20mg stat, or SC infusion 60mg up to 120mg in 24 hours

Tablets are poorly absorbed

**Preparations:**

**Tablets:** 10mg

**Injection:** 20mg/ml

Contraindicated in patients with myasthenia gravis, megacolon, narrow angle glaucoma, tachycardia, prostatic enlargement with urinary retention, mechanical stenoses in the region of the gastrointestinal tract or paralytic ileus.

Glycopyrronium

**Dose SC:** 200 micrograms stat and SC infusion 600 mcg up to 1200 mcg in 24 hours

Contraindicated in patients with myasthenia gravis, megacolon, narrow angle glaucoma, tachycardia, prostatic enlargement with urinary retention, mechanical stenoses in the region of the gastrointestinal tract or paralytic ileus.

**NB:** Glycopyrronium is more sedating than hyoscine butylbromide
**Tenesmus**
Treat initially as for Neuropathic pain (see separate section below). Additional option is Nifedipine.

**Nifedipine**

**Oral:** 5mg–20mg BD

**Preparations:**
- **Capsules:** 5mg, 10mg
- **Tablets SR:** 10mg, 20mg

There is a risk of rapid onset hypotension with immediate release preparations and reflex tachycardia therefore immediate release preparation should not be used in patient with angina.

Should be brand prescribed due to non-bioequivalence.

Also consider nerve block.

**Neuropathic pain**

**Step 1**
Antidepressant (tricyclic) e.g. Amitriptyline OR anticonvulsant

**Step 2**
Antidepressant (tricyclic) PLUS anticonvulsant

For nerve compression pain consider steroids also consider Transcutaneous Nerve Stimulation (TENS) or nerve block.
Neuropathic agents

Amitriptyline

**Oral:** 10mg–25mg at night increasing slowly up to 75mg nocte

**Preparations:**
- **Tablets:** 10mg, 25mg, 50mg
- **Solution:** 10mg/5ml, 25mg/5ml and 50mg/5ml

Gabapentin

**Oral:** 100mg–300mg nocte increasing gradually to maximum daily dose of 900mg–1800mg in divided doses.

**Preparations:**
- Capsules 100mg, 300mg, 400mg (Can be opened and sprinkled on food or administered via PEG tube for patients with impaired swallow)
- Tablets 600mg, 800mg

Caution: Dose adjust in renal failure (See chapter: Renal Failure)

Pregabalin

**Oral:** 150mg daily in divided doses (25mg–50mg bd in frail patients) increasing gradually to maximum daily dose of 600mg in divided doses.

**Preparations:**
- Capsules 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 300mg

Caution: Dose adjust in renal failure (See chapter: Renal Failure)
**Sodium Valproate**

**Oral Starting Dose:** 200mg m/r PO, increase as per BNF

**Preparations:**
- **Tablet EC** 200mg and 500mg
- **Crushable tablets** 100mg
- **MR tablets** 200mg, 300mg, 500mg
- **Oral Solution** 200mg/5ml

**Caution:** Not for use in women and girls of childbearing potential.

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**Carbamazepine**

**Oral:** 100mg BD increasing gradually if tolerated up to 1200mg daily in divided doses if necessary.

**Preparations:**
- **Tablets** 100mg, 200mg, 400mg
- **Chewable tablets** 100mg and 200mg
- **MR Tablets** 200mg, 400mg
- **Oral liquid ‘sugar free’** 10mg/5ml
- **Suppositories** 125mg (equivalent to 100mg tablets)

**Monitoring:**
Check LFT's and FBC once started.

**Caution:**
Potent inducer of CYP3A4 therefore, can reduce the levels of buprenorphine, methadone, paracetamol (long term administration of carbamazepine and paracetamol (acetaminophen) may be associated with hepatotoxicity), tramadol.

Please see the current BNF for all other drug interactions.
Clonazepam

**Oral:** 500 micrograms nocte; increasing gradually to 2mg nocte

**Preparations:**
**Tablets** 500 micrograms and 2mg

Use with caution in patients with chronic pulmonary insufficiency, or with renal or hepatic function impairment, and in the elderly or debilitated. In these cases dosage should generally be reduced.

**Advice:** to start small and titrate up.

Duloxetine

**Oral:** 60mg OD (consider 30mg OD orally in frail patients) increasing gradually up to maximum daily dose of 120mg in divided doses.

**Preparations:**
**Cymbalta®** 30mg capsules and 60mg capsules

Contraindicated in severe renal impairment (creatinine clearance <30 ml/min) and severe hypertension.

Monitor blood pressure and heart rate.

Lidocaine plaster

Consider in localised neuropathic pain one 5% plaster; use up to three plasters over 12hrs per 24hrs

**Preparations:**
**Versatis®** 5% medicated plaster
Capsaicin

Consider in localised neuropathic pain

Preparations:

- **Cream: Topical**: 0.025% and 0.075% cream. Apply using gloves 2 to 4 times daily.
- **Patch**: 8%. Qutenza® Apply for one hour only.

Advice to patients: Burning sensation can occur during initial treatment.

Mirtazapine

Benefit reported in neuropathic pain but not tested in RCT.
References

- NPSA MANAGING HIGH DOSE OPIOIDS
- www.medicines.org.uk/emc
- www.cqc.org.uk
Nausea & Vomiting

This chapter will guide you through the causes and treatment of nausea and vomiting.

The management and choice of antiemetic will be influenced by the cause(s) of nausea and vomiting. These are identified from a thorough patient history, physical examination and investigations where appropriate.
Assessment & Management Principles

Identify and treat underlying cause

- **Abnormal biochemistry** (e.g. hypercalcaemia, uraemia or hyponatremia), treat where appropriate.

- **Drugs** (e.g. opioids, oral bisphosphonates, metronidazole, anticonvulsants) – Anti-emetics may be necessary for a few days when opioid treatment is initiated. Not all patients require this.

- **Exacerbating factors** such as severe pain, cough, infection, and anxiety need to be treated.

- **Avoid** drugs with anticholinergic effects in patients with gastric stasis (e.g. hyoscine, antidepressants, cyclizine).

- **Constipation** – Prevent and treat aggressively.

- **Gastritis** – Use a proton pump inhibitor e.g. lansoprazole or H2 antagonist ranitidine.

- **Chemotherapy induced nausea & vomiting** – A short course of 5HT3-receptor antagonists may be appropriate.

- **Mechanical bowel obstruction** – See section Intestinal Obstruction.

- **Raised intracranial pressure** – See chapter: Corticosteroids.

- **Anxiety**: Psychological care with or without benzodiazepines.

- **Oropharyngeal thrush**: a course of anti-fungal treatment.
Management Plan

• Consider non–pharmacological measures, e.g. advice on posture and diet, acupuncture/acupressure, removal of unpleasant stimuli, complementary therapies, psychological treatments such as anxiety management.

• Ensure the most appropriate anti-emetic is used regularly, to a maximum dose and for a sustained period of time (e.g. 24hrs).

*See section: Anti-emetic Medications*

• Ensure additional PRN anti-emetics are available.

• Remember the oral route is often ineffective when someone has nausea or vomiting in which case alternative route should be considered.

If Management is Ineffective

• Reconsider the likely cause(s).

• Review the route of administration.

• Another complementary anti-emetic drug may be added (see second line treatment). For example haloperidol with cyclizine is often effective, especially by continuous subcutaneous infusion.

• NB. Cyclizine and other anticholinergic drugs may antagonise some of the effects of metoclopramide and other prokinetic agents. The combination should therefore be avoided if possible.

• Consider using a syringe driver: a continuous subcutaneous infusion via a syringe driver/pump may be considered for patients who are vomiting for longer than 24 hours or have nausea unresponsive to appropriate oral anti-emetics or are unable to swallow oral antiemetics.

*See chapter: Syringe Driver*
Anti-emetic choice should be selected depending on the cause of the nausea, treating underlying cause if possible. Medications should be used regularly and by a route which allows effective absorption. Non-pharmacological measures should also be considered.

Prescribe a single agent based on underlying cause (see below). Use regularly and to maximum dose before changing. N.B. Avoid using Metoclopramide and Haloperidol in those with Parkinson’s spectrum disorders.

### Drug Induced and Biochemical Cause

**Haloperidol**

(most potent dopamine D2 receptor antagonist)

**Oral**: 1.5mg–3mg/24hrs  
**SC**: 2.5mg–5mg/24hrs

**Preparations:**  
**Tablets**: 500 micrograms, 1.5mg, 5mg, 10mg  
**Oral solution**: 1mg/ml, 2mg/ml  
**Injection**: 5mg/1ml, 20mg/2ml

**CAUTIONED USE IN EPILEPSY**  
**AVOID IN PATIENTS WITH PARKINSON’S DISEASE & LEWY BODY DEMENTIA**  
as has Extrapyramidal side effects (EPSEs)
Evidence of Gastric Stasis

**Metoclopramide**
(dopamine D2 receptor antagonist)

**Use with caution in young adults** aged 15-19 (see BNF)

**Oral:** 10mg TDS to QDS before meals  
**SC:** 30mg–100mg/24hr

**Preparations:**  
**Tablets:** 10mg  
**Oral solution:** 5mg/5ml  
**Injection:** 10mg/2ml

AVOID IN PATIENTS WITH PARKINSON’S DISEASE as can cause EPSEs  
AVOID IN PATIENTS WITH COMPLETE (MECHANICAL) BOWEL OBSTRUCTION

**OR Domperidone**
(dopamine D2 receptor antagonist; does not cross blood brain barrier so fewer side effects)

**Oral:** 10mg TDS

**Preparations:**  
**Tablets:** 10mg  
**Suspension:** 5mg/5ml (Maximum dose is 30mg/24 hours)

Domperidone is now contraindicated in people:  
- with conditions where cardiac conduction is, or could be, impaired with underlying cardiac diseases such as congestive heart failure receiving other medications known to prolong QT interval or potent CYP3A4 inhibitors.  
- with severe hepatic impairment.
Cyclizine
(anticholinergic antihistamine)

Oral: 50mg TDS
SC: 75mg - 100mg / 24hours

Preparations:
Tablets: 50mg
Injection: 50mg / 1ml

**CAUTIONED USE IN EPILEPSY**
**CONTRAINDICATED IN SEVERE HEART FAILURE**

Broad Spectrum anti-emetic

Useful if multiple possible causes or if the above have not worked

Combine *first-line agents e.g. haloperidol and cyclizine*
or use single broad spectrum agent

Levomepromazine
(acts at multiple receptor sites: dopamine D2, anticholinergic antihistamine)

Oral: 6mg P.R.N. (Up to 25mg/24hr)
SC: 2.5mg - 6.25mg P.R.N. (Up to 25mg/24hr)

Preparations:
Tablets: 25mg, 6mg (6mg unlicensed available on named patient basis).
Injection: 25mg/1ml

**CAUTIONED USE IN EPILEPSY**
**CAUTIONED USE IN PARKINSON’S DISEASE & LEWY BODY DEMENTIA**
Chemotherapy and radiotherapy induced

3 Day Course of 5HT3 - Receptor Antagonist
For example ondansetron and granisetron

**Ondansetron Oral**: 8mg OD- BD
**SC**: up to 24mg over 24 hours

**Granisetron / Oral SC**: 1mg–2mg per 24 hours

**Preparations:**
**Ondansetron**
Tablets and dispersible tablets: 4mg, 8mg
**Syrup**: 4mg/5ml | **Suppositories**: 16mg | **Injection**: 4mg/2ml, 8mg/4ml

**Granisetron Tablets**: 1mg, 2mg
**Solution**: 1mg/5ml | **Injection**: 1mg/1 ml, 3mg/3ml
**Patch**: 3.1mg/24 hours - Change patch every 7 days (restrictions apply)

Contraindicated in congenital prolonged QT interval.
Serious drug interaction: a combination of IV metoclopramide and IV ondansetron occasionally causes cardiac arrhythmias
Constipation is a side effect.

Caused by moderately-high emetogenic chemotherapy

**Neurokinin receptor antagonists for example Aprepitant**

**Aprepitant**: 80mg–125mg OD PO
**Capsules**: 80mg, 125mg

Raised intracranial pressure or intractable vomiting

*Please see chapter: Corticosteroids*
Management of Intestinal Obstruction

Antiemetics for inoperable bowel obstruction are best given via CSCI

- It is always worth performing a rectal examination to rule out constipation before confirming a diagnosis of intestinal obstruction.

- Development of malignant bowel obstruction can be a slow and insidious process with episodes of paralytic ileus and mechanical obstruction over days to weeks.

- Careful assessment of the clinical symptoms/signs is essential for the most appropriate management.

- **Paralytic ileus** (e.g. electrolyte disturbance or autonomic dysfunction) may mimic intestinal obstruction but is potentially reversible. Colic is usually not a feature in such patients and clinical examination may reveal absence of or reduced bowel sounds.

- Mechanical intestinal obstruction (e.g. as a result of adhesions or tumour) will usually present with colic and clinical examination may reveal increased bowel sounds. This can generally be divided into:-

  - **Subacute or partial obstruction** (intermittent symptoms of colicky abdominal pain, nausea and vomiting, reduced frequency of passing flatus and opening bowels) which may resolve for a limited time

  - **Complete obstruction** (sustained symptoms of colicky abdominal pain, nausea and vomiting and absence of flatus and stool) which is irreversible

- Surgical intervention or stenting may be helpful for a small number of patients. A palliative bypass with or without stoma formation may be indicated if there is single level obstruction. Diffuse intra-abdominal disease or ascites are contraindications for palliative surgery.
Management of Intestinal Obstruction (continued)

- The main principles of management are to control nausea, colic and other abdominal pain using drugs shown in the section: *Syringe Driver*

- It is possible to keep a patient’s symptoms controlled with subcutaneous medications given via a syringe driver/pump. Some patients may prefer occasional vomits (as long as nausea is well controlled) to avoid nasogastric tube (NGT) insertion. Other patients with obstruction and large volume vomiting may prefer NGT insertion to avoid persistent vomiting.

- Dry mouth can be managed with regular oral care and ice cubes to suck

- Intravenous or subcutaneous fluids may be considered if the patient is dehydrated and thirsty

- In partial malignant obstruction the combination below can be effective in restoring bowel function:-
  - Metoclopramide and dexamethasone
    *(See chapter: Corticosteroids)*

*Do not use metoclopramide in patients with intestinal colic and in those with Parkinson’s spectrum disorders.*

- When complete intestinal obstruction occurs, prokinetic agents and bulk-forming or stimulant laxatives are contra-indicated.

- Patients may be able to tolerate small amounts of food and drink, if the nausea is well controlled. A low residue diet may be better tolerated (soft low fibre foods)
Syringe Driver Use

Nausea

Metoclopramide (only in absence of colic): 30mg–100mg/24hr
Or Haloperidol: 2.5mg–5mg/24hr and/or Cyclizine: 75mg–100mg/24hr

Colic

Hyoscine butylbromide: 60mg–120mg/24hr
(higher doses have been used up to 300mg)

Glycopyrronium: 600 micrograms –1.2 mg/24hr

Abdominal Pain

Strong opioid may be continued via a non-oral route.
Titrate/convert according to pain “requirements”. Please see chapter: Pain

Vomiting with Large Volume of Intestinal Secretions

1. Hyoscine butylbromide:
60mg–120mg/24hr (higher doses have been used up to 300mg).
Or 2. Octreotide 2nd line (if hyoscine butylbromide ineffective with specialist advice): 500 microgram / 24hr initially. Can be increased to 750 micrograms/24hrs if necessary.
If ineffective stop after 48 hours.
If octreotide is effective titrate to lowest effective dose.
Can add: 3. A three day trial of 5HT3 – receptor antagonists: e.g. Ondansetron or granisetron.

References

• Joint Formulary Committee (British Medical Association and Royal Pharmaceutical Company). British National Formulary (BNF 68). 2015
• www.gov.uk/drug-safety-update/domperidone-risks-of-cardiac-side-effects
Constipation

This chapter will guide you through the assessment and management of constipation.

Constipation is a common cause of distress. Prevention is better than waiting until treatment is needed. Symptoms can include anorexia, occasional vomiting, colic, tenesmus, overflow diarrhoea, urinary retention and confusion.
Constipation Assessment

Assessment and treatment of existing constipation.

1. Identify and treat underlying cause

Constipation should be anticipated in all patients:

• Taking opioids (Opioid Induced Constipation) or anticholinergics (e.g. tricyclic antidepressants, cyclizine, etc.).
• Those who are either inactive or have a reduced fluid or dietary fibre intake.
• Lack of privacy and pain may be contributing factors.
• At risk of hypercalcaemia which could be treated.
• Bowel obstruction should be considered and if clinically suspected further advice sought.

2. Management should then be guided by clinical assessment
Treatment of Existing Constipation

Use the information in this section to aid in the treatment of constipation.

Is the Rectum Impacted?

Yes. With Hard Stool
Lubricate using glycerol suppositories or soften with oil enema followed by stimulant e.g. phosphate enema once softened.
Once impaction is resolved commence or increase a laxative combining stimulant and softening actions.

Yes. Stool is Soft
Use a rectal stimulant, e.g. bisacodyl suppositories or phosphate enema.
Once impaction is resolved commence or increase a laxative combining stimulant and softening actions.

If no success using measures above
Commence a Macrogol preparation at faecal impaction dose.
Manual evacuation (consider sedation).

Is the Rectum Empty?

The Rectum is Empty
May still be constipated with a loaded colon.
Stimulant laxative may be of benefit (but avoid in patients with severe colic). Consider bowel obstruction.
Choice of Laxatives

Laxatives should be prescribed on a regular basis as soon as weak or strong opioids are prescribed (except those with ileostomy or diarrhoea), with full explanation to the patient.

Many ill patients will not tolerate a high-fibre diet or bulk forming laxatives and these are not usually recommended in palliative care. Many patients become expert at adjusting their own laxatives. However a regular regime will be essential for those on opioids.

A combination of stimulant laxative with a softening / osmotic agent is a good first choice.

25% of patients on oral laxatives may still need rectal measures at times.

Oral Preparations

The information below includes commonly used laxatives – higher than licensed doses may be recommended for opioid induced constipation and for more resistant cases (seek specialist advice).

Stimulants
Increase intestinal motility. Often cause abdominal cramp / colic. Do not use if patient has complete bowel obstruction.

Senna

Onset of action: 6–12 hours
Dose: 15mg OD – BD
Formulations: Tablets, syrup, and granules
**Bisacodyl**

**Onset of action:** 10–12 hours  
**Starting dose:** 5mg–20mg nocte  
**Formulations:** Tablets

**Sodium Picosulphate**

**Onset of action:** 6–14 hours  
**Starting dose:** 5mg–10mg nocte. Stimulant laxative indicated where other stimulant laxatives have failed  
**Formulations:** Capsules and elixir

**Softeners**

Faecal softening by acting as a surface wetting agent

**Docusate Sodium**

(also stimulant action in higher doses)  
**Onset of action:** 1-3 days  
**Starting dose:** 100mg -200mg bd  
**Formulations:** Capsules and elixir

**Combined Softeners and Stimulants**

Combines faecal softening and increased intestinal motility.  
Do not use if patient has complete bowel obstruction.  
Dantron stains urine red (warn patient) and can also cause perianal skin irritation, especially in incontinent patients. It may be prudent to avoid dantron-containing products in dying patients or those who are faecally incontinent or have a colostomy.
Co-danthrusate
Co-danthrusate (dantron 50mg, docusate 60mg)

Onset of action: 6–12 hours

Starting dose: 1–2 capsules at bedtime

Formulations: Capsules 50/60

Osmotic agents - oral
Increase the amount of water in the large bowel. Avoid if patient is dehydrated or has electrolyte disturbances. Avoid if patient has complete bowel obstruction.

Macrogol
Macrogol preparations may be preferable to lactulose if additional softener is required.

Up to 8 sachets a day may be used in faecal impaction.

Onset of action: 1–2 days

Starting dose: 1 sachet dissolved in 125ml water or concentrated oral liquid 25ml dissolved in 100ml water

Formulations: Macrogol oral powders (brands include Movicol®, Dulcobalance®, Laxido®, Molaxole®)

Lactulose
Lactulose alone in usual recommended doses is not effective for opioid induced constipation and should not be used in patients with inadequate fluid intake.

Lactulose can cause flatulence and abdominal cramps.

Onset of action: 1–2 days

Starting dose: 15ml bd

Formulations: Solution
Rectal Preparations

**Stimulants**
Local stimulation of intestine.
Do not use if patient has complete bowel obstruction.

**Bisacodyl Suppositories**
**Onset of action:** 20–60 minutes
**Starting dose:** 10mg suppository

**Glycerol Suppositories**
**Onset of action:** 1–6 hours
**Starting dose:** 4g suppository

**Softeners**
Lubricate and soften faeces.

**Arachis Oil Enema**
**DO NOT USE IN PATIENTS WITH PEANUT ALLERGY**
**Onset of action:** Normally administered at night (retention enema)
**Starting dose:** 130ml (warm before use)

**Docusate Sodium Enema**
**Onset of action:** 15–60 minutes. Normally administered at night (retention enema).
**Starting dose:** 120mg in 10g pack.
Osmotic agents - oral
Increase the amount of water in the large bowel.

**Phosphate Enema**
Ensure the patient is hydrated and that recent U&E’s have been taken.
**Onset of action:** 15–60 minutes
**Starting dose:** 1 enema

**Sodium Citrate Enema**
**Onset of action:** 15–60 minutes
**Starting dose:** 5ml enema

**Spinal cord compression:**
If normal sphincter sensation and function is present, titrate laxatives as normal; avoid excessive softening.
If normal sphincter sensation and function is absent, bisacodyl suppositories or other rectal interventions should be prescribed, aiming for a planned bowel action every two to three days.

**If standard measures fail**
In patients recognised to have significant and on going constipation as a result of opioid use despite measures above, specialist advice may be sought regarding the use of drugs such as the Oxycodone/Naloxone combination (Targinact®) and the opioid antagonists methylnaltrexone injection (Relistor®) and oral Naloxegol (Moventig®).

**References**
- Palliative Care Formulary Quick Prescribing Guide: Bowel management in paraplegia and tetraplegia.
Corticosteroids

This chapter will guide you through the principles of the use of corticosteroids in people with advanced malignancy, the choice of drug and dose as well as monitoring and withdrawal.

Patients with advanced malignancy may benefit from corticosteroids for a variety of symptoms.
Principles of corticosteroid use

There should always be a clear indication to justify starting corticosteroids and benefits should always be balanced against the side effects.

- Doses should be tailored to the individual and regularly reviewed, as responses may not be prolonged.
- Each stage of the corticosteroid plan should be documented and shared with relevant health care professionals, e.g. indication(s), expected outcome(s), and expected response time. Risk vs benefit should be considered for each patient.
- Side effects include diabetes, proximal myopathy, candidiasis, osteoporosis, pseudorheumatism, peptic ulceration, salt and fluid retention, Cushingoid features, sleep and psychiatric disturbance.
- Dexamethasone is the corticosteroid of choice. There are however few trials on which to base guidance for indications and dosing.
- Where possible prescribe as a single morning dose. If not practical, use twice daily doses with last dose before 2 pm. (This reduces suppression of hypopituitary-adrenal axis and may prevent corticosteroid induced insomnia).
- Use a 5–7 day corticosteroid ‘trial’ and unless desired effect achieved, corticosteroid should be stopped.
- Prescribe a gastro-protective agent such as PPI or H2 antagonist Ranitidine.
- If beneficial, corticosteroids should only be continued at a set dose for a maximum of 2–4 weeks, with planned review date to consider withdrawal. Aim to prescribe the lowest dose that controls the symptoms.
- Vigilance for oral thrush is needed.

Steroids are contraindicated in:
- Systemic infection, unless considered to be lifesaving and specific anti-infective therapy is employed.
- Active GI bleeding.
- Previous steroid-induced psychosis.
Choosing the right dose

Patients with advanced malignancy may benefit from corticosteroids for a variety of symptoms. There should always be a clear indication to justify starting corticosteroids and benefits should always be balanced against the side effects.

Neurological

Spinal cord compression or cauda equina syndrome

Dexamethasone: 16mg/day

Symptoms secondary to cerebral tumour(s).

Dexamethasone: 16mg/day
(4mg-8mg/day often sufficient for headache. More than 16mg may be required for patients with high risk of coning, or those taking enzyme inducing medications e.g. phenytoin, carbamazepine, phenobarbitone)

Nerve compression pain

Dexamethasone: 8mg/day

Respiratory

Superior vena caval obstruction SVCO

Dexamethasone: 16mg/day

Pneumonitis after radiotherapy

Dexamethasone: 16mg/day
Lymphangitis carcinomatosa
Dexamethasone: 16mg/day

Large airways obstruction
Dexamethasone: 16mg/day

Gastrointestinal Tract

Dysphagia
Dexamethasone: 6mg-16mg/day

Intestinal obstruction
Dexamethasone: 6mg-16mg/day

Rectal discharge
Rectal corticosteroid preparations e.g. hydrocortisone or prednisolone foam enema, or prednisolone suppositories. Once at night.

Miscellaneous

Ureteric obstruction/pelvic disease.
Dexamethasone: 6mg-16mg/day

Pain from hepatic metastases
Dexamethasone: 4mg–8mg/day

Bone pain (occasionally helpful)
Dexamethasone: 4mg–8mg/day

Anti-emetic
Dexamethasone: 4mg–8mg/day

Anorexia/to improve wellbeing (short term)
Dexamethasone: 2mg–4mg/day Prednisolone 15mg–40mg/day
Monitoring

Check capillary blood glucose before starting steroids (to assess risk), within 7 days of commencing steroids and on a regular basis while the patient remains on steroids. Monitor for symptoms which might indicate hyperglycaemia e.g. increased thirst, increased frequency of micturition.

What should the patient be told?

- Give patient a steroid card if they do not already carry one.
- Explain the reason(s) for prescribing steroid, including anticipated benefits and side effects.
- Take early in the day.
- Don’t stop suddenly, especially if steroids have been taken for more than 3 weeks – give a plan for dose reduction.
- Improvement does not mean tumour regression.
- To seek medical help if more unwell while taking corticosteroids, or come into contact with infectious disease (as recommended on steroid card).

Withdrawal

What should the patient be told?

Corticosteroids may be withdrawn abruptly provided that the patient has:

Received less than 3 weeks treatment
And not received recent repeated courses of corticosteroids
And received doses less than 4mg-6mg dexamethasone (or equivalent) total daily dose
And adverse effects are not anticipated by an abrupt withdrawal.
Gradual withdrawal of corticosteroids method

1. Initially reduce rapidly (e.g. halving the dose daily) to physiological doses (dexamethasone 1mg/24h or prednisolone 7.5mg/24h).

2. Subsequently more gradual reduction is advised (e.g. by 1mg–2mg prednisolone per week).

3. Patients should be monitored for any deterioration, in particular for signs of adrenal insufficiency.

If beneficial, corticosteroids should only be continued at a set dose for a maximum of 2–4 weeks, with planned review date to consider withdrawal. Aim to prescribe the lowest dose that controls the symptoms.

If oral route is no longer available

- Dexamethasone may be given by infusion but may need to be given in a separate syringe driver/pump (see chapter: Syringe driver) or as a stat subcutaneous dose depending on volume. If volume of a stat injection of dexamethasone would be more than 2ml, then the same injection can be split between two different sites e.g. left arm and right arm to allow more comfortable once daily administration.

- The oral bioavailability of dexamethasone tablets is 80%, compared with intravenous doses. There is no published literature comparing oral and subcutaneous administration. Generally oral and subcutaneous doses are considered equivalent. Other sources state dexamethasone to be twice as potent by the subcutaneous route, compared to oral.

- It may be appropriate to stop corticosteroids in the last days of life unless they have been essential in achieving good symptom control for the patient e.g. to manage headaches, seizures or pain.
## Preparations and doses

### Doses

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Approximate equivalent anti-inflammatory dose of corticosteroids*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>750 micrograms</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5 mg</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>20 mg</td>
</tr>
</tbody>
</table>

*(N.B. this chart dose not reflect the mineralocorticoid actions of these drugs)*

### Preparations

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Preparations</th>
</tr>
</thead>
</table>
| Dexamethasone  | **Oral tablets:** 0.5mg, 2mg, 4mg, 8mg  
**Oral soluble tablets:** 2mg, 4mg, 8mg  
**Oral suspension:** dexamethasone 2mg in 5ml  
**Injection:** Dexamethasone or dexamethasone phosphate (as dexamethasone sodium phosphate) 3.3mg/ml 1ml and 2ml ampoules, 3.8mg/ml 1ml ampoules  
Dosing regimen should be obtained from the individual drug Summary of Product Characteristics |
| Prednisolone   | **Oral tablets:** 1mg, 5mg, 25mg  
**Soluble tablets:** 5mg  
**Enteric coated tablets:** 2.5mg, 5mg  
**Suppositories:** prednisolone 5mg (Predsol)  
**Rectal foam:** prednisolone (as metasulphobenzoate) 20mg/metered application: 14 applications  
**Retention enemas:**  
Predsol retention enema 20mg (as sodium phosphate) in 100ml  
Prednisolone retention enema, 20mg (as sodium metasulphobenzoate) in 100ml |
| Hydrocortisone | **Oral tablets:** 10mg, 20mg  
**Oral MR tablets:** 5mg, 20mg  
**Mucoadhesive buccal tablets:** 2.5mg  
**Injection:** hydrocortisone 100mg/ml 1ml amp, 100mg/2ml 2ml amp, 500mg/5ml 5ml amp |
References

• NICE Guidelines (2004). Improving Supportive Palliative Care for Adults with Cancer.


Breathlessness

This chapter aims to prescribe general symptom prescribing advice and non-pharmacological approach for patients with a palliative diagnosis who are breathlessness.
Introduction to Breathlessness

Breathlessness is a common symptom in both malignant and non-malignant disease. Up to 70% patients with cancer experience breathlessness in the 6 weeks prior to death, and this may be greater in lung cancer patients because of co-existent chronic obstructive pulmonary disease (COPD).

Up to 40% of heart failure patients are breathless in the 6 months before death, rising to 65% in the three days leading up to death. Breathlessness is almost universal in patients with more than mild COPD or Interstitial Lung Disease (ILD). With very advanced disease, specific pharmacological treatment aimed at particular lung pathology (e.g. bronchodilators for bronchospasm) may have limited success and more general symptom control measures are often necessary.

The use of low dose opioids, titrated carefully, can help to relieve the sensation of breathlessness in patients with lung pathology, heart failure and cancer.

Oxygen therapy should not be used routinely. It may give symptom benefit if the patient is known to be hypoxic, including if they desaturate on exertion. For most, the use of a fan or other draught of air may be just as effective as oxygen.

Non-drug intervention may be of benefit in helping patients manage their symptoms; however, in advanced illness patients may often require opioid and/or benzodiazepine medication. These can be given by different routes of administration e.g. orally, sublingually (lorazepam), by continuous subcutaneous infusion via syringe driver/pump or bolus PRN dosing (subcutaneously or in exceptional circumstances intravenously).
Assessment of the Breathless Patient

• Determine the correct diagnosis
• Consider any other contributing factors e.g. dysrhythmia, anaemia
• Is there anything that can be corrected or treated? Seek advice if unsure
• Consider the use of oximetry, if available, to guide if oxygen therapy is likely to be of benefit (i.e. if oxygen saturation less than 90%)
• Consider psychological factors especially anxiety and the fear of choking/suffocation
• Decide on the optimal management
• Only consider investigations which are likely to lead to a change in clinical management

Management of Breathlessness

General (non-drug) Measures

• Explanation of cause/reassurance
• Calm manner; fan or open window in acute attack
• Posture – ideally upright and leaning forward if possible
• Diaphragmatic breathing through pursed lips; visualisation techniques to encourage longer expiratory phase
• Nutritional advice (e.g. small frequent meals, easily chewed)
• Relaxation training and/or complementary therapy
• Energy conservation/pacing training/equipment
• Treat depression and anxiety if present
• Benefits advice
• Encourage social interaction (e.g. peer group support, Breathe Easy Club, breathlessness management in a hospice day unit)
Specific Measures

Conditions such as pneumonia, COPD, asthma, effusions etc. should be dealt with using standard management. Seek further advice if needed.

For patients with SVC obstruction see chapter: Palliative Care Emergencies.

For patients with stridor consider urgent referral to oncology or respiratory colleagues – high dose dexamethasone 16mg per day may be of benefit. For some patients however this may be part of a terminal process – see section: Management of breathlessness in the dying phase.

Nebulised saline (sodium chloride 0.9%) may be of some benefit to patients to aid in the expectoration of secretions. Carbocisteine can also be used to reduce sputum viscosity (capsules or oral liquid – 750mg tds initially, reducing to 750mg bd once satisfactory response obtained).

Psychological Measures

Psychological factors (e.g. anxiety, fear of death from choking or suffocation) often exacerbate any breathlessness resulting from physical disease.

Occasionally breathlessness may be largely due to psychological factors.

In such circumstances, good palliation depends on exploring the patient’s beliefs about their breathlessness and their concerns. Reliance on drug treatment alone will only result in partial control of breathlessness.
Oxygen

- Oxygen should be prescribed with a target oxygen saturation specified.
- Limited value if oxygen saturation is already >90% prior to starting oxygen therapy.
- 1-2 litres per minute would be usual flow rate unless blood gases dictate otherwise.
- In palliative care routine monitoring with blood gases is not usually required but use oxygen with caution in patients who are known to retain CO2.
- Risk factors for CO2 retention:
  - Previous episode of CO2 retention
  - Known COPD/other lung pathology
  - Long history of smoking

Monitor for signs of CO2 retention e.g. drowsiness, tremor, new confusion

Non-opioid drugs

**Bronchodilators** – via inhaler +/- spacer or nebuliser. Stop if no benefit.

**Steroids** – especially if previous therapy has been beneficial e.g. for COPD.

Typical doses are:

- 30mg prednisolone (or 4 mg dexamethasone) per day for exacerbations;
- 2.5mg-10mg prednisolone per day for maintenance (not normally recommended because of long term side effects – see chapter: *Corticosteroids* and consider osteoporosis prophylaxis).
- May be worth considering as a therapeutic trial in patients with lymphangitis (typically dexamethasone 16 mg per day).
- High dose dexamethasone (20mg-40mg daily) can also be used to relieve stridor due to malignant upper airway obstruction.
Benzodiazepines

- May be useful for those patients with marked anxiety/panic attacks associated with episodes of breathlessness
- Less evidence for efficacy vs opioids in relieving breathlessness
- E.g. Lorazepam (scored 1mg blue tablet – Genus brand) 0.5mg sublingual 4–6 hourly P.R.N. or Diazepam 2mg–5 mg o.n. regularly for patients with ongoing debilitating anxiety

Opioid drugs

- Can relieve the sensation of breathlessness, this is of most benefit for breathlessness at rest rather than on exertion
- More evidence of efficacy vs. benzodiazepines in relieving breathlessness
- Give as a therapeutic trial – monitor benefits and side effects. Titrate up slowly if required
- Long acting opioids may be considered for some patients with continuous breathlessness who gain relief from regular immediate release preparations.
- Alternative opioids may be considered in some patients who cannot tolerate morphine (seek specialist palliative care advice)

Prescribing for Opioid-naïve patients:

- Explain to the patient that morphine may be useful to relieve the sensation of breathlessness
- For patients with breathlessness due to cancer prescribe immediate release oral morphine (e.g. Morphine IR such as Oramorph®) 2.5mg–5mg po PRN, then regularly 4–6 hourly if beneficial

Prescribing for patients on opioids for pain currently:

- Explain to the patient that morphine may also be useful to relieve the sensation of breathlessness
- Some patients may find a lower opioid dose than their current breakthrough analgesic dose sufficient for breathlessness, e.g. 25-50% of the current P.R.N. breakthrough analgesic dose; others may require 100%
Lower doses of morphine

(e.g. Oral Morphine IR liquid 1mg-2mg po P.R.N.) may be more appropriate in the following patients:

- Elderly
- Frail
- Severe lung disease
- Heart failure
- Renal or hepatic impairment

A low-dose and slow titration is recommended for patients with COPD and significant breathlessness despite usual treatments. Start with morphine (e.g. Oral Morphine IR liquid 1mg po bd, increasing to 1mg po qds over one week. Thereafter increase dose gradually each week until satisfactory relief obtained.

Please also see section: Management of breathlessness in the dying phase.
References


- Jennings A. Opioids for the palliation of breathlessness in terminal illness. Cochrane Database of Systematic Reviews 2001, Issue 3

This chapter will guide you through managing palliative care emergencies.
Superior Vena Cava Obstruction (SVCO)

If SVCO is suspected, discuss this with an oncologist within 24 hours. The investigation of choice is a CTPA (CT Pulmonary Angiogram). SVCO is usually due to malignant involvement of upper mediastinal lymph nodes or a right upper lobe lung cancer; intraluminal thrombus may also be a feature.

Symptoms and signs: headache, breathlessness, swelling of face and arms, fixed raised JVP, dilated veins on chest wall and around costal margin.

Initial treatment consists of dexamethasone 16 mg daily orally aiming to reduce any oedema around the tumour. Definitive treatment may include insertion of a vascular stent, radiotherapy or chemotherapy.
Hypercalcaemia of malignancy

Normal range: adjusted calcium 2.1–2.6 mmol/l

The majority of calcium circulates bound to albumin, but a small amount is present as the physiologically active “ionised” calcium. The adjusted calcium or “ionised” calcium should be used when the patient has a low albumin.

Corrected calcium (mmol/l) = measured calcium + (0.02 x [40-albumin g/l]).

Occurs in about 10–20% of patients affected by cancer. It is generally indicative of a poorer prognosis in solid tumours.

Symptoms and signs:

Confusion, drowsiness, nausea and vomiting, thirst, polyuria, constipation, lethargy, bradycardia, myoclonus, seizures and coma.

Severity of symptoms are not necessarily indicative of the level of hypercalcaemia.

Generally when managing hypercalcaemia, an adjusted calcium level greater than 3.0 should be treated whether the patient is symptomatic or not.

Treatment:

It is important to carefully balance the benefits versus burdens of treating hypercalcaemia in a patient with advanced disease, considering the care setting, previous history of hypercalcaemia and patient preferences.

Treatment includes IV rehydration and use of intravenous bisphosphonates.

Bisphosphonates start to take effect after 48 hours to lower serum calcium, however the maximum effect may not be seen for 5 to 7 days. Bisphosphonates therefore may not be indicated in a patient whose estimated prognosis is very short.
Discontinue any calcium, vitamin D or vitamin A supplements.

Review and consider discontinuing any drugs which may affect renal blood flow e.g. NSAIDs, diuretics, ACE inhibitors, Angiotensin II receptor antagonists.

Renal function and albumin should be checked prior to giving infusion. In renal failure consult product literature for dosing guidance.

Recent studies have shown zoledronic acid to be superior to pamidronate in terms of more rapid onset and longer duration of action but please refer to your local policy for guidance.

Ensure the patient is appropriately hydrated before giving a bisphosphonate (e.g 1–3 litres of parenteral sodium chloride 0.9%) volume and rate should be adjusted according to age and other co-morbidities.

Depending on local policy, pamidronate or zoledronic acid is used:

**Either:** Disodium pamidronate IV infused at a rate not exceeding 1 mg/min (see manufacturer’s guidance for patients with renal impairment):

<table>
<thead>
<tr>
<th>Corrected calcium (mmol/l)</th>
<th>Pamidronate (mg)</th>
<th>0.9% saline (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3</td>
<td>30</td>
<td>250</td>
</tr>
<tr>
<td>3 - 3.5</td>
<td>60</td>
<td>250</td>
</tr>
<tr>
<td>&gt; 3.5</td>
<td>90</td>
<td>500</td>
</tr>
</tbody>
</table>

However one systematic review of bisphosphonate use states that 90mg pamidronate may be given irrespective of the initial calcium level, in order to increase the likelihood of successful and sustained normocalcaemia.

**Or:** Zoledronic acid IV 4mg in 100ml 0.9% saline infused over 15 minutes at least (see manufacturer’s guidance for patients with renal impairment).

Repeated infusions of bisphosphonates carry an increased risk of developing osteonecrosis of the jaw (rare before 4 months of treatment). Patients should avoid invasive dental procedures while receiving ongoing bisphosphonate therapy.
Monitoring

Repeat calcium levels are best monitored at 5–7 days post infusion as it takes this length of time for the bisphosphonate to have reached its maximum effect. It is advisable to recheck the calcium level when patient experiences symptoms or every 3-4 weeks.

Management of resistant / recurrent hypercalcaemia

- For resistant hypercalcaemia (hypercalcaemia not responding to initial bisphosphonate therapy at appropriate dose) seek specialist palliative care advice.

- Recurrent hypercalcaemia, that has recurred within a short time (e.g. 1 to 2 weeks) after previous appropriate treatment may represent advancing disease and may be less likely to respond to further treatment. If required, a further dose can be administered at 5–7 days. Seek specialist palliative care advice.

Metastatic Spinal Cord Compression (MSCC)

This occurs in 5–10% of cancer patients, the most common underlying tumours being lung, breast and prostate (40% of all cases). Early detection has a significant outcome on morbidity and mortality.
NICE recommends that in the following instances the Metastatic Spinal Cord Coordinator (e.g. Acute Oncology Nurse Specialist, on call Consultant Oncologist/Spinal Surgeon/Neurosurgeon) is contacted:

1. Within 24 hours to discuss the care of patients with cancer and any of the following symptoms suggestive of spinal metastases:
   - Pain in the middle (thoracic) or upper (cervical) spine
   - Progressive lower (lumbar) spinal pain
   - Severe unremitting lower spinal pain
   - Spinal pain aggravated by straining (for example, at stool, or when coughing or sneezing)
   - Localised spinal tenderness
   - Nocturnal spinal pain preventing sleep

2. Immediately to discuss the care of patients with cancer and symptoms suggestive of spinal metastases who have any of the following neurological symptoms or signs suggestive of MSCC, and view them as an oncological emergency:
   - neurological symptoms including radicular (nerve root) pain, any limb weakness, difficulty in walking, sensory loss or bladder or bowel dysfunction
   - neurological signs of spinal cord or cauda equina compression

Immediate treatment

Oral dexamethasone 16 mg daily.

If a patient with suspected MSCC is considered fit for investigation and treatment an urgent MRI of the whole spine is the investigation of choice.
Corticosteroid use and withdrawal in MSCC

- Give a loading dose of 16mg dexamethasone as soon as possible after assessment, followed by a short course of 16mg dexamethasone daily while treatment is being planned.
- Continue dexamethasone 16mg daily in patients awaiting surgery or radiotherapy for MSCC. After surgery or the start of radiotherapy the dose should be reduced gradually over 5–7 days and stopped.
- If neurological function deteriorates at any time the dose should be increased temporarily.
- Reduce gradually and stop dexamethasone 16mg daily in patients with MSCC who do not proceed to surgery or radiotherapy after planning.
- If neurological function deteriorates at any time the dose should be reconsidered.
- Monitor blood glucose levels in all patients receiving corticosteroids.

*Please also see chapter: Corticosteroids.*

**Major Haemorrhage**

Clinically significant bleeding occurs in 6-10% of patients with advanced cancer, often this may be internal.

The most common primary cancer sites include:

- Lung
- Head and neck
- Upper GI
Coagulopathy (includes patients on aspirin and NSAIDs, anti-coagulant therapy or intrinsic coagulation problems, such as bone marrow failure)

Proximity of the tumour to major blood vessels

Presence of fungating or infected wounds

Sometimes patients may be known to be particularly at risk of major haemorrhage because smaller (herald) bleeds have occurred. Smaller bleeds can be palliated using topical adrenaline or tranexamic acid, or haemostatic dressings e.g. CELOX (for further information seek specialist palliative care advice).

Sensitive exploration of the patient and carer’s understanding of the clinical situation and potential risk for significant bleeding may reduce distress by providing a clear plan of action in the event.

It is essential to stay with the patient, as loss of consciousness can happen rapidly. Priority should be to stay and comfort patient and family rather than leaving patient to access drugs. If appropriate to leave patient or second health care professional available – consider giving medication as per guidance.

Dark coloured towels may be helpful in disguising the appearance of the blood. Anticipatory prescribing with an anxiolytic/sedative such as midazolam (IV or IM) is the recommended management in the event of an acute terminal bleed.

<table>
<thead>
<tr>
<th>Route &amp; onset of effect</th>
<th>Midazolam Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV 2 – 3 minutes</td>
<td>10mg</td>
<td>Repeat after 10 minutes if needed</td>
</tr>
<tr>
<td>IM 5 – 15 minutes (preferably deltoid)</td>
<td>10mg</td>
<td>Repeat after 10 minutes if needed</td>
</tr>
</tbody>
</table>

The subcutaneous route is inappropriate due to peripheral shut down and unpredictable absorption. Buccal midazolam can also be used.

*If the patient is already on large background doses of midazolam or other benzodiazepines seek specialist palliative care advice if required.*
References


The Syringe Driver / Pump

The following guidelines acknowledge that subtle changes in clinical practice may occur between hospital, hospice and community practice and endeavour to promote safe and consistent methods of practice, based on collaborative experience around the West Midlands Region.
At the time of writing it is assumed that all palliative care teams have phased out the use of Graseby syringe driver/pumps in accordance with NPSA Alert Dec 2010.

The guidance, therefore focuses on the use of McKinley T34 devices.

The syringe driver/pump is a small portable battery-driven infusion pump, used to deliver medication as a continuous sub-cutaneous infusion (CSCI) usually over 24 hours.

It can be used when other routes (e.g. oral, buccal, rectal, transdermal) are unsuitable.
Syringe Driver/Pump Usage

The following guidelines acknowledge that subtle changes in clinical practice may occur between hospital, hospice and community practice and endeavor to promote safe and consistent methods of practice, based on collaborative experience around the West Midlands Region.

Indications for Starting a Syringe Driver/Pump

The syringe driver/pump may be indicated in the following situations:

- persistent nausea or vomiting
- difficulty swallowing
- poor alimentary absorption
- intestinal obstruction
- profound weakness / cachexia
- comatose or moribund patient
- administration of drugs that cannot be given by non-parenteral routes

Care of the Syringe Pump/Driver

If doses of drugs need to be changed then change the syringe and the infusion line. It is best not to alter the rate.

Check the syringe driver/pump and infusion regularly for:

- irritation at the injection site (site reaction), change site or ask advice
- crystallisation of drug (seek specialist advice)
- discolouration (seek specialist advice)
- light flashing (if not check the battery)
- secure connections or kinked tubing
- leakage
- correct volume remaining
Sites of choice include:

- anterior chest wall
- lateral upper arms
- anterior abdominal wall
- anterior outer thigh
- area over scapula (in confused or disorientated patient)

Avoid areas of inflammation, oedema, broken skin, bony prominences, recently irradiated areas, sites of tumour, sites of infection, skin folds or lymphoedema.

Selection of Drugs

The choice of drug is dictated by the symptom, and the compatibility with other drugs to be delivered. See Compatibility Chart below:

Compatibility Chart For Two Drugs in Water for Injections
The dose of each drug to be given by infusion over a specified time period (usually 24 hours) should be clearly written.

- Opioids via the syringe driver/pump will not give better analgesia than orally unless there is a problem with absorption or administration of the drug.
- Long term use is rarely indicated but if required a syringe driver/pump may be maintained as long as is necessary.

McKinley Syringe Driver/Pump

McKinley® T34 infusion pump (syringe driver/pump)

About the McKinley® T34 infusion Pump

- The McKinley® T34 syringe driver/pump is used to deliver drugs at a predetermined rate via the subcutaneous route over a 24 hour period.
- A maximum of 3 compatible drugs can be mixed in a syringe for administration via this route.
- Staff should only use this equipment if trained to do so.
- With a McKinley® syringe driver/pump it is the volume of the infusion fluid that is important as only Becton Dickinson® (BD Plastipak®) syringes are recommended.
- The syringe driver/pump calculates and displays the deliverable volume, duration of infusion and rate of infusion (ml/hr).
You will need:
- McKinley® T34 syringe driver/pump
- 9v alkaline/lithium battery – PP3 recommended
- 20ml or 30ml BD Plastipak® Luer-lok syringe
- If a large volume of medication is required then a 50ml syringe is also an option (this will not fit in the lockable case device); it may not be possible for syringes to be filled to capacity i.e. 34-44ml can be delivered from a 50ml syringe and 24ml can be delivered from a 30ml syringe
- Infusion (or giving) set
- 22 G cannula
- Clear adhesive film dressing
- Diluent (usually water for injection)
- Medication as prescribed
- Label to be attached to syringe
- Holster for ambulatory patients
With McKinley® T34 the final volume in the syringe will determine the rate of infusion (ml/hr)

- Dissolve powdered drugs with sterile water for injection if necessary (sterile water for injections may not be needed if other drugs can act as the diluent)
- Draw up drugs into syringe and dilute to volume required with sterile water for injection
- Rock the syringe to ensure mixing of the contents
- Label the syringe clearly with the:–
  - Patient’s name
  - Infusion contents and doses
  - Date and time
  - Initials of persons preparing and checking
- Prime the infusion line and cannula
- Insert the cannula subcutaneously into the patient in an appropriately identified area for administration
- Secure with clear film adhesive

Preparing the McKinley® Syringe Pump/Driver

- Install the battery in the syringe driver/pump (a battery of 100% has a 3-4 day life only)
- Ensure barrel clamp arm is down
- Press and hold the ON/OFF key until "pump identification" screen appears
- Screen will indicate “Pre-Loading” and then syringe sensor detection screen will appear
- Press INFO key several times to check battery power (and discard if e.g. <40% according to local policy), then press YES to confirm
Fitting the McKinley® Syringe Pump/Driver

- Check patient’s name is correct with the patient’s ID label (e.g. wrist band label)
- Check drugs are correct with the prescription chart
- Lift and turn barrel arm
- Seat the filled syringe collar and plunger so the back of the collar sits in the central rest, the collar should be vertical and the scale on the barrel should face forward and be easily read
- Lower the barrel clamp arm (syringe graphic will stop flashing when syringe correctly seated)
- Syringe brand and size will be displayed

20ml BD Plastipak
Select ↑↓, Press YES

Commencing Syringe Pump/Driver Infusion

- After confirming the syringe the display will show the deliverable volume, duration and rate of the infusion e.g.

<table>
<thead>
<tr>
<th>Volume</th>
<th>20.3ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>24.00</td>
</tr>
<tr>
<td>Rate</td>
<td>0.85ml/hr</td>
</tr>
<tr>
<td>Confirm,</td>
<td>Press YES</td>
</tr>
</tbody>
</table>
• Check the line is connected to the syringe driver/pump and press YES
• Press YES to confirm or ON/OFF to return to syringe options
• Pump screen will prompt – Start Infusion?
• Check the line is connected to the syringe driver/pump and press YES
• When the syringe driver/pump is running the screen will display e.g.

<table>
<thead>
<tr>
<th>Time Remaining</th>
<th>23:59</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td>0.66ml/h</td>
</tr>
<tr>
<td>&lt;&lt;&lt; Pump Delivering</td>
<td></td>
</tr>
</tbody>
</table>

• Green LED light will flash every 32 seconds
• A breakthrough dose of analgesia may be needed as it will take 4 to 6 hours for therapeutic blood plasma levels to be reached using the syringe driver/pump for the first time or for dose increments
• To lock the keypad: press and hold down the INFO key (screen shows a progress bar moving from left to right) until the bar has moved completely to the right and a beep is heard to confirm lock has been activated. (When keypad is locked the buttons NO/STOP; YES/START; INFO are still active)
• To unlock the keypad: repeat this procedure, the bar will run from right to left and a beep is heard to confirm the keypad is unlocked
• A lockbox is available for the McKinley® syringe driver/pump – see photo below (this lockbox will not take a syringe larger than 30ml although the McKinley® syringe driver/pump will take a 50ml syringe)
Mixing Drugs in the Syringe Driver/Pump

Definitive data on compatibility, stability and efficacy are still lacking. Generally all of the drugs included in the section: *Common Medicines* are compatible with morphine and diamorphine, however cyclizine compatibility is concentration dependent. Cyclizine does not mix with oxycodone at therapeutic doses.

Dexamethasone compatibility is unpredictable and is best given in a separate syringe driver/pump if possible or as a bolus subcutaneous dose once daily. A compatibility chart based on studies performed at specified drug concentrations is shown below.

<table>
<thead>
<tr>
<th>Glycopyrronium</th>
<th>?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td></td>
</tr>
<tr>
<td>Hyoscine Hydrobromide</td>
<td></td>
</tr>
<tr>
<td>Hyoscine Butylbromide</td>
<td></td>
</tr>
<tr>
<td>Levomepromazine</td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td></td>
</tr>
<tr>
<td>Morphine / Diamorphine</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td></td>
</tr>
</tbody>
</table>

- **Incompatible - DO NOT USE**
- **Caution** - reports of incompatibility
- **Caution** - reports of incompatibility at doses outside of those commonly used in palliative care
- **Compatible**
- **Combination not advised clinically**
- **No published data available**

Mixing Drugs in the Syringe Driver/Pump

<table>
<thead>
<tr>
<th>Cyclizine</th>
<th>Glycopyrronium</th>
<th>Haloperidol</th>
<th>Hyoscine HBr</th>
<th>Hyoscine BBr</th>
<th>Levomepromazine</th>
<th>Metoclopramide</th>
<th>Midazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycopyrronium</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyoscine Hydrobromide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyoscine Butylbromide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levomepromazine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine / Diamorphine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mixing Drugs in the Syringe Driver/Pump (continued)

The following precautions will minimise the risk of problems of incompatibility and instability:

- A maximum of 3 compatible drugs in any one syringe driver/pump is recommended.
- Do not leave drugs in a syringe driver/pump for more than 24 hours.
- Seek advice from the Specialist Palliative Care Team if necessary.

The book called The Syringe Driver: Continuous subcutaneous infusions in palliative care (by Andrew Dickman and Jennifer Schneider) serves as a valuable reference source, providing comprehensive review of syringe driver use and administration of drugs by CSCI. It contains an extensive, referenced list of compatibility and stability data relating to drug combinations administered by CSCI.

Notes:

Although subcutaneous administration of these drugs is common and accepted good practice in palliative care, the use of this route lies outside the product license for most of these preparations.
Common Medicines

The use of common medicines in syringe driver/pumps

Start at lowest dose in the range especially in frail elderly patients; review dose every 24 hours and adjust if necessary and seek Specialist Palliative Care Team advice if needed.

For further guidance on prescribing in organ failure see chapters Symptom Control in Patients with: Cardiac Failure, Liver Failure, & Renal Disease.

Analgesics

Diamorphine

Indication: Pain

Subcutaneous starting dose over 24 hrs
1/3 total daily dose of oral morphine

Ampoules available
5mg, 10mg, 30mg, 100mg, 500mg

Morphine

Indication: Pain

Subcutaneous starting dose over 24 hrs
1/2 total daily dose of oral morphine

Ampoules available
10mg/ml, 15mg/ml, 20mg/ml, 30mg/ml as 1ml and 2ml ampoules
Analgesics (continued)

**Fentanyl**

**Indication:** Pain and chronic renal failure eGFR < 30

**Dose:** Seek Specialist palliative care advice

**Oxycodone**

**Indication:** Pain

**Subcutaneous starting dose over 24 hrs**
1/4 total daily dose of oral morphine or 1/2 total daily dose of oral oxycodone

**Ampoules available**
10mg/ml as 1ml and 2ml ampoules  |  50mg/ml as 1ml ampoules

Morphine or diamorphine should be the opioids of first choice for injection.

**Antiemetics**

**Metoclopramide**

**Indication:** Delayed gastric emptying

**Subcutaneous starting dose over 24 hrs**
30mg–40mg (range 30mg–100mg)

**Ampoules available**
10mg/2ml
Antiemetic and sedative

**Haloperidol**

*Indication:* Drug induced or metabolic cause of nausea

**Subcutaneous starting dose over 24 hrs**
2.5mg (range 2.5mg–10mg)

*Ampoules available*
5mg/1ml and 20mg/2ml

**Cyclizine**

*Indication:* Bowel obstruction

**Subcutaneous starting dose over 24 hrs**
75mg

*Ampoules available*
50mg/1ml

**Levomepromazine**

*Start at lowest dose in the range especially in frail elderly patients*

*Indication:* Nausea

**Subcutaneous dose**
P.R.N. Dose 2.5mg - 6.25mg four hourly

**Subcutaneous starting dose over 24 hrs**
5mg (range 5mg – 25mg)

*Indication:* Agitation and Confusion

SC P.R.N. Dose 5mg - 12.5mg four hourly

**Subcutaneous starting dose over 24 hrs**
10mg (range 10mg - 75mg)

*Ampoules available*
25mg/1ml
**Sedative**

**Midazolam**

Start at lowest dose in the range especially in frail elderly patients

**Indication:** Terminal restlessness

**Subcutaneous starting dose over 24 hrs**

5mg (range 5mg–30mg)

**Indication:** Seizure prevention (no recent seizures)

**Subcutaneous dose range over 24 hrs**

10mg–30mg, starting dose will depend on frailty and previous medications

**Indication:** Ongoing seizure activity

**Subcutaneous starting dose over 24 hrs**

30mg (range 30mg–60mg)

**Ampoules available**

10mg/2ml, 10mg/5ml, 5mg/5ml,

**Anticholinergic**

**Hyoscine Butyl Bromide**

**Indication:** Terminal respiratory secretions with colic / Intestinal obstruction

**Subcutaneous starting dose over 24 hrs**

60mg (range 60mg–120mg) (SC as required dose is 20mg)

**Ampoules available**

20mg/1ml
**Glycopyrronium**

**Indication:** Terminal respiratory secretions with colic/intestinal obstruction.

**Subcutaneous starting dose over 24 hrs**
600mcg (range 600mcg–1200mcg) (SC as required dose is 200 micrograms)

**Ampoules available**
200mcg/1ml and 600mcg in 3ml

---

**Hyoscine Hydrobromide (also anti-emetic)**

**Indication:** Terminal respiratory secretions with colic/intestinal obstruction.

**Subcutaneous starting dose over 24 hrs**
600mcg (range 600mcg–1200mcg) (SC as required dose is 400 micrograms)

**Ampoules available**
400mcg/1 ml and 600mcg/1ml

---

**Steroid**

**Dexamethasone**

**Indication:** *See chapter: Corticosteroids*

**Subcutaneous starting dose over 24 hrs**
This will depend on previous oral steroid dose. Seek specialist advice.

**Ampoules available**
Dexamethasone as dexamethasone sodium phosphate 4mg/ml, 3.3mg/ml, 3.8mg/ml
Anti-secretory

**Octreotide**

**Indication:** Intestinal obstruction to reduce secretions if hyoscine butylbromide ineffective (with Specialist Palliative Care advice)

**Subcutaneous starting dose over 24 hrs**

500 micrograms/24hr initially

- Can be increased to 800 micrograms/24hrs if necessary
- If ineffective stop after 48 hours
- If octreotide effective titrate to lowest effective dose

*See chapter Nausea and Vomiting – Syringe Driver Use*

**Ampoules available**

50mcg/1ml, 100mcg/1ml, 500mcg/1ml, 1000mcg/5ml

**Contraindicated**

DIAZEPAM, PROCHLORPERAZINE AND CHLORPROMAZINE are too irritant to be used subcutaneously.
References

- NPSA Alert December 2010; NPSA/2010/RRR019
- Dickman A. Drugs in Palliative Care.
- Dickman A. Schneider J. The Syringe Driver: Continuous subcutaneous infusions in palliative care
- www.palliativedrugs.com
Symptom Control in Patients with Cardiac Failure

This chapter aims to provide general symptom prescribing advice for patients who are being managed palliatively with cardiac failure sitting alongside advice from the patient’s cardiac team and the Specialist Palliative Care Team if necessary.
Background

Heart failure is classified as either:

1. Cardiac failure with Left Ventricular Systolic Dysfunction, (LVSD) (as seen on echocardiography) Or

2. Diastolic heart failure (with echocardiographic evidence of an ejection fraction of greater than 40-50%) also known as heart failure with:
   - Preserved ejection fraction or
   - Preserved systolic function or
   - Normal ejection fraction (‘HFNEF’)

Diastolic heart failure may occur in patients with hypertension, hypertrophic cardiomyopathy or aortic stenosis.

Cardiac failure can be described by stage according to the New York Heart Association (NYHA) classification:

<table>
<thead>
<tr>
<th>NYHA Class</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>Cardiac disease not limiting physical activity; no symptoms with ordinary activity</td>
</tr>
<tr>
<td>II.</td>
<td>Symptom-free at rest; slight limitation of physical activity; symptoms with ordinary activity but resolve with rest</td>
</tr>
<tr>
<td>III.</td>
<td>Symptom-free at rest; ordinary activity markedly limited due to symptoms</td>
</tr>
<tr>
<td>IV.</td>
<td>Symptomatic at rest. Unable to carry out ordinary activity</td>
</tr>
</tbody>
</table>

50% of patients with heart failure (all classes) die within 4 years and 50% of those with class IV heart failure die within 1 year.

Symptoms: The physical and psychological symptom burden from heart failure in the dying phase is similar to that in the cancer patient in the dying phase.

Their frequency: Pain (78%), dyspnoea (61%), depression (59&), insomnia (45%), anorexia (43%), anxiety (30%), constipation (37%), nausea/vomiting (32%), fatigue (62-70%), difficulty ambulating, and oedema.
Symptoms and Management Options

Breathlessness
- Optimally treat heart failure and co-morbidities, including anxiety
- Consider referral for Exercise Rehabilitation
- Oral morphine 2.5mg-5mg 4 hourly and titrate (in normal renal function)

Fatigue
- Search for reversible factors
- Consider treatment of anaemia
- Appropriate exercise
- Avoid steroid and progestogens

Pain
Use WHO Analgesic ladder (in normal renal function):
- Step 1: Paracetamol 1g QDS (not soluble as high Na+ content)
- Step 2: Paracetamol 500mg + codeine 30mg, 2 tablets QDS or tramadol 50mg-100mg QDS +/- regular paracetamol
- Step 3: Morphine 5mg-10mg 4 hourly and PRN, titrate every 48 hours if pain not controlled

Seek advice if renal function poor, opioid toxicity or inadequate pain control.
For further information see chapter: Pain and chapter: Renal Failure

Nausea and vomiting
- Search for reversible factors
- Oral Metoclopramide 10mg TDS or Haloperidol 1.5mg-3mg O.D.
- Avoid Cyclizine

Constipation
Laxative:
- 1st line: Stimulant (e.g. Senna); provide routinely to patients on opioids
- 2nd line: Softener (e.g. lactulose, polyethylene glycol)
Dry Mouth
• Avoid acids
• Mucin-based saliva substitutes, sugar free chewing gum

Skin
• Use aqueous cream as soap substitute, use emollient as moisturiser
• 2% menthol in aqueous cream for itch

Depression
• Have a low index of suspicion for depression
• Short-term Psychotherapeutic interventions
• Avoid Tricyclic antidepressants and drugs with many potential drug interactions (e.g. Fluoxetine)
• Consider Sertraline 50mg OD, Citalopram 10mg-20mg OD, Mirtazapine 15mg OD

Anorexia / Cachexia
• Look for reversible problems e.g. dry mouth, oral candida, untreated nausea or constipation, ill-fitting dentures
• Have small meals
• Help preparing food – if patient too fatigued to cook
• Dietician advice

Specific causes of pain
• Angina (consider transdermal nitrate if patient cannot take oral nitrate medication)
• Claudication
• Diabetic neuropathy
• Abdominal bloating (due to e.g. liver capsule distension, gut wall oedema, constipation)
Many cardiac medications will remain important in managing the patient’s symptoms even in the advanced stages of cardiac failure, e.g. furosemide for breathlessness secondary to fluid overload and their management is often done in discussion with the Cardiac Failure Team.

Cardiac failure with LVSD

- Loop diuretic if fluid overload (e.g. furosemide – may be given subcutaneously via syringe driver/pump if necessary in end-stage cardiac failure)
- Angiotensin-converting enzyme inhibitor (ACE inhibitor) e.g. Ramipril.

Or

- Angiotensin-receptor blocker (ARB e.g. candesartan) if intolerant to ACEI, e.g. cough
- Spironolactone for NYHA class III and IV (beware hyperkalaemia)
- Beta-blocker (e.g. bisoprolol, carvedilol, nebulol*)
- Digoxin (for positive inotropic effects and/or rate control in atrial fibrillation)
  *Best tolerated and licensed in the elderly

Diastolic heart failure

- Loop diuretic if fluid overload (e.g. furosemide)
- Rate control (to prolong LV diastole)
- Converting to sinus rhythm if in AF (discuss with the Heart Failure Team)
## Potentially reversible symptoms

<table>
<thead>
<tr>
<th>Symptom/s</th>
<th>Reversible cause/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, diarrhoea, drowsiness, confusion</td>
<td>Consider Digoxin toxicity</td>
</tr>
<tr>
<td>Dry mouth, dizziness, falls</td>
<td>Reduced blood pressure, diuresis and fluid restriction</td>
</tr>
<tr>
<td>Cough</td>
<td>ACE inhibitor therapy</td>
</tr>
<tr>
<td>Malaise, lethargy</td>
<td>Hypokalaemia, beta-blocker therapy</td>
</tr>
<tr>
<td>Abdominal bloating</td>
<td>Gut wall oedema, constipation</td>
</tr>
</tbody>
</table>
Drugs to avoid

Some drugs used generally in palliative care for symptom control may worsen heart failure and these should be avoided or used with caution. The following table gives guidance with regard to drugs which may cause particular problems. Advice should be sought from the Specialist Palliative Care Team or Heart Failure Team if there are particular concerns.

<table>
<thead>
<tr>
<th>Drug to avoid</th>
<th>Problematic Side Effects In Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>Cause sodium and water retention and can worsen renal function</td>
</tr>
<tr>
<td>Steroids</td>
<td>Cause water retention. Risk of hyperglycaemia</td>
</tr>
<tr>
<td>Progestogens</td>
<td>Cause water retention.</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Anticholinergic: Can cause cardiac arrhythmias</td>
</tr>
<tr>
<td></td>
<td>Hyponatraemia and postural hypotension</td>
</tr>
<tr>
<td></td>
<td>Should be avoided in cardiac disease particularly if there is a history of arrhythmias</td>
</tr>
<tr>
<td></td>
<td>SSRI’s and mirtazapine are safer</td>
</tr>
<tr>
<td>Cyclizine</td>
<td>Anticholinergic antihistamine: May cause arrhythmias and hypotension.</td>
</tr>
<tr>
<td></td>
<td>Avoid in severe cardiac failure</td>
</tr>
<tr>
<td>Glycopyrronium, Hyoscine, hydrobromide, Hyoscine butylbromide</td>
<td>Anticholinergic: Use with caution in cardiac disease.</td>
</tr>
<tr>
<td>Haloperidol and Levomepromazine</td>
<td>Avoid as contains high sodium load and requires increased fluid intake which may not be appropriate with cardiac failure</td>
</tr>
</tbody>
</table>
Cardiac Interventions

Some cardiac interventions may improve quality of life in cardiac failure even in advanced disease.

For patients who have an implantable device, it is important to establish whether it is purely a pacemaker or a device which includes defibrillator function.

**Cardiac resynchronization therapy (CRT)**

Also known as the biventricular pacemaker, may be beneficial in carefully selected patients to correct cardiac ‘dyssynchrony’ (uncoordinated and inefficient pumping of the right and left ventricles).

**CRT pacing therapy in advanced cardiac failure can improve:**

- haemodynamics
- symptoms
- quality of life

**Types of device include:**

- CRT-P (pacing mode)
- CRT-D (pacing and defibrillator function)

Some ICDs (Implantable Cardioverter Defibrillators) function purely as defibrillators reducing sudden cardiac death in patients with cardiac failure in those surviving a ventricular arrhythmic event (secondary prevention) and for primary prevention.
The Dying Phase

Medicines review

In the dying phase, it will be appropriate to review and discontinue some of the patient’s medication (in consultation with the Cardiology or Specialist Palliative Care Team).

In general continue with medications with symptomatic benefits and stop those aimed at medium to long term reductions in morbidity and mortality.

Consider continuing with following as they may be providing symptomatic benefit:

- diuretics (unless too dehydrated, may be appropriate as CSCI)
- antianginal medication (consider transdermal nitrate if patient is not able to take oral medication)
- digoxin (stopping digoxin may worsen heart failure due to the positive inotropic effects of digoxin)

Reassess the value of the following and consider stopping:

- lipid lowering drugs
- spironolactone
- beta-blockers
- ACE inhibitors or ARBs
- antihypertensives (monitor BP initially)
- antiplatelet medication
- anticoagulants
- antianginal medication if no symptoms (monitor for symptom recurrence; consider transdermal nitrate if patient is no able to take oral medication)
Device Management

For patients who are in the dying phase and who have an active defibrillator in situ, there is a risk of inappropriate shocking by the device; metabolic or biochemical abnormalities may lead to an agonal cardiac rhythm triggering the defibrillator, a situation which must be avoided in the dying patient.

Proactive deactivation of the defibrillator function of a device according to local guidelines and policy prevents the distress of inappropriate shocks as a patient dies.

It is possible to deactivate the defibrillator function but preserve the pacing mode of CRT-D devices.

References


• “Medical Therapy Guidelines for Chronic Heart Failure”, Coventry and Warwickshire Cardiovascular Network, multi-professional working group, version 6, 2007, UHCW e-guidelines 2011 available at www.c-a-s-t-l-e.org.uk

• Zacharias H, Raw J, Nunn A et al “Is there a role for subcutaneous furosemide in the community and hospice management of end-stage heart failure?” Pall Med. 25 (6) pp65
Symptom Control in Patients with Liver Failure

This chapter aims to prescribe general symptom prescribing advice and non-pharmaceutical approach for patients with palliative liver disease.
Introduction

Liver disease is a significant public health issue. In 2010 it represented the fifth biggest cause of death after cancer, circulatory disease, respiratory disease and dementia. Strikingly, whilst the mortality for cancer, circulatory and respiratory disease is falling, the number of deaths due to liver disease continues to rise.

The most common diagnosis for liver impairment is alcohol-related liver disease which accounts for well over a third (37%) of all deaths from liver disease.

Furthermore, 22% of deaths due to liver disease are from primary liver cancer, the majority of which will have alcohol-related liver disease as the underlying cause.

Other major causes of liver disease include:

• Non-alcoholic steatohepatitis (NASH) or “Fatty Liver” associated with obesity
• Viral hepatitis
• Other chronic liver diseases
• Hepato-biliary disorders
• Pancreatic disorders

Many patients with advanced liver disease experience repeated episodes of deterioration, otherwise termed ‘decompensation’. This is when one or more of the sequelae of liver disease (e.g. ascites, oedema, encephalopathy, jaundice, bleeding) become more progressive, leading to a decline in the patient’s ability to function.
Symptoms may fully or partially resolve, either spontaneously or as a result of medical intervention, leading to an improvement in the patient’s ability to function. Some patients experience an episode of decompensation from which they do not recover and death follows. Several factors may influence whether a particular episode leads to terminal decompensation, including:

• The patient’s physiological reserve (‘fitness’)
• Presence of multiple symptoms
• Presence of added complications such as infection or kidney failure
• Timing, appropriateness and vigour of medical intervention
• The patient’s preferences and engagement with active treatment

Patients with end stage liver disease experience significant symptom burden, either through the impact of their deranged liver function or through complications to which they are particularly vulnerable. These can include:

• Fluid retention
  ▪ Generalised oedema, secondary to reduced serum albumin levels
  ▪ Ascites, leading to abdominal distension, gastric compression and breathlessness
• Muscle wasting and cramps, secondary to protein calorie malnutrition
• Hepatic encephalopathy (HE), causing delirium and confusion: a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction and portal-systemic shunting diagnosed after exclusion of other known brain diseases. It affects 30% to 45% of patients with cirrhosis, and its presence and degree of progression signify poor prognosis and high mortality. It can be exacerbated by:
  ▪ Infection
  ▪ Constipation: a reduced bowel transit time may cause increased ammonia absorption and precipitate encephalopathy. Non-absorbable disaccharides such as lactulose have traditionally been the mainstay of treatment.
Non-absorbable antibiotics such as rifaximin may also be used.

- Opioid analgesics and sedatives
- Worsening liver function

• Jaundice and itching, secondary to reduction in the breakdown of bilirubin
• Nausea and vomiting due to:
  - Ascites causing gastric compression
  - Increase in circulating toxins
  - GI bleeding and associated raised 5HT3

• Gastrointestinal bleeding due to oesophageal varies, secondary to reduced synthesis of clotting factors, reduced absorption of vitamin K and portal hypertension
• Increased risk of spontaneous bacterial peritonitis
• Fatigue
• Anxiety and depression

Prescribing for a patient with liver disease can be complex as it is affected by the specific cause of the liver disease and the degree of liver damage. As the hepatic reserve is large, liver disease must be severe before changes in drug metabolism occur. Traditionally, markers such as raised bilirubin, raised INR/prothrombin time, raised ALT, low albumin, and the presence of ascites, encephalopathy or jaundice are principally used to assess disease severity. However, there are no adequately sensitive biochemical markers or formulae that can accurately predict drug clearance and there is a lack of reliable information on drugs commonly used in palliative care.

Advice regarding drug treatment therefore, should be individualised to each patient and prescribing should be kept to a minimum where possible. Known hepatotoxic drugs should be avoided if possible.
Pain Management

For opioids, start with a low dose immediate release preparation and titrate slowly according to response and side effects. Regular review is essential with careful monitoring for signs of toxicity and prevention of constipation. Once established on immediate release opioids, the dose can then be converted to slow release preparations or transdermal patches. When transdermal patches are being considered, fentanyl should be used in preference to other opioids.

Analgesics: Based on Type of Liver Disease

Mild hepatitis without cirrhosis

**Paracetamol:** Normal therapeutic doses (caution in malnourished or acute viral hepatitis)

**NSAID:** Normal doses

**Opioid:** Normal therapeutic doses

Cholestasis

**Paracetamol:** Normal therapeutic doses

**NSAID:** Avoid if possible. If necessary, ibuprofen may be best option

**Opioid:** Use with caution. Monitor for adverse effects. May worsen pruritus.
Compensated cirrhosis

**Paracetamol:** Normal therapeutic doses (caution in malnourished and chronic alcoholics)

**NSAID:** Avoid

**Opioid:** Avoid where possible.

**Weak opioids:** Dihydrocodeine may be preferred compared to codeine.

**Preferred strong opioid:** Morphine. Use small doses with reduced frequency of administration.

Decompensated cirrhosis

**Paracetamol:** Normal dose with caution. Half-life may be prolonged

**NSAID:** Avoid

**Opioid:** As for compensated cirrhosis but greater caution needed as increased accumulation likely

Acute liver failure

**Paracetamol:** Extend dose interval

**NSAID:** Avoid

**Opioid:** As for compensated cirrhosis. Strong opioids preferably only considered after discussion with liver unit.
The use of Analgesics in Liver Disease

Paracetamol

Class: Non-opioid

**Recommendations in liver disease:** Use with caution

**Comments:** Can opt for a sub-maximal dose 500mg-1g TDS-QDS especially if at higher risk for paracetamol toxicity *

* Some patients may be at increased risk of experiencing paracetamol toxicity at therapeutic doses, particularly those with a body-weight under 50kg and those with risk factors for hepatotoxicity. Clinical judgement should be used to adjust the dose of oral and intravenous paracetamol in these patients.

Codeine

Class: Weak opioid

**Recommendations in liver disease:** Avoid use

Dihydrocodeine

Class: Weak opioid

**Recommendations in liver disease:** Use with caution

Tramadol

Class: Weak opioid

**Recommendations in liver disease:** Avoid if severe

**Comments:** Moderate impairment – increase dosing interval
**Tapentadol**

Class: Strong Opioid and NARI

Recommendations in liver disease: Avoid if severe

Comments: Immediate-release tablets, initial max. daily dose 150 mg; for modified-release tablets, initial max. daily dose 50 mg

**Morphine & Diamorphine**

Class: Strong Opioid

Recommendations in liver disease: Use with caution

Comments: Moderate impairment – use lower doses
Severe impairment – lower doses and extend dosing interval

**Buprenorphine**

Class: Strong Opioid

Recommendations in liver disease: Use with caution

Comments: May be opioid of choice in hepatorenal syndrome

**Oxycodone**

Class: Strong Opioid

Recommendations in liver disease: Contra-indicated moderate to severe liver disease

Comments: Moderate impairment – lower doses; minimum dosing interval of 6 hourly for immediate release products
Targinact® oxycodone/naloxone

Class: Strong Opioid

**Recommendations in liver disease:** Contra-indicated moderate to severe liver disease.

**Comments:** Naloxone component may be systemically absorbed resulting in opioid withdrawal and thus precipitate pain.

Fentanyl

Class: Strong Opioid

**Recommendations in liver disease:** Use with caution

**Comments:** Avoid transdermal products when initiating opioids. Single doses appear unaltered by liver disease. May be suitable for treatment of breakthrough pain.

Hydromorphone

Class: Strong Opioid

**Recommendations in liver disease:** Use with caution

**Comments:** Dosage reduction necessary

Alfentanil

Class: Strong Opioid

**Recommendations in liver disease:** Use with caution

**Comments:** Dosage reduction necessary

Methadone

Class: Strong Opioid

**Recommendations in liver disease:** Seek specialist advice

**Comments:** Seek specialist advice
**NSAIDs**

**Class:** Adjuvant  
**Recommendations in liver disease:** Avoid

---

**Amitriptyline**

**Class:** Adjuvant  
**Recommendations in liver disease:** Use with caution  
**Comments:** Avoid in severe liver disease

---

**Pregabalin**

**Class:** Adjuvant  
**Recommendations in liver disease:** Not affected by liver impairment  
**Comments:** Normal doses can be used

---

**Ketamine**

**Class:** Adjuvant  
**Recommendations in liver disease:** Use with caution  
**Comments:** Dosage reduction necessary

---

**Gabapentin**

**Class:** Adjuvant  
**Recommendations in liver disease:** Not affected by liver impairment  
**Comments:** Normal doses can be used

---

Co-administration of enzyme inducing antiepileptic medications may increase paracetamol toxicity – doses should be reduced.
Nausea and Vomiting

A management approach should be based upon the clinically determined mechanism of nausea and/or vomiting, which can be multifactorial.

The pressure from ascitic fluid may cause gastric compression. The patient may benefit from treatment of ascites alongside a prokinetic anti-emetic such as metoclopramide.

Nausea may be secondary to accumulation of toxins and therefore centrally acting anti-emetics, such as haloperidol, may be indicated.

Upper gastro-intestinal bleeding due to portal hypertension may damage enterochromaffin cells, leading to release of the neuro-transmitter serotonin (5HT3) which can cause vomiting. 5HT3 antagonists, such as ondansetron and granisetron, could be tried.

Cyclizine and levomepromazine may also be useful treatment options.

Choices of anti-emetics

Haloperidol, Levomepromazine and Cyclizine

Can be used in normal doses for mild to moderate impairment but can precipitate coma in severe impairment.
Advisable to start with a low dose and titrate slowly in this scenario.

Metoclopramide

Can be used in normal doses in mild to moderate impairment.
However, the half-life can double in severe impairment, so it may be advisable to reduce the daily dose by 50%.
Cholestatic Pruritis

Cholestatic pruritus is secondary to obstruction of common bile duct and can be relieved by inserting an intra-ductal stent. Treatment should be based upon the severity of the pruritus and the following approaches can be considered:

- Warm baths and emollients
- Topical antipruritic: Levomenthol (menthol) cream BP 0.5-2% may be helpful
- Anti-histamine: consider a trial either at bed time or around the clock. Chlorphenamine 4mg TDS may be effective. Higher doses can be used but may precipitate coma or mask signs of encephalopathy in severe liver disease
- Sertraline 50mg-100mg once daily
- Other drugs include Rifampicin, Danazol and Naltrexone – please seek specialist advice

Ondansetron

Dose not to exceed 8mg/day in moderate or severe impairment as clearance is significantly impaired.

Granisetron

Can be used in normal doses.
Prescribing Benzodiazepines

Sedatives can lead to coma in advanced liver disease and a general approach would be to start with a reduced dose and titrate slowly. If treatment is necessary, benzodiazepines with shorter half-lives are safer.

Some benzodiazepines are metabolized by the liver more extensively than others, and some knowledge of this can help with therapeutic decisions.

- **Lorazepam and Temazepam** can be used at normal doses, but there is still a risk of coma, so a reduced dose may be advisable initially.
- **Midazolam** – elimination is significantly reduced in cirrhosis and therefore a reduced dose is advisable to avoid prolonged sedation.
- **Diazepam** – half-life more than doubles in cirrhosis and should therefore be avoided in severe impairment.
- **Clonazepam** – avoid due to prolonged half-life. Can be useful for severe agitation/pain in terminal care – please seek specialist advice.

Fluid Overload

The ascites associated with liver failure is secondary to portal hypertension (seen in cirrhosis, hepatocellular cancer and extensive hepatic metastases).

The ascitic fluid has a relatively low albumin concentration, a difference of >11g/L between serum and ascitic fluid. This often responds well to a median daily dose of 200mg-300mg spironolactone, with up to 90% of cirrhotic patients noticing a benefit.

If a patient fails to respond to or tolerate diuretic treatment, paracentesis can be considered. If a patient requires frequent paracentesis, a tunneled drain can be considered, depending on the prognosis. Contact your local service for further advice.
References


Symptom control in patients with Renal Failure

Identification of the palliative phase in renal failure can be more difficult and unpredictable than in cancer patients and they often have palliative care and symptom control needs.
Introduction

Symptom control measures should be modified in cancer patients who have concurrent renal failure as well as those with non-malignant causes of end stage renal failure.

Cancer patients may develop renal impairment due to:

- ureteric obstruction caused by compression by a pelvic tumour, or
- as a consequence of a concurrent illness

If clinically appropriate the origin of the renal impairment should be investigated and corrected if possible

e.g. stenting in ureteric obstruction

Causes of pain and other symptoms should be identified and treated appropriately.

Disease specific causes of pain include:

- Underlying disease e.g. polycystic kidney disease, diabetic neuropathy
- Renal disease and its treatment e.g. calciphylaxis (tissue ischaemia due to calcification of tissue and small arteries in dialysis patients); ischaemic neuropathies due to A-V fistulae; peritonitis due to peritoneal dialysis
Stage of renal disease will guide management.

<table>
<thead>
<tr>
<th>Stage</th>
<th>eGFR</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;90 ml/min</td>
<td>Normal renal function</td>
</tr>
<tr>
<td>2</td>
<td>60–89 ml/min</td>
<td>Mildly reduced renal function</td>
</tr>
<tr>
<td>3</td>
<td>30–59 ml/min</td>
<td>Moderately reduced renal function</td>
</tr>
<tr>
<td>4</td>
<td>15–29 ml/min</td>
<td>Severely reduced renal function</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15 ml/min</td>
<td>Very severe or ESRD</td>
</tr>
</tbody>
</table>

*eGFR estimated glomerular filtration rate*

## Analgesia in Patients with Renal Disease

Many analgesics are excreted by the kidneys and any degree of renal impairment can reduce drug clearance, and therefore the dose of drug required. Glomerular filtration rate (eGFR) gives an indication of how much drug clearance will be affected by renal impairment. Renal dysfunction can also influence the absorption, metabolism, distribution and pharmacodynamics of many drugs.

### End Stage Renal Disease (ESRD) correlates to:

- eGFR of less than 15ml/min or
- Stage 5 (UK CKD Guidelines 2005)

Patients with eGFR 15-29ml/min (Stage 4) will also be more safely managed with medication dose reductions recommended for Stage 5 disease.

### In general when prescribing analgesics in ESRD:

- immediate release preparations are safer than sustained/ modified/ controlled release preparations
- P.R.N. (as required) prescriptions are safer than regular prescriptions
- extended dose intervals are better tolerated
WHO Ladder Step 1 analgesics

Paracetamol

Generally safe.

Metabolism: Extensively metabolised by liver

Dose adjustments: Maximum 3g/24hrs. Minimum dose interval 6hrs.

Comments: Avoid effervescent tablets (high sodium content)

NSAIDS

Avoid (unless risk of deteriorating renal function outweighed by need for NSAID analgesia or patient is on dialysis).

Mechanism: Inhibits COX enzymes. Excreted mainly by the liver.

Comments: Can cause severe and irreversible reduction in eGFR. Avoid in renal failure.

WHO Ladder Step 2 analgesics

Codeine

Avoid

Metabolism: Metabolites excreted by the kidneys and accumulate.

Tramadol

Generally tolerated at reduced doses.

Metabolism: Metabolised by the liver. Excreted in urine.

Dose adjustments: Dose reduction required in patients over 75 years and in renal failure.
eGFR less than 30ml/min at dose of 50mg-100mg BD PO
eGFR less than 10ml/min at dose of 50mg BD PO (50mg QDS PO if on dialysis)

Comments: Use immediate release preparation.

Generally has fewer opioid side effects than other opioids at an equivalent dose.
WHO Ladder Step 3 analgesics

N.B. No opioid is completely safe in ESRD. Patients should be monitored for signs of opioid toxicity when commencing any strong opioid. e.g. respiratory depression, myoclonic jerks, drowsiness, confusion, hallucinations, agitation. See chapter on Pain for dose conversions and seek specialist advice.

**Alfentanil**

Suitable parenteral opioid for use in advanced renal disease.

**Metabolism:** Extensively metabolised in the liver.

**Dose adjustments:** No change in dose required. See conversions in Pain chapter.

**Comments:** Can be given via s.c. syringe driver/pump. Short duration of action limits its use for breakthrough analgesia.

**Buprenorphine**

Use with caution.

**Metabolism:** Metabolised in liver but metabolites, excreted in the urine.

**Dose adjustments:** Limited data. Use lowest dose possible.

**Comments:** Available as transdermal patch and sublingually. Accumulation of metabolites in renal failure may cause respiratory depression.

**Fentanyl**

Suitable parenteral opioid for use in advanced renal disease.

It is not advisable to use immediate release fentanyl preparations in patients who are naive to step 3 opioids. Seek specialist advice.

**Metabolism:** 90% metabolised in the liver.

**Dose adjustments:** Does not appear to significantly accumulate in renal failure. Use according to guidelines for non-renal failure patients. (see Pain chapter)

**Comments:** Available as immediate release preparations and as a transdermal patch.
(Can be given s.c. via a syringe driver/pump but the more soluble Alfentanil may be preferable if large dose volumes of Fentanyl are required).

**Hydromorphone**

Use with caution.

**Metabolism:** Primarily metabolised in the liver but excreted in the urine.

**Dose adjustments:** Use immediate release preparation 4–6 hourly initially and titrate cautiously. Remember that the lowest oral dose is 1.3mg which is equivalent to 10mg p.o. morphine.

**Comments:** Theoretically may cause similar problems to morphine but in practice often better tolerated than morphine. Available in immediate release and slow release oral preparations and s.c. Injection.

**Oxycodone**

Use with caution. Avoid in stage 5 CKD.

**Metabolism:** Eliminated mainly by the liver, 10% excreted unchanged in urine.

**Dose adjustments:** If used, start with smallest dose possible in an immediate release preparation. Consider extending dose interval.

**Comments:** Elimination half-life is prolonged, therefore may accumulate in advanced renal disease.

**Methadone**

Use by experienced clinician only.

**Metabolism:** Metabolised in liver. Excreted mainly in faeces

**Dose adjustments:** Significant individual variation makes titration of doses difficult as in patients with normal renal function.

**Comments:** May be a useful alternative to other opioids in advanced renal disease BUT requires specialist supervision.
WHO Ladder Step 3 Analgesics (continued)

Diamorphine

**Not well tolerated. Avoid if possible.**

**Metabolism:** Major metabolite (morphine-3-glucuronide) excreted by kidneys and accumulates in renal failure.

**Dose adjustments:** If necessary to use, start with an immediate release preparation in small doses e.g. 1.25mg–2.5mg every 4 to 6 hours.

**Comments:** Likely to cause toxicity and have a longer duration of action. Not well tolerated in patients with advanced renal disease.

Morphine

**Not well tolerated. Avoid if possible.**

**Dose adjustments:** If necessary to use, start with small doses e.g. 1.25mg – 2.5mg every 4 to 6 hours.

**Comments:** Likely to cause toxicity and have a longer duration of action. Not well tolerated in patients with advanced renal disease.

Adjuvant Analgesics for Neuropathic Pain

Tricyclic Antidepressants

**Metabolism:** Metabolised by the liver.

**Dose adjustments:** Dose reduction is not usually necessary in renal failure.

**Comments:** Start with low doses e.g. amitriptyline 10mg - 25mg, increasing slowly. Beware increased risk of cardiovascular side effects in patients with renal impairment.
Anticonvulsants

**Carbamazepine**

**Metabolism:** Metabolised by the liver.

**Dose adjustments:** No dose adjustment required. Commence at 200mg daily.

**Comments:** Usually well tolerated.

**Gabapentin**

Use with caution.

**Metabolism:** Excreted unchanged by the kidneys.

**Dose adjustments:** Dose depends on eGFR: if eGFR < 15 max 300mg OD if eGFR 15-29 max 300mg BD.

**Comments:** May accumulate in renal failure.

**Pregabalin**

Use with caution.

**Metabolism:** Excreted unchanged by the kidneys.

**Dose adjustments:** Dose depends on eGFR: if eGFR < 15 max dose 75mg OD if eGFR 15–29 max dose 150mg OD.

**Comments:** May accumulate in renal failure.

**Sodium Valproate**

Use with caution.

**Metabolism:** Excreted unchanged by the kidneys.

**Dose adjustments:** Dose depends on eGFR: if eGFR < 15 max dose 75mg OD if eGFR 15–29 max dose 150mg OD.

**Comments:** May accumulate in renal failure.
Adjuvant analgesics for Neuropathic Pain (continued)

**Clonazepam**

**Metabolism:** Metabolised by the liver eliminated by the kidneys.

**Dose adjustments:** 0.5mg to 1mg nocte PO.

**Comments:** May accumulate in renal failure.

---

**Anti-emetics in Renal Disease**

**Cyclizine**

**Metabolism:** Metabolised by the liver.

**Dose adjustments:** Avoid or use smallest dose possible in severe renal failure.

**Comments:** May induce hypotension and tachyarrhythmia and is not recommended.

**Haloperidol**

**Metabolism:** Metabolised mainly by the liver.

**Dose adjustments:** Reduced doses may be required e.g. 1.5mg OD nocte PO/SC.

**5-HT3 receptor antagonists**

**Metabolism:** Ondansetron is metabolised mainly by the liver.

**Dose adjustments:** Reduced doses may be required e.g. Ondansetron 8mg BD PO.
**Levomepromazine**

**Metabolism:** Metabolised by the liver but excreted in the urine and faeces.

**Dose adjustments:** Reduced doses may be required e.g. 2.5mg SC, 6mg PO

**Metoclopramide**

**Metabolism:** Excreted by the kidneys.

**Dose adjustments:** Avoid or use smallest dose possible in severe renal failure.

**Comments:** Does not cross blood-brain barrier.

---

**Glycopyrronium**

**Indication:** Upper respiratory tract secretions.

**Metabolism:** Excreted via the kidneys.

**Dose adjustments:** Use at 50% dose.

**Comments:** Does not cross blood-brain barrier.

**Hyoscine Butylbromide**

**Indication:** Upper respiratory tract secretions.

**Metabolism:** Excreted via the kidneys.

**Dose adjustments:** No dose reductions necessary.

**Comments:** Does not cross blood-brain barrier.

---

**Drugs used in the dying phase**
Drugs used in the dying phase (continued)

**Hyoscine Hydrobromide**

**Avoid**

**Comments:** Crosses blood-brain barrier and can cause agitation.

**Midazolam**

**Indication:** Agitation.

**Metabolism:** Predominantly metabolised by the liver.

**Dose adjustments:** Start with small doses e.g. 1.25mg–2.5mg SC p.r.n. and 5mg/24hr via a syringe driver/pump.

**Comments:** Increased cerebral sensitivity can occur.

**Alfentanil**

**Indication:** Pain.

**Metabolism:** Extensively metabolised in the liver.

**Dose adjustments:** No change in dose required. See conversions in Pain chapter.

**Comments:** Can be given via s.c. syringe driver/pump. Short duration of action limits its use for breakthrough analgesia.

**Fentanyl**

**Indication:** Pain.

**Metabolism:** Extensively metabolised in the liver.

**Dose adjustments:** No change in dose required. See conversions in Pain chapter.

**Comments:** Can be given via s.c. syringe driver/pump. Short duration of action limits its use for breakthrough analgesia.
References


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End of Life Care

The following pages provide practical guidance and support to help health and social care staff to look after people at the end of life.
Introduction

There are a number of End of Life Care tools which provide practical guidance and support to help health and social care staff to implement the national Ambitions for Palliative and End of Life Care.

Key points include:

- A palliative care register – this is held by the GP and identifies patients approaching the end of their life. It enables the primary care team to monitor the patient’s progress, anticipate their health and social care needs (including preemptive prescribing for anticipated symptoms or complications) and prioritise Advance Care Planning (enabling patients to express their preferences for care at the end of their life).

- Education for all staff involved with end of life care should be available.

- Improved communication between disciplines and across care settings during the day and out-of-hours.

Advance care planning tools

There are a number of different documents available. They are all aimed at prompting patients to discuss and document their Preferred Priorities for Care as they approach the end of life.

This might include:

- The patient’s preferences for their health and social care e.g. where they would prefer to be cared for in the final days of life.

- Which treatments, if clinically indicated, they would choose to accept or decline, given the likely progression of their condition including CPR.
Recognising the Dying Phase

It is important that the patient is known to have advanced disease or frailty and that reversible causes of deterioration have been excluded.

Usually the dying phase can be recognised from the following features:

- Unconscious / sleeping much of the time
- Little interest in food/fluids
- Unable to swallow tablets
- Largely bed-bound

The assessment that a patient is in the last days of life should be made by the multidisciplinary team in discussion with the patient and relatives as appropriate.

Priorities for care of the dying person.

When it is thought that a person may die within the next few days or hours:

1. This possibility is recognised and communicated clearly, decisions made and actions taken in accordance with the person's needs and wishes, and these are regularly reviewed and decisions revised accordingly.

2. Sensitive communication takes place between staff and the dying person, and those identified as important to them.

3. The dying person, and those identified as important to them, are involved in decisions about treatment and care to the extent that the dying person wants.

4. The needs of families and others identified as important to the dying person are actively explored, respected and met as far as possible.

5. An individual plan of care, which includes food and drink, symptom control and psychological, social and spiritual support, is agreed, coordinated and delivered with compassion.
At this stage, only drugs that are required for comfort and symptom control should be prescribed:

a) Stop non-essential medication e.g.
   • cholesterol-lowering agents such as statins
   • anti-hypertensive drugs
   • levothyroxine

b) Prescribe medication via a suitable route (e.g. subcutaneous injection or syringe driver/pump) for:
   • pain
   • nausea and vomiting
   • sedation
   • secretions
   • breathlessness

There will be geographical variation in recommended drugs for the dying phase (e.g. morphine vs diamorphine). Please cross reference with local guidelines/prescribing policies.

Consider appropriate dose reductions in severe frailty or organ failure (see previous chapters)

c) Essential drugs that cannot be given by the usual route should be changed to an alternative (e.g. anticonvulsants converted to subcutaneous midazolam, steroids to dexamethasone sc).
Pain in the Dying Phase

When the patient is no longer able to swallow oral morphine, change to:

- Continuous morphine (or diamorphine) infusion via a syringe driver/pump *(see opioid conversion table in the chapter Pain).*

- Prescribe a p.r.n. dose of subcutaneous morphine (or diamorphine) for breakthrough pain one sixth of the total 24-hour dose of morphine (or diamorphine). This can be given as frequently as necessary, up to 1 hourly when pain severe, and increased in proportion to any increase in 24-hour dose.

- If the patient is still in pain and the p.r.n. morphine (or diamorphine) has been found to be effective, the 24-hour dose of subcutaneous morphine (or diamorphine) may be increased by the sum of the PRN doses given in the previous 24 hours.

- For patients requiring rapidly escalating doses of opioids or frequent use of p.r.n. doses, i.e. ≥2 a day, should prompt a review of pain management plan and consider contacting the Specialist Palliative Care Team for advice.

- If an opioid naïve patient does not currently have pain, prescribe subcutaneous morphine 2.5mg–5mg (consider starting at 1.25mg for frail elderly) p.r.n. If after review at 24 hours two or more doses have been required, set up a syringe driver/pump containing morphine (or diamorphine).

If the patient is on an alternative strong opioid and needs to switch to a syringe driver / pump, see here for conversion doses or seek Specialist Palliative Care Team advice.

Nausea and Vomiting

*See the chapter Nausea and Vomiting for the management of nausea and vomiting and the medical management of intestinal obstruction.*
Restlessness and Agitation in the Dying Phase

In advanced illness, confusion and terminal restlessness/agitation are common. A prognosis of only hours to days may leave insufficient time for a response to some specific treatments and therefore confusion or agitation should be managed symptomatically.

Before prescribing medication for this condition, all efforts should be made to consider non-drug intervention. For example reassurance from staff, a calm environment, the presence of relatives or carers who are close to the patient, items from home which help to orientate the patient, appropriate diurnal lighting, the possibility of one-to-one nursing.

Common causes of confusion or agitation in the dying phase:

- Adverse effects of medication (e.g. opioids, steroids)
- Pain
- Constipation
- Urinary retention
- Hypoxia
- Hypercalcaemia
- Infection
- Uraemia/ hepatic encephalopathy
- Primary brain tumour
- Cerebral metastases
- Spiritual distress

When considering whether or not to treat these causes of confusion or agitation, the burdens of treatment need to be weighed up against the potential for improving comfort at the end of life.

It may be difficult to address psychological causes of distress and anguish in the last few days of life. Reliance is placed on improving environmental factors and appropriately titrating sedation.
General Management of Restlessness & Agitation

**Midazolam**

SC stat: 2.5mg–5mg

**SC 24-hour Syringe Driver/pump: 5mg–30mg**

*Start at the lowest dose in the range especially in the frail or elderly.*

*Useful if anxiety/restlessness predominates however caution as can cause disinhibition and paradoxical agitation, particularly at high doses.*

**Haloperidol**

Oral PRN: 1.5mg–2.5mg

SC stat: 1.5mg–2.5 mg (0.5mg in elderly & frail)

**SC 24-hour Syringe Driver/pump: 1.5mg–5mg**

*Start at the lowest dose in the range especially in the frail or elderly.*

*Useful if features of paranoia or psychosis are present. Also useful as an anti-emetic.*

**Levomepromazine**

Oral PRN: 6mg–25mg

SC stat: 2.5mg–12.5mg

**SC 24-hour Syringe Driver/pump: 5mg–75mg**

*Start at the lowest dose in the range especially in the frail or elderly as very sedative.*

*Useful if features of paranoia or psychosis are present. Also useful as an anti-emetic.*
• Patients who are dying with severe agitation may be very resistant to the effects of sedatives and may need repeat doses at 30–60 minute intervals until settled.
• Occasionally the combined administration of an anti-psychotic and benzodiazepine is required.
• For patients requiring rapidly escalating doses of sedatives, contact the Specialist Palliative Care Team for advice.

Breathlessness in the dying phase

For many patients the fear of dying in a state of marked breathlessness with acute anxiety / panic is their biggest, if unspoken, fear.

Advance care planning is essential in order to ensure that patients and their family are as well prepared as possible.

For many patients advancing disease is often associated with reduced awareness. However it is usually prudent to discuss the option of sedation should increasing distress become an issue. Most patients are comforted by the knowledge that medication is helpful and available if required.

In the last days of life:
• Review the ongoing plan of care and ensure that it remains appropriate for the patient’s changing needs. Think specifically about ceiling of treatment including DNACPR.
• Prescribe PRN drugs as described below in anticipation of anxiety or distress caused by breathlessness. Many patients will become unable to take drugs by the oral route so prescribe medication to be given parenterally e.g. subcutaneously.
• Consider stopping or reducing clinical (artificial) hydration if this is causing fluid overload leading to pulmonary oedema or excessive upper airway secretions.
Breathlessness in the dying phase (continued)

Drugs for breathlessness

There will be geographical variation in recommended drugs for the dying phase (eg morphine vs diamorphine). Please cross reference with local guidelines/prescribing policies.

• Midazolam 2.5mg–5mg SC hourly P.R.N.

• Morphine (or diamorphine) 2.5mg–5mg SC 1–2 hourly PRN (higher doses may be appropriate in patients who are already receiving regular strong opioids. In patients who need repeated (hourly) doses seek specialist palliative care advice.

See the chapter Palliation of Breathlessness and the chapter Symptom control in patients with renal disease and cardiac failure.

Patients who are persistently breathless and distressed may benefit from a continuous infusion of opioid and/or midazolam – in practice try to ascertain the required dose(s) by observing and titrating according to usage of opioid or midazolam over the previous 24–48 hours.

For some patients in the dying phase it may be more practical to commence an infusion of morphine/diamorphine or midazolam at an earlier stage alongside the provision of additional PRN medication.

The following ranges are usually appropriate:

• Morphine 5mg–10mg subcut infusion over 24 hours. See conversion chart in pain chapter for other opioids (higher doses of morphine may be appropriate if the patient is already receiving regular strong opioids for pain).

• Combining opioids and midazolam to manage breathlessness and anxiety in the last days of life is common practice in palliative care.

See also the chapter Palliation of Breathlessness.
Respiratory Secretions in the Dying Phase

Dying patients may be unable to cough effectively or swallow which can lead to retained secretions in the upper respiratory tract.

Noisy, bubbly breathing may occur in 70% patients in the terminal phase. There is little evidence to support the effectiveness of drug treatment for this symptom. However it is established clinical practice to use anticholinergic drugs to try to reduce the accumulation of further secretions.

- Explanation and reassurance for relatives and carers is paramount.
- Re-positioning the patient in bed may be very helpful, for example ‘high side lying’ where the patient is positioned more upright with their head tilted to one side to aid drainage of secretions. A fan may also be beneficial.
- On occasion, for example where there is pooling of saliva in the oropharynx, gentle suction may be appropriate.
- Hyoscine butylbromide and glycopyrronium do not usually cause drowsiness, confusion and paradoxical excitation since they do not cross the blood-brain barrier.

Anticholinergic, Subcutaneous Route

**Hyoscine butylbromide**

**STAT/PRN Injection**: 20mg

**Syringe Driver/pump over 24 Hours**: 60mg – 120mg

**Glycopyrronium**

**STAT/PRN Injection**: 200 micrograms

**Syringe Driver/pump over 24 Hours**: 600 micrograms – 1200 micrograms
Seizures & Diabetes in the dying phase

Both diabetes and pre-existing seizures require pre-emptive planning and prescribing to ensure smooth symptom management.

Seizures:
Where seizures are anticipated in the dying phase (e.g. primary or secondary brain tumours or in known patients with a previous history of seizures) pre-emptive prescribing of an anti-epileptic by an appropriate route is recommended. This is particularly important in patients who have had recent seizures.

Anti-convulsant medication is usually administered bucally or via a continuous subcutaneous syringe driver/pump (see chapter on Syringe drivers for guidance on dosing in continuous subcutaneous infusion).

Seek specialist palliative care team advice.

Diabetes in the dying phase:
Treatment depends on whether the patient has type I, type II or steroid induced diabetes, as well as current diabetes management. Please refer to Diabetes UK or local guidelines.
References


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