

PALLIATIVE CARE PRESCRIBING GUIDELINES

LANCASHIRE AND SOUTH CUMBRIA
PALLIATIVE AND END OF LIFE CARE
ADVISORY GROUP 2014

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NAVIGATIONAL INSTRUCTIONS

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ABBREVIATIONS

BNF	British National Formulary
bd	twice daily
COPD	chronic obstructive pulmonary
disease csci	continuous subcutaneous infusion
CV	Cardiovascular
DS	Data Sheet
E.O.L	end of life
g	grams
GI	Gastrointestinal
HOOF	Home Oxygen Order
Form iv	intravenous
LAB	long-acting bronchodilator
LTOT	long term oxygen therapy
MAOI	mono-amine oxidase inhibitor
mg	milligrams
ml	millilitres
NICE	National Institute for Clinical Excellence
NSAID's	non-steroidal anti-inflammatory drugs
od	once daily
PEG	percutaneous endoscopic
gastrostomy po	oral
pr	per rectum
prn	as required
qds	4 times a day
s/c	subcutaneous
sl	sub-lingual
SPC	Summary of Product Characteristics
SSRI	selective serotonin re-uptake inhibitor
stat	immediately
TCA	tricyclic antidepressant
TD	transdermal
tds	3 times a day

1 : INTRODUCTION

This booklet is limited to prescribing issues in adult palliative care.

Whilst every care has been taken to ensure accuracy, prescribers are still required to exercise clinical judgement. It is the prescriber's personal responsibility to decide how far to apply the information in this booklet.

Consult BNF for cautions, contraindications, advice in renal, liver impairment etc as usual. Further information may be obtained from the specialist sources listed at the back of this guide.

The evidence base for prescribing in palliative care is not extensive or robust. Certain areas of prescribing practice rely on consensus guidelines produced by experts rather than randomised controlled trials.

2 : GENERAL PRESCRIBING POINTS

Polypharmacy in palliative and end of life care may be unavoidable for some patients. As a result prescribers must be aware of potential drug interactions and their clinical relevance to a patient. Many interactions pose a theoretical rather than an actual clinical risk. A common sense approach should be taken when assessing the relative risk to each patient.

Some medications prolong the QT interval and may be clinically significant when two or more medications that prolong the interval are used together. Consider performing an ECG if a patient is known to have ischemic heart disease before starting medication known to have such an effect, for example methadone or haloperidol.

Important points around prescribing in palliative and end of life care include:

- Balance the potential benefits of the medication and the potential or actual burdens placed on the patient by taking it.
- The risk and benefits of any drug will be different for each individual. Risk/benefit ratio will be dependent on the severity of the symptom being experienced, as well as the stage of the illness the patient.
 - o For example the use of a NSAID in a patient with renal impairment should be avoided in most instances, but where a patient has pain responsive to such medication the doctor must judge if the risk of worsening renal function outweighs the possibility of pain relief
- Many medications in palliative care are used beyond licence, by routes that are effective but unlicensed or in ways different from mainstream medicine. Patients should be aware of this and consent to receiving medication beyond its licence.
 - o When a drug is used in this way the person prescribing the drug must be able to justify their decision to do so
 - o Some doses exceed those on the Data Sheet (DS) or Summary of Product Characteristics (SPC). See DS or SPC for full prescribing information.
- Give any medication regime sufficient time to work, using as needed medication to manage symptoms whilst a regime becomes established.

3 : PAIN

PITFALLS IN THERAPY

Pain is common in advanced disease, and patients may have more than one type. Pain management must take into account not only physical pain but also emotional, psychological and spiritual needs. If these are overlooked analgesic failure may result.

It is vital to diagnose the cause or mechanism of each pain before choosing therapy. This is because some pains respond only partially or poorly to oral opioids alone, e.g. bone or nerve pain. See Table 1, Common Pain Types, page 8.

Others respond to non-analgesics e.g. painful swallowing from candida infection will need an antifungal. Managing insomnia, anxiety, depression and breathlessness may also improve pain tolerance. In some cases non-drug treatments may be the first choice.

Take a good pain history. Identify character, location, frequency, relieving and aggravating factors. Assess severity e.g. numerical analogue scale 0-10 or verbal rating scale (mild, moderate or severe). Seek specialist advice if pain is not controlled.

ANALGESICS

Oral therapy is the route of choice. Other routes are only used if there are specific problems e.g. vomiting or swallowing difficulties (see section on Syringe Driver, page 58). The WHO analgesic ladder provides a rational basis for prescribing in cancer pain, advocating analgesia "by mouth, by clock, by ladder".

Key points include:

1. Continuous pain warrants continuous analgesia.
2. Combinations of analgesics may be more effective than single agents.
3. When mild analgesics fail, change to a stronger one up the ladder, not to one of similar potency.

Adjuvants are those drugs not normally considered to be classical analgesics. They relieve pain in specific situations due to their mode of action or effect. They are used with or without conventional analgesics, at any step of the WHO analgesic ladder. Examples include anticonvulsants, tricyclic antidepressants, corticosteroids, antibiotics and antifungals.

TABLE 1. COMMON PAIN TYPES

Pain	Examples	Character	Initial Management	Adjuvants	Consider a
Deep somatic	Bone metastases	Gnawing, aching. Worse on moving or weight bearing	WHO ladder	NSAID's	Radiotherapy Surgery Bisphosphonate
Visceral	Liver, lung, bowel	Sharp ache or deep throbbing Worse on bending or breathing	WHO ladder	Corticosteroid NSAID's	Nerve block Surgery
Neuropathic	Nerve compression, Nerve damage	Burning, shooting Sensory disturbance in affected area	WHO ladder	Tricyclic antidepressant Anticonvulsant Corticosteroid	Radiotherapy TENS Nerve block
Smooth muscle spasm	Bowel obstruction, Bladder spasm	Deep, twisting, colicky in waves	May be sensitive to opioid - variable	Anticholinergic e.g. hyoscine butylbromide	Surgical relief of obstruction

THE WHO ANALGESIC LADDER

There are three steps on the ladder.

Step 1: Non-opioids for mild pain, with or without adjuvants

Step 1 uses simple non-opioids e.g. paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs).

Paracetamol 1g four times daily.

NSAIDs* have a role at all stages of the analgesic ladder if there is an inflammatory component e.g. pleuritic chest pain, soft tissue injury, bone pain. Differences between NSAIDs relate more to adverse effects than efficacy. All NSAIDs are associated with renal adverse effects in addition to cardiovascular (CV) and/or gastrointestinal (GI) toxicity. Naproxen reportedly has a superior CV safety profile, while celecoxib has a superior GI safety profile. Before prescribing a NSAID, consider whether alternative treatment would be appropriate. Prescribe the lowest effective dose of NSAID for the shortest time necessary. Review response to treatment after 14 days and discontinue if no improvement.

Patients receiving long-term treatment with a NSAID/COX-2 inhibitor should receive gastroprotective therapy i.e. Proton Pump Inhibitor, misoprostol.

The following approach is suggested:

1. Ibuprofen 400mg TDS. Higher doses e.g. up to 600mg QDS can be used but the risk of adverse effects increases

If ineffective:

2. Naproxen 500mg BD or nabumetone 500mg -1000mg ON
3. Avoid diclofenac due to the increased cardiovascular risks

If above ineffective consider alternative analgesia or consult a palliative care specialist

* NSAIDs are often described as adjuvant analgesics (see page 25) due to their analgesic and antipyretic properties.

Step 2: Weak opioids plus non-opioids, with or without adjuvants, for mild to moderate pain

If non-opioids fail to relieve pain at maximum tolerated dosage, add a weak opioid.

Codeine or dihydrocodeine 30mg-60mg every four to six hours, maximum 240mg in 24 hours. Higher doses are associated with significant increase in adverse effects. Modified release preparations are available for dihydrocodeine only.

Oral codeine and dihydrocodeine are approximately one-tenth as potent as oral morphine, i.e. 60mg of oral codeine is the equivalent to approximately 6mg of oral morphine. See opioid conversion chart page 24.

Tramadol is also listed as a step 2 weak opioid analgesic. It has opioid and non-opioid properties, which are only partially reversed by naloxone.

Tramadol dose: 50mg-100mg four to six hourly, maximum dose 400mg per 24 hours.

Modified release and immediate release preparations are available.

Tramadol is approximately one-tenth as potent as oral morphine, i.e. 50mg of oral tramadol is approximately equivalent to 5mg of oral morphine. Caution in epilepsy or patients with susceptibility to seizures. Convulsions reported at therapeutic doses. Risk increases if tramadol prescribed with other drugs lowering seizure threshold. Also an increased risk of CNS toxicity when given with SSRIs and TCAs, caution with MAOIs.

Buprenorphine transdermal patches (BuTrans®) may also be considered a step 2 analgesic. The initial dose of 5micrograms/hour is equivalent to 120mg/day codeine.

Move to Step 3 if maximum dose weak opioid +/- adjuvants become ineffective.

Step 3: Strong opioids plus non-opioid, with or without adjuvants, for severe pain

STRONG OPIOIDS

NICE clinical guidance 140 should be referred to when starting a strong opioid. Seek specialist advice before prescribing strong opioids for patients with moderate to severe renal or hepatic impairment.

The patient should be offered frequent review for efficacy and adverse effect. When considering treatment with strong opioids, the patient should be asked about concerns such as:

- Addiction
- Tolerance
- Side effects
- Fears that treatment implies the final stages of life

In addition, the patient and carer should be provided with written information that explains:

- When and why strong opioids are used to treat pain
- How effective they are likely to be
- Taking strong opioids for background and breakthrough pain, addressing:
 - How, when and how often to take strong opioids
 - How long pain relief should last
- Adverse effects and signs of toxicity
- Safe storage
- Follow-up and further prescribing
- Information on who to contact out of hours, particularly during initiation of treatment

MORPHINE

Morphine is recommended as the oral strong opioid of choice. If a pain is opioid responsive, oral morphine will be effective. However, pain poorly responsive to opioids should be suspected if escalating doses of morphine fail to bring relief.

Morphine: Unfounded fears

- 1) Respiratory depression is not a problem as long as the opioid has been started appropriately and titrated correctly against the patient's pain. Pain prevents respiratory depression by stimulating the respiratory centre. If pain is relieved by other methods e.g. nerve block, respiratory depression may occur. If this occurs, reduce the dose or stop the opioid as necessary - seek specialist advice.
- 2) Addiction (i.e. psychological dependence and craving) is not a problem in the palliative care setting. Abrupt withdrawal may cause an escalation of pain and an abstinence syndrome. These are not signs of addiction, which is characterised by loss of self-control, compulsive behavior and use of the drug despite potential harm to self or others.
- 3) There is evidence that the appropriate use of opioids for symptom control in this setting does not shorten life (see references, Thorns & Sykes). Adequate pain relief can only enhance quality of life.
- 4) Tolerance may develop which may require a gradual increase in dose in order to achieve the same effect. Requests for increasing analgesia, however, may reflect progressive disease and necessitate reassessment of pain syndromes.

Morphine Side Effects

Consider renal impairment if toxicity occurs on a previously tolerated dose. Alternative opioids e.g. oxycodone or fentanyl, may be more appropriate in renal impairment. Seek specialist advice.

- 1) Mild drowsiness is common and may occur at the start of therapy and when the dose is increased. Usually diminishes after a few days. If persistent, consider alternative.
- 2) Constipation is very common. Prescribe concurrent laxative, see constipation guidelines, see guidelines on managing constipation on page 36 and table of laxatives on page 37.
- 3) Nausea and vomiting occurs in approximately 30% of patients. Consider metoclopramide 10mg tds for five days or haloperidol 1.5mg at night. Nausea often settles and anti-emetics may be discontinued, but may recur when dose increased.
- 4) Dry mouth is very common and occurs in most patients. Advise good oral hygiene. See dry mouth guidelines, page 45.
- 5) Delirium, myoclonus and hallucinations are signs of toxicity and should prompt a review of the dose. Decrease or stop. Also review patient's renal function.
- 6) Usually well tolerated in hepatic impairment. If severe e.g. prolonged prothrombin time, metabolism may be reduced and require dose reduction or less frequent dosing.
- 7) Respiratory depression and coma - unlikely if opioids used correctly. If occurs, may require naloxone. See BNF or contact National Poisons Information Service. Also see severe opioid toxicity guidelines page 19. Specialist Palliative Care advice may be required for subsequent pain management.

Writing prescriptions for morphine and other Controlled Drugs

When writing an outpatient or take-home prescription for a controlled drug, the total quantity to be supplied should be written in both words and figures. If more than one strength of a preparation is needed to achieve a dose, these details are required for each strength (e.g. 40mg MST® can only be achieved by using a combination of 30mg and 10mg tablets). For the principal legal requirements see BNF: Guidance on prescribing /Controlled Drugs and drug dependence. If unsure, seek advice from a pharmacist.

Prescribe the dose in milligrams or micrograms etc. Do not prescribe liquid preparations by volume alone because serious errors may result.

When prescribing strong opioids use brand names, e.g. MST®, Zomorph®, OxyContin®, Longtec®, Durogesic D-Trans®. Changing between brands may affect pain control and lead to altered uptake or absorption.

TITRATION WITH ORAL MORPHINE

- 1) For patients with no renal or hepatic comorbidities, offer a typical total starting dose over 24 hours of:
 - 20–30 mg of oral morphine [NICE suggests 10–15 mg oral modified release morphine twice daily];
 - Ensure 5 mg oral immediate-release morphine is prescribed for rescue doses during the titration phase. Usually give every 4 hours as necessary, but in some situations this may be required more frequently up to hourly.

Remember that 60 mg of oral codeine or dihydrocodeine is approximately equivalent to 6mg oral morphine; therefore a total daily dose of 240 mg codeine is approximately equivalent to 24 mg of oral morphine. This should be taken into account when moving from step 2 to step 3 on the WHO ladder.

- 2) Review analgesic requirements within the first 24-48 hours. If 2 or more rescue doses have been given in the preceding 24 hours, the background dose will need adjusting by no more than 50%.

To adjust the background dose, total the number of rescue doses administered in the preceding 24 hours and adjust the background dose as follows:

- 1 rescue dose increase background dose by 20%
 - 2 rescue doses increase background dose by 30%
 - 3 or more increase background dose by 50%
- 3) Calculate the new rescue dose for the titration phase (one sixth of the total daily background dose).

Calculation Example 1

Patient started taking Oramorph® solution 10 mg, 4 hourly 2 days ago. Rescue dose = 10mg. On review, patient has taken two rescue doses of 10 mg Oramorph in last 24 hours. Total background dose of Oramorph® = 60 mg
Patient had two rescue doses, therefore increase the background dose by 30% (approximately 20mg)

New background dose = 80 mg morphine

Convert to modified release formulation:

e.g. MST® dose = 80mg divided by 2 = 40mg 12 hourly. Stop regular Oramorph® solution.

The new rescue dose will be $80\text{mg} \div 6 = 10\text{-}15\text{ mg}$. This is usually given 4 hourly but in some situations may be needed more frequently, up to hourly.

Calculation Example 2

Patient started on MST® 10 mg 12 hourly 2 days ago, with a rescue dose of 2.5 mg of Oramorph®

On review patient has taken 4 rescue doses of Oramorph® solution in last 24 hours.

Total background dose = 20 mg

Patient had four rescue doses, therefore increase the background dose by 50% (10 mg)

New background dose of MST® is $30\text{ mg} \div 2 = 15\text{ mg}$ 12 hourly

New rescue dose of Oramorph® is $30\text{ mg} \div 6 = 5\text{ mg}$, 4 hourly (or up to hourly if necessary)

N.B. If use of rescue analgesia has been particularly high, seek Specialist Palliative Care advice urgently. It is not advised to increase the background dose by more than 30% to 50%. Alternative strategies or review of the cause of the pain may be required.

Poor response may require the use of other drugs in combination. Reassess the cause of pain if a dose of more than 120 mg per day of morphine or equivalent drugs has been taken but the patient is still in pain.

PREPARATIONS

Standard Oral Release

Oramorph® Oral solution 10mg/5mL
Oramorph® Concentrated oral solution 20mg/mL
Sevredol® Tablet: 10mg, 20mg, 50mg
Generic oral solutions are available

Parenteral Products

Injection: 10mg/mL; 15mg/mL; 20mg/mL; 30mg/mL (all in 1mL and 2mL amps)

12hourly modified release (MR) morphine for twice daily use

Morphgesic® Tablet: 10 mg, 30 mg, 60 mg, 100 mg
MST® Continus Tablet: 5 mg, 10 mg, 15 mg, 30 mg, 60 mg, 100 mg, 200 mg
MST® Suspension (granules): 20 mg, 30 mg, 60 mg, 100 mg, 200 mg
Zomorph® Capsule: 10 mg, 30 mg, 60 mg, 100 mg, 200 mg

- The capsules can be opened and the contents sprinkled on soft food or mixed with liquid. They are used in the same way as 12 hrly MR tablets and can be given via gastrostomy tubes. When giving via a percutaneous endoscopic gastrostomy (PEG) tube, do not give with oral rehydration therapies, concentrated lactate solutions or similar treatments

24 hourly Modified Release (MR) morphine for once daily use. MXL® capsules

Do not confuse these with 12 hourly MR products - see above.

- a. Convert to once daily morphine from immediate-release oral morphine.

Add up the total background dose given as oral morphine over the preceding 24 hours.

Prescribe the nearest strength of MXL® capsules once daily. Patients must also have rescue doses prescribed to ensure adequate titration of the background dose. Give the first dose of MXL® four hours after the last dose of immediate-release oral morphine – there is no need to overlap. The capsule contents may be sprinkled onto a small amount of soft cold food but not chewed (this ensures full dose taken). The capsule contents may be given via a PEG tube. The inner diameter of the tube needs to be about 3.6mm. The dry granules are introduced into the tube and the system rinsed with about 50ml of liquid intragastric diet from a syringe. Do not rinse with water, because this may block the tube due to the lipophilicity of the granules.

- b. Convert to once daily morphine from 12 hourly modified release morphine.

Do not overlap. Give the first MXL® dose when the next 12 hourly modified release morphine dose would have been due, then once every 24 hours. See page 22 for dose conversions.

- c. Change from MR morphine to the syringe driver

See under "Pain" in Syringe Driver Section, page 62.

DIAMORPHINE / MORPHINE BY INJECTION

Very few patients need injections to actively manage pain. If the pain type is poorly responsive to opioids, simply changing the route to injections will not relieve it - use alternative therapy. For those who cannot swallow and are either opioid naive or on oral morphine, diamorphine or morphine are the opioid of choice for injection. The high solubility of diamorphine in water means that only small volumes of injection are needed, even for high doses and so it is often preferred. Morphine is less soluble and so the volume of injection is larger and may be more painful in higher doses. The subcutaneous route is preferred over the intramuscular route in chronic cancer pain as it is less painful.

When other drugs are needed for subcutaneous injection at the same time as diamorphine (e.g. hyoscine or midazolam) they may be used as the diluent for diamorphine.

NB - do not use cyclizine with diamorphine

As a rough guide, the equivalent dose of diamorphine subcutaneously is about one-third of the oral morphine dose.

e.g. 15mg immediate release oral morphine (e.g. Oramorph) = 5mg subcutaneous diamorphine.

The equivalent dose of morphine subcutaneously is about one-half of the oral morphine dose. e.g. 15mg immediate release oral morphine = 7.5mg subcutaneous morphine.

If a patient is opioid naive a suggested starting dose would be diamorphine 2.5mg subcutaneously as required four hourly or morphine 5mg as required subcutaneously four hourly (in some situations may be required more frequently).

If regular parenteral analgesia is necessary, see section on syringe driver page 58.

STRONG OPIOID SUBSTITUTION

The following alternative strong opioids are not in order of preference. Selection depends on the profile of the individual drug and suitability of available presentations. Seek specialist palliative care advice.

If contemplating substitution to control unacceptable side effects or achieve analgesia, first consider simple measures including

- Dose reduction
- Adjuvant medication to control side effects such as haloperidol, laxatives etc.
- Management of dehydration if appropriate
- Co-analgesics such as neuropathic pain agents, NSAIDs
- Use of techniques appropriate to the pain syndrome such as nerve blocks

On present evidence, alternative opioids are no more effective than morphine as analgesics, but may be better tolerated in some circumstances. "Dose equivalents" are only approximate and can be unpredictable. When substituting opioids close monitoring for side effects and efficacy is mandatory, especially at higher doses.

Indications for choosing alternatives to morphine

1. When dose limiting side effects prevent titration to effective analgesic doses.
2. When intolerable central nervous system side effects develop during use (e.g. agitation, delirium, myoclonic jerks, hallucinations and in extreme cases hyperalgesia and allodynia) which are unresponsive to dose reduction, or when dose reduction leads to increased pain.
3. When the patient is unable to swallow, and parenteral or rectal routes are inappropriate in that individual – when a patch formulation may be needed

If pain is uncontrolled /escalating

Oral oxycodone may permit dose titration.

If pain is stable

In patients with malabsorption, dysphagia, poor compliance, renal impairment or resistant severe constipation, fentanyl or buprenorphine patches maybe indicated.

Although comments on use in renal impairment are made in the following sections, always seek specialist advice before use in any patient with significant renal impairment (grade 3 or 4).

OXYCODONE (OXYNORM AND OXYCONTIN)

The SPC advises conservative, reduced-dose initiation in mild-moderate renal impairment and mild hepatic impairment. It is contra-indicated in severe renal impairment and moderate to severe hepatic impairment. Seek specialist advice if there is renal or hepatic impairment.

Oxycodone is a strong opioid. It provides another Step 3 alternative to morphine. As a guide oral oxycodone is approximately 1.5 times as potent as oral morphine: 10 mg of oral oxycodone is approximately equivalent to 15 mg of oral morphine. See opioid conversion chart, page 22.

Titration with oral oxycodone

If converting a patient from oral SR morphine to oral SR oxycodone (e.g. OxyContin, Longtec) take the total daily background dose of morphine and divide by 1.5.

Calculation example

1. Patient taking MST ® 60 mg BD. Total dose in 24 hours = 120 mg
2. MR oxycodone dose = 120 mg divided by 1.5 = 80 mg per 24 hours = 40 mg BD.
3. Stop MST ® and rescue doses of Oramorph. Calculate and prescribe new rescue dose of immediate-release oxynorm (e.g. OxyNorm ®, Shortec ®). i.e. one sixth the total daily dose of SR oxycodone = $10 = 15$ mg usually 4 hourly, but in some situations may be required more frequently up to hourly.
4. Use the same process as titrating oral morphine (See section on titrating morphine starting on page 11) but the starting doses will be lower.

For example:

- a. Starting dose of immediate release oral oxycodone is 2.5 – 5 mg every 4 hours. Rescue dose is also 2.5 – 5 mg 4 hourly as needed (up to hourly may be necessary).
- b. Alternatively, starting dose of oral MR oxycodone of 5 mg – 10 mg BD, with rescue doses of 2.5-5 mg 4 hourly as needed (up to hourly may be necessary)

Modified release oxycodone preparations

The modified release preparation is suitable for dose titration and maintenance. It is given 12 hourly, reaching steady state plasma levels in about one day. The makers advise that these tablets must not be divided, because this destroys the controlled release matrix and could lead to an increase in oxycodone release.

OxyContin® tablets: 5mg, 10mg, 15mg, 20mg, 30mg, 40mg, 60mg, 80mg and 120mg.
Longtec® tablets: 5 mg, 10 mg, 20 mg, 40 mg, 80 mg
Other branded generic products are available.

Immediate release oxycodone preparations

The immediate release capsules are usually given as rescue doses.
OxyNorm® capsules 5mg, 10mg, 20mg.
OxyNorm® liquid 5mg/5ml.
OxyNorm® liquid concentrate 10mg per ml.

OXYCODONE (OXYNORM) BY INJECTION

If a patient is unable to swallow oral oxycodone then it is available by injection either intravenously or subcutaneously as a bolus or by infusion. As a guide, the subcutaneous dose of oxycodone is approximately half the oral dose.

Example

Oxycodone modified release 40mg bd = Oxycodone injection 40mg over 24 hrs via continuous subcutaneous infusion in syringe driver. (see opioid conversion chart page 22).
Oxycodone injection (as OxyNorm®) is available in 10mg/mL and 50mg/mL.
Generic preparations are available (10mg/mL)
If the patient is opioid naive a suitable starting dose would be oxycodone 2.5mg subcutaneously as required, 4 hourly (in some situations may be required more frequently).

FENTANYL PATCH

The fentanyl patch provides a transdermal strong opioid. Fentanyl may be useful where adverse effects prevented adequate doses of oral morphine being given.

Patients using these patches require rescue doses of an immediate-release oral opioid preparation to titrate analgesia. The patches are suitable only when pain is stable, not if rapidly changing. Be aware that patients who sweat, or are very thin or cachetic may not absorb fentanyl effectively.

Titration with fentanyl

See opioid conversion chart for dose conversion scheme, page 22.
Note: these are only approximate. Patients must be titrated and monitored.

- 1) It is recommended that patients have been titrated with opioids prior to starting a fentanyl patch. The dose equivalent of a fentanyl 25 microgram patch is oral morphine 60 mg per 24 hours. Fentanyl patches are also available as a 12 microgram strength but these are not licensed as an initiating dose but as a titrating dose. If a patient has not been on the equivalent of 60 mg of oral morphine per 24 hours, seek specialist advice before commencing fentanyl patches.
- 2) Onset is gradual, so evaluate the initial effect only after the first 24 hours. Phase out previous analgesic therapy gradually during this time e.g. continue 4 hourly oral morphine for about 6 -12 hours, or apply patch at same time as the last 12 hourly MR morphine dose, or 12 hours after the last once daily MR morphine.
- 3) Carry out dose adjustments in 72-hour steps of 12 to 25 micrograms/hour. Many patients need a higher strength patch after the first three days. Remember to adjust the 'as required' dose if this occurs. If more than one patch needs to be used, apply at the same time to avoid error. Vary the site to rest the skin.
- 4) If pain relief does not last three days, some practitioners have found that occasionally, patients do better changing the patch every two days. However, others prefer to increase to the next patch strength and assess response, and only try changing every two days if pain is still poorly controlled. If pain relief does not last for the full three days seek specialist palliative care advice. Sudden escalation of pain always warrants reassessment of the pain syndrome.
- 5) Opioid withdrawal symptoms (such as colic, diarrhoea, nausea, sweating and restlessness) may occur for a few days on switching to the fentanyl patch, even though pain is relieved. Treat with rescue doses of oral morphine (see previous advice on Rescue Doses under MR morphine section page 13).

At doses above 300 micrograms/hour, consider additional or alternative analgesia.

Fentanyl is an option in renal impairment because there is no accumulation of active metabolites. However dose reduction may still be required and depends on renal function. Seek specialist advice.

Fentanyl patch presentations: 25 micrograms/hour, 50 micrograms/hour, 37 micrograms/hour, 75 micrograms/hour, 100 micrograms/hour. Patches are also available in 12 micrograms/hour for titration between above patch doses.

To convert from fentanyl patches to an alternative opioid, seek specialist advice.

PRESCRIBING FENTANYL PATCHES

In addition to the usual Controlled Drug prescribing requirements, this is an example of the specific fentanyl details required for the prescription:

Fentanyl patch 25 microgram per hour
Supply 10 (ten) patches
One patch to be applied every 72 hours

Remember to include the brand name on the prescription as changing between brands may lead to altered absorption and affect pain control.

Transdermal Fentanyl Preparations

Matrix Patch:	12 microgram/hour; 25 microgram/hour; 50 microgram/hour; 75 microgram/hour; 100 microgram/hour
Brand:	Durogesic DTrans®
Generics (include):	Fencino®, Matrifen®, Mezolar®, Osmanil®, Tilofyl®, Vicity®
Reservoir Patch	25 microgram/hour; 50 microgram/hour; 75 microgram/hour; 100 microgram/hour
Generics (include)	Fentalis®

OTHER FENTANYL PRODUCTS

The following products should only be initiated by a specialist. They are used to treat breakthrough cancer pain in patients receiving opioid therapy.

Oral transmucosal lozenges (Actiq®)
Fentanyl sublingual tablets (Abstral®)
Fentanyl buccal film (Breakyl®)
Fentanyl buccal tablets (Effentora®)
Fentanyl intra nasal spray (Instanyl®)
Fentanyl pectin nasal spray (Pecfent®)

Fentanyl is also available for injection. Only use with specialist advice.

OTHER STRONG OPIOIDS

Buprenorphine

Sublingual and injectable forms of buprenorphine are not recommended for routine use in chronic cancer pain. There are two different preparations of transdermal buprenorphine. They should not be used for acute or intermittent pain or when rapid dose titration is required.

BuTrans® is licensed for non-malignant pain of moderate intensity unresponsive to non-opioid analgesics. It is considered a Step 2 analgesic, e.g. a 5 microgram/hour patch is approximately equivalent to codeine 30 mg QDS. The analgesic effect should not be evaluated for at least 72 hours after application to allow for plasma buprenorphine concentration. The patch is replaced every seven days and the same site must not be used for at least three weeks.

Transec® is a Step 3 analgesic licensed for moderate to severe cancer pain and severe pain unresponsive to non-opioid analgesics. Patients must be titrated with a strong opioid prior to commencement. A Transec® 35microgram patch is approximately equivalent to oral morphine 80 mg per 24 hours. The analgesic effect should not be evaluated for at least 24 hours to allow for increase in plasma buprenorphine concentration. The patch is replaced every four days but the same site should be avoided for at least six days.

Transdermal Buprenorphine Preparations

BuTrans® (7 day patch): 5, 10 and 20 microgram/hour

Transtec® (4 day patch): 35, 52.5 and 70 microgram/hour

Methadone

Methadone is a third-line strong opioid substitute with complex properties, only initiated under specialist supervision – usually initiated in an inpatient setting.

Pethidine

Shorter duration of action and less potent than morphine. Toxic potentially fatal metabolite accumulates with regular use. AVOID. (Used in those countries where first line choices not available).

Tapentadol

Tapentadol has two mechanisms of action, having both opioid and non-opioid effects similar to tramadol. Tapentadol is approximately 2.5 times weaker than morphine (100 mg tapentadol = 40 mg morphine). It is less likely to produce typical opioid adverse effects, such as constipation, than other strong opioids.

The place of tapentadol in cancer pain management is presently unknown and should only be used on specialist advice.

SEVERE OPIOID TOXICITY

Opioids used inappropriately or as a result of an overdose can cause respiratory depression and coma. The specific antidote is naloxone. It has a shorter duration of action than many opioids around 30-60 minutes. Close monitoring and repeated injections or an iv infusion may be required. Some opioids e.g. buprenorphine may require repeated injections or infusions of naloxone.

See BNF or contact National Poisons Information Centre.

Use of Naloxone will result in loss of analgesic effect of the opioid being used.
Seek advice from a specialist about maintaining pain control.

BREAKTHROUGH CANCER PAIN

When patients are on a stable background dose of analgesia, pain may also occur spontaneously, or in relation to specific issues such as dressing changes or on movement. If this pain is predictable then administration of a dose of immediate release morphine, e.g. Oramorph 30 minutes before the event is appropriate. The dose of immediate-release morphine would be the same as the as rescue dose i.e. one-sixth of the total daily dose.

NB - rescue doses of morphine (or oxycodone) used for breakthrough cancer pain must not be used as an indication to adjust the background dose (by definition, breakthrough cancer pain occurs when background pain is relatively stable and adequately controlled).

Fast acting fentanyl preparations may be indicated for pain of rapid onset and short duration (less than 60 minutes) but must only be initiated by a specialist.

PALLIATIVE CARE GUIDANCE ON OPIOID CONVERSION

GENERAL POINTS

1. Ratios are for guidance only. The ratios used are listed in the text. Please note there is a variation in available literature. Considerable variation may occur between patients. Seek advice if concerned. The prescriber should consider co-morbidities and check for drug interaction.
2. At higher doses, e.g. the equivalent of 180mg oral morphine per 24 hours. Consider reducing the equi-analgesic dose by 30%-50%. The sedative effects of an equi-analgesic dose may be much greater.
3. Please do not compare doses between charts. They are not interchangeable.

Conversion between oral morphine, oral oxycodone and fentanyl patches

Morphine			Oxycodone		Fentanyl
4 hourly oral	MR BD oral	MR OD oral	4 hourly oral	MR BD oral	3 day patch
5 mg	15mg	30 mg	2.5 mg	10 mg	12 microgram
10 mg	30mg	60 mg	5 mg	20 mg	25 microgram
15 mg	45mg	90 mg	10 mg	30 mg	37 microgram
20 mg *	60mg *	120 mg *	15 mg*	40 mg*	50 microgram*
30 mg	90mg	180 mg	20 mg	60 mg	75 microgram
40 mg	120mg	240 mg	25 mg	80 mg	100 microgram
50 mg	150mg	300 mg	35 mg	100 mg	125 microgram
60 mg	180mg	360 mg	40 mg	120 mg	150 microgram
70 mg	210mg	420 mg	45 mg	140 mg	175 microgram
80 mg	240mg	480 mg	55 mg	160 mg	200 microgram
90 mg	270mg	540 mg	60 mg	180 mg	225 microgram
100 mg	300mg	600 mg	65 mg	200 mg	250 microgram
110 mg	330mg	660 mg	75 mg	220 mg	275 microgram
120 mg	360mg	720 mg	80 mg	240 mg	300 microgram

*Specialist advice should be sought if patients require more than 120 mg morphine (or equivalent) daily.

Notes: 1. Fentanyl 12 microgram per hour patch is licensed for dose titration between 25-50-75 microgram patches but not as a starting dose.

2. This chart represents current BNF recommendations (September 2013). Oral oxycodone is considered to be 1.5 times more potent than oral morphine; transdermal fentanyl is considered 100 times more potent than oral morphine. Please note these figures differ from manufacturers' recommendations.

Conversion between oral morphine, s/c morphine and s/c diamorphine.

MST bd (oral morphine)	Morphine syringe driver s/c in 24 hours	Diamorphine syringe driver s/c in 24 hours
15mg	15mg	10mg
30mg	30mg	20mg
45mg	45mg	30mg
60mg	60mg	40mg
90mg	90mg	60mg
120mg	120mg*	80mg
135mg	135mg*	90mg
150mg	150mg*	100mg
180mg	180mg*	120mg

Conversion factors:

1. Oral morphine to s/c morphine – divide by 2 (NB – some guidelines recommend divide by 3)
2. Oral morphine to s/c diamorphine – divide by 3

Conversion between oral oxycodone and s/c oxycodone

Oxycodone 4hly oral (Oxynorm)	Oxycodone bd oral (Oxycontin)	Oxycodone injection s/c 4hly (Oxynorm)	Oxycodone syringe driver s/c in 24 hours (Oxynorm)
5mg	15mg	2.5mg	15mg
10mg	30mg	5mg	30mg
15mg	45mg	7.5mg	45mg
20mg	60mg	10mg	60mg
25mg	75mg	10mg-15mg	75mg
30mg	90mg	15mg	90mg
40mg	120mg	20mg	120mg*
50mg	150mg	25mg	150mg*
60mg	180mg	30mg	180mg*
70mg	210mg	35mg	210mg*
80mg	240mg	40mg	240mg*
90mg	270mg	45mg	270mg*

Conversion Factors

1. Oral oxycodone to s/c oxycodone – divide by 2 (note some guidelines suggest divide by 1.5)

* Morphine in doses above 120mg given by a syringe driver may result in a volume unsuitable for administration in a 20ml syringe. Oxycodone in doses above 100 mg given via a syringe driver may necessitate the use of the 50 mg/mL preparation. Seek advice from Specialist Palliative Care Team.

Dose conversion for weak opioids to oral morphine

Drug	To obtain equivalent oral morphine dose, multiply by:	For example, if the patient is having:	Dose in 24h	Approximate oral morphine equivalent In 24 h
Dihydrocodeine	1/10	30mg q.d.s	120mg	10mg
Codeine	1/10	30mg q.d.s	120mg	10mg
Tramadol	1/10	100mg q.d.s	400mg	40mg

Notes: 1. Some literature suggests oral tramadol is 1/5 as potent as oral morphine.

Conversion from transdermal buprenorphine

In these tables transdermal buprenorphine is considered 100 times more potent than oral morphine. Some texts quote transdermal buprenorphine as 75 times more potent.

BuTrans® lower dose buprenorphine formulation patch designed to deliver 5, 10, or 20 microgram per hour changed every seven days, and approximately equivalent to the doses of morphine listed below:

BuTrans	5Microgram/hour	10Microgram/hour	20Microgram/hour
Oral Morphine	12mg per 24 hour	24mg per 24 hour	48mg per 24 hour

Transtec® higher dose buprenorphine formulation patch designed to deliver 35, 52.5 or 70 microgram per hour changed every four days.

Transtec®	35microgram/hour	52.5microgram/hour	70microgram/hour
Oral Morphine	80mg per 24 hour	120mg per 24 hour	160mg per 24hour

4. BONE PAIN

Local bone pain from bone metastases and bone marrow infiltration is a common pain syndrome in advanced cancer. It may be a dull ache or intense, often worse on movement and weight bearing. It is appropriate to continue to use an overall approach based on the analgesic ladder, as described in section 3. NSAIDs are often useful adjuvant analgesics. Bone pain may be accompanied by neuropathic pain, and adjuvant neuropathic analgesia can also be helpful.

It is important to remember the roles of radiotherapy, orthopaedic techniques and bisphosphonates, particularly for pain that is difficult to manage. Treatment of the underlying malignancy, where possible, may also improve pain from bone metastases. If other measures reduce pain, reduce the opioid dose to avoid opioid side effects.

OPIOIDS

Background opioid analgesia may relieve continuous dull aching pain, but often not pain on movement (incident pain). Physical measures may help. Also see page 19 “Breakthrough pain”.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

Their precise mechanism in this situation is not fully understood, but inhibition of prostaglandin synthesis is important. They are widely used for bone pain, although views differ on their efficacy and they are often used with paracetamol and opioids. The choice of an NSAID depends on gastric and cardiac comorbidity and the potential adverse effects. NSAID therapy should be reviewed regularly, for example within 2 weeks of initiation, or after radiotherapy; in the absence of any benefit, they must be discontinued.

See section on Pain: Step 1 of the Analgesic ladder, page 9 for details of NSAIDs.

BISPHOSPHONATES AND DENOSUMAB

Bisphosphonates have been shown to reduce pain from bony metastases, and should be considered if other methods of pain relief have failed. An effect is generally seen within two weeks. The evidence suggests that benefit is more likely with an IV bisphosphonate in patients with breast cancer, prostate cancer or myeloma.

Denosumab is a monoclonal antibody that reduces bone destruction; it is used under specialist advice as an alternative to bisphosphonates for bone metastases from solid tumours and myeloma, but in prostate cancer should only be used if other methods have failed. It has been shown to manage the pain from bone metastases.

ALTERNATIVES

Orthopaedic techniques such as prophylactic fixation, vertebroplasty or percutaneous cementoplasty for pelvic metastases have important roles in palliation. Radiotherapy, either with external beam radiotherapy or radioisotopes, also has a major role or should be considered early if pain is not responding to analgesia. Following radiotherapy there may a short-term increase in pain, and it may be several weeks before full benefit occurs. TENS and acupuncture may be beneficial, but the evidence to support its use on a routine basis currently insufficient. Consider referral to anaesthetists specialising in pain if the pain is difficult to control for pain block.

5. NEUROPATHIC PAIN

Pure non-cancer nerve injury pain e.g. post-operative scar pain, post-herpetic neuralgia and diabetic neuropathy may respond to treatment with antidepressants and anticonvulsants.

Cancer related nerve pain may be associated with nerve root/trunk compression or infiltration. Paracetamol, non-steroidal anti-inflammatory drugs and opioids may be tried. Antidepressants and anticonvulsants may be helpful. Corticosteroids may be helpful in nerve root compression and are essential in diagnosed or suspected spinal cord compression until a more definitive management plan has been completed.

Chemotherapy induced peripheral neuropathy can be persistent and difficult to treat. It may respond to similar approaches to those used for diabetic neuropathy.

SPECIALIST REFERRAL

Refer early if any of these apply:

1. If the guidelines below do not help.
2. If urgent control is required for severe uncontrolled pain.
3. If clinical features of “wind up” (magnified pain response) are present e.g. allodynia, hyperalgesia, hyperpathia.
4. If dose-limiting side effects of opioid preclude further dose escalation.

There are other drugs and routes available to pain specialists including lidocaine plasters; ketamine; methadone; spinal analgesia with bupivacaine, opioids, clonidine; plus a wide range of anaesthetic techniques and procedures.

OPIOIDS

Opioids may be continued, but be prepared to add or change drugs at an earlier stage if there is lack of response or toxicity.

PARACETAMOL

Regular paracetamol may be beneficial in some circumstances Do not exceed the maximum dose of 1g (8 tabs a day). Some patients use this as an alternative breakthrough medication.

DEXAMETHASONE

Tumour pressure on a peripheral nerve can cause nerve compression pain and loss of function. Dexamethasone is particularly useful in nerve compression pain. Corticosteroids relieve pain within 48 hours, probably through reduction of oedema around the tumour. If there are no contra-indications, prescribe dexamethasone 8 mg as a single morning dose with food. If ineffective after 5 days, stop. There is no need to taper the dose; it is usually safe to stop abruptly after this length of course. If there is a response, decrease gradually to the minimum effective maintenance dose e.g. by one quarter of the dose per week. Note if there is a good response to steroids radiotherapy may be effective.

In the emergency situation of spinal cord compression, refer urgently for an oncology opinion. Most protocols include the use of high dose dexamethasone (i.e. 16 mg) daily. Corticosteroids may cause gastric irritation, particularly if a NSAID is co-prescribed. Gastroprotection may be provided by a proton pump inhibitor such as lansoprazole. Oral candidosis and hyperglycaemia are treatable corticosteroid adverse effects, so warn the patient of these, and the possible symptoms.

ANTIDEPRESSANTS

Tricyclic antidepressants such as amitriptyline or imipramine are used, which are mixed serotonin/noradrenaline re-uptake inhibitors (selective SSRIs lack useful analgesia). Pain relief may begin after about 1-7 days, but a trial of several weeks may be needed. There is usually a favourable effect after one week on an effective dose. The maximum effect may evolve over days/weeks.

Start with 25 mg amitriptyline (10 mg in elderly) taken in the early evening to avoid a hangover effect. The rate of increase depends on pain level and degree of supervision. If tolerated, the dose may be increased by about 25 mg every three days to 100 mg at night. In the elderly the rate of increase may need to be slower e.g. 25 mg per week. The maximum dose is a balance between efficacy and side effects.

If there is no response after a reasonable trial, stop the drug. If there is a partial response, continue the amitriptyline and add an anticonvulsant if there is no contra-indication (see Anticonvulsants). Some clinicians would only stop if the pain was no better or there were intolerable side effects, after 2-3 weeks on 75 mg/day. Avoid abrupt withdrawal, however, as symptoms such as nausea, headache and malaise can occur. Although generally mild, they can be severe in some patients. Withdrawal symptoms usually occur within the first few days of discontinuing treatment and they usually resolve within 2 weeks, though they can persist in some patients for up to 3 months or longer.

Antidepressants:-

- must be taken regularly.
- side effects precede analgesic effects.
- are not addictive.
- benefit is independent of effect on mood.
- the standard patient information leaflets do not discuss this indication. Inform the patient of the reason for its use.

ANTICONVULSANTS

There is little comparative evidence between anticonvulsants, so the choice depends on the clinician's experience and preference. If unsure, seek specialist advice.

Gabapentin

This is licensed for neuropathic pain. The SPC advises rapid dose titration, but palliative care patients may tolerate the following regimen better:

- Day 1 – 100 mg ON
- Day 2 – 100 mg BD
- Day 3 – 100 mg TDS
- Increase by 100 mg TDS every 2 days as necessary up to a maximum of 600mg TDS.
Seek specialist advice if relief is not obtained

Generally well tolerated, although high doses may cause dizziness and sedation.

Few interactions.

Dose adjustment is required in renal impairment and with haemodialysis. See BNF

Pregabalin

Pregabalin is also licensed for neuropathic pain. It is no more effective than gabapentin, but unlike gabapentin, oral absorption is not dose-dependent or saturable. Therefore, patients who fail to respond to gabapentin may respond to pregabalin. In addition, dose administration is usually twice daily, which may be simpler for certain patients for titration purposes. Again, the licensed dosage regimen advocates rapid titration, but palliative care patients may tolerate the following better:

The following regime is suggested:

- Day 1 – 25 mg ON
- Day 2 – 25 mg BD
- Day 4 – 50 mg BD
- Day 6 – 75 mg BD
- Increase as necessary by 25 mg BD every 2 days, to a maximum of 300 mg BD.
Seek specialist advice if relief is not obtained.

Dose adjustment is required in renal impairment and with haemodialysis. See BNF

6. NAUSEA AND VOMITING

This section covers:

- Causes
- Antiemetic therapy
- Hypercalcaemia
- Raised intracranial pressure
- Intestinal obstruction

CAUSES

There are many causes of nausea and vomiting in advanced cancer, which often present in combination:

- Constipation
- Gastric stasis e.g. opioids, antimuscarinics
- 'Squashed stomach syndrome'
- Hepatic metastases
- Drugs e.g. opioids, NSAIDs, aspirin, corticosteroids, SSRIs, antibiotics, iron, digoxin, proton pump inhibitors
- Metabolic e.g. uraemia, hypercalcaemia
- Severe pain
- Pharyngeal stimulation e.g. thrush, tenacious sputum
- Raised intracranial pressure
- Intestinal obstruction
- Severe anxiety

ANTIEMETIC THERAPY

Non-drug measures are very important.

The vomiting reflex is complex, with many neurotransmitters and pathways. There is no single antiemetic panacea. The choice depends on the cause of vomiting and site of drug action (see Table 2 page 31).

Key Points

- Look for possible causes (including medication review) and pathways.
- Treat reversible underlying causes if possible (and if appropriate). Cover with most specific antiemetic whilst awaiting response.
- If not reversible, look for most likely causes and target with specific antiemetic.
- Check which antiemetics have already been tried, and by which dose and route.
- Choose appropriate antiemetic drug, dose and route. The oral route is only suitable for mild nausea or prophylaxis. In established nausea, gastric stasis interferes with oral absorption, so suppositories are useful.
- Subcutaneous administration is possible for many antiemetics. This route is usually preferred, with subcutaneous infusion in severe cases. Consider a syringe driver if vomiting for more than one day, or moderate/severe nausea unresponsive for more than 48 hours. (see section on Syringe Driver).
- Give antiemetics regularly, not just “when required” or before meals.
- Review often. If symptoms persist, are there any new or overlooked causes?
- If an optimal dose of an appropriate drug is ineffective, switch to an alternative.
- About a third of patients may need more than one antiemetic, with different sites of action, but do not persist with an ineffective drug. To reduce side effects, avoid combining drugs of the same class.
- Consider adjuvants: Antisecretory drugs (e.g. antimuscarinics or octreotide) may be used to reduce the volume of gut secretions. Corticosteroids such as dexamethasone may enhance anti-emetic effect.
- Set realistic goals, e.g. suppression of nausea with intermittent vomits may be acceptable to the patient.
- After 72hrs of good control with the subcutaneous route, consider converting to oral. If the patient is anxious when switching back to oral, phase out the subcutaneous drugs one at a time and replace with oral.
- Unless the cause is self-limiting, continue antiemetics indefinitely.

TABLE 2: ANTIEMETIC THERAPY

SITE OF ACTION / CAUSES	RECEPTOR / ANTIEMETIC DRUG
<p>Vomiting Centre Raised intracranial pressure, intestinal obstruction, pharyngeal stimulation e.g. candida, tenacious sputum</p>	<p>H1 Antihistamine Cyclizine, levomepromazine</p> <p>Antimuscarinic Cyclizine, levomepromazine, (hyoscine hydrobromide)</p> <p>Corticosteroids Dexamethasone</p> <p>5HT2 antagonist Levomepromazine</p>
<p>Chemoreceptor Trigger Zone (Area Postrema) Drugs, uraemia, hypercalcaemia, ketosis, radiotherapy, chemotherapy, toxins.</p>	<p>Dopamine D2 antagonist Haloperidol, levomepromazine, metoclopramide, domperidone</p> <p>5HT3 antagonist Ondansetron, granisetron, tropisetron, metoclopramide high dose.</p>
<p>Gastrointestinal tract Prokinetic Oesophageal reflux, gastric stasis, squashed stomach, gastric irritation</p> <p>Antisecretory Intestinal obstruction</p> <p>Vagal 5HT3 –receptor blockade Chemotherapy, radiotherapy, intestinal obstruction</p>	<p>5HT4 agonist Metoclopramide Dopamine D2 antagonist Metoclopramide, domperidone</p> <p>Antimuscarinic Hyoscine butylbromide, glycopyrronium</p> <p>Somatostatin Analogues Octreotide, lanreotide</p> <p>5HT3 antagonist As above</p>
<p>Broad Spectrum Intractable nausea and vomiting. Uncertain cause</p>	<p>Broad spectrum Levomepromazine</p>
<p>Cerebral cortex Anxiety, anticipatory nausea</p>	<p>Benzodiazepine Lorazepam, diazepam</p>
<p>Vestibular Motion, positional stimuli</p>	<p>H1 Antihistamine Cyclizine</p> <p>Antimuscarinic Hyoscine hydrobromide</p>
<p>Other Tumour mass, liver metastases</p>	<p>Corticosteroid Dexamethasone</p>

ANTI-HISTAMINES

Cyclizine

50mg three times daily PO or S/C. 75-150mg by 24 hour CSCI.

DOPAMINE ANTAGONISTS

Beware of combining two of these - may increase risk of extrapyramidal side effects.

Haloperidol

Anti-emetic of choice for opioid induced nausea and vomiting, hypercalcaemia and renal failure. More potent at chemoreceptor trigger zone than phenothiazines 1.5mg at night, PO or SC. Up to a maximum of 5mg by 24 hour CSCI. Side effects infrequent at this low dosage. Commonly used in combination with cyclizine.

Levomopromazine (Nozinan)

This powerful broad spectrum antiemetic acts at several sites. This means greater potential for side effects (sedation, postural hypotension, antimuscarinic effects). Low doses retain antiemetic activity with less sedation. It is useful in intractable nausea and vomiting, including that of unknown aetiology. It is used to replace previous drugs, not as an addition (but hyoscine butylbromide can be retained if antisecretory needed). Levomopromazine is twice as potent subcutaneously as orally.

Regimens include:

Often reserved for second or third line use some units use as first-line:

Tablets 3-6mg PO once – twice daily and PRN 8hrly.
Titrated up to a maximum dose 25mg over 24 hours.

Liquid 2.5-5mg PO once –twice daily and PRN 8hrly.
Titrated up to a maximum dose 25mg over 24 hours.

Injection 2.5-5mg S/C once – twice daily and 8hrly PRN.
Titrated up to a maximum of 12.5mg over 24 hours.

CSCI 5mg – 12.5mg over 24 hours. Some units use up to 18.75mg over 24hours.

Use the lowest effective dose. If Symptoms are not controlled at these doses contact the Specialist Palliative Care Team. Levomopromazine is available in the UK as a 6mg tablet which is scored and available on a named patient basis. A liquid formulation is available from a number of 'Special Manufacturers'.

Domperidone

MHRA states that adults should take no more than three 10mg tablets per day. Aim to control symptoms using the lowest effective dose for the shortest possible duration. In palliative care settings doses of 10-20mg 4-8 hourly orally or 30-60mg every 4-8hrs rectally. Will not control severe nausea. Domperidone and metoclopramide improve gastric and small bowel motility. Domperidone is less likely to cause sedation and dystonia than phenothiazines or metoclopramide as it does not cross the blood-brain barrier.

Metoclopramide

MHRA states that adults should take no more than three 10mg tablets per day. Aim to control symptoms using the lowest effective dose for the shortest possible duration. In palliative care settings doses of 10mg three or four times daily orally or subcutaneously; 30-60mg by CSCI. S/C boluses may be uncomfortable due to the volume required (10mg/2ml). The action of prokinetic drugs such as metoclopramide or domperidone is antagonised by the gut-motility reducing effects of antimuscarinics such as hyoscine or cyclizine. Avoid such combinations if possible.

ANTIMUSCARINICS

In this context they tend to be used as adjuvants for their antispasmodic effect in bowel colic, and antisecretory effect which reduces the volume of vomits (see section on Intestinal Obstruction for specific details). They are also used to reduce respiratory secretions and drooling.

Hyoscine butylbromide (“Buscopan”)

This has no central antiemetic action because it does not cross the blood-brain barrier. For the same reason, it does not cause drowsiness. Poor oral absorption limits the use of the tablets to mild/moderate colic. The S/C route is preferred. Antisecretory drug of choice in inoperable intestinal obstruction.

Hyoscine hydrobromide

This also has a central action which provides an antiemetic effect, but may cause side effects such as drowsiness, hallucinations, excitement and ataxia.

Not routinely used as an antiemetic in palliative care.

A transdermal patch delivering hyoscine 1mg over 72 hours (Scopoderm TTS) is available, but plasma levels are low. In practice, its use as an antiemetic is limited to motion sickness.

Glycopyrronium bromide

This is a more powerful antisecretory agent than hyoscine hydrobromide, and may help where this has failed. It has no central effects because it does not cross the blood-brain barrier, so may be better tolerated.

5HT₃ RECEPTOR ANTAGONISTS

These are mainly useful in situations where excessive amounts of 5HT are released, such as chemotherapy, radiotherapy, renal failure or gastro-intestinal obstruction. They do not reverse opioid-induced nausea. Side effects include constipation. In practice there may be little to choose between them.

The doses in palliative care are: Granisetron 1-2mg PO or S/C once daily.
Ondansetron 8mg twice daily PO or S/C or 8-24mg by 24 hour CSCI.

If there is no benefit after three days, discontinue. In intractable vomiting, additional haloperidol may be needed. Their action is potentiated by dexamethasone.

OTHERS

Octreotide

Seek advice from the Specialist Palliative care Team.

Dexamethasone

May enhance the action of other antiemetics.

Dose range 8-16mg once daily PO or S/C (divide sites if the volume is too large).

If effective, consider decreasing the dose after 5-7 days. May be given by 24 hour CSCI e.g. if high plasma concentrations after individual injections are thought to have caused psychosis. In practice, oral and parenteral doses are equivalent. A licensed oral solution is available, 2mg in 5ml. Remember potential for raised glucose on steroids.

HYPERCALCAEMIA

This is defined as a serum corrected calcium above 2.63mmol/L. It is a common complication of advanced cancer, which may be associated with nausea, vomiting, constipation, anorexia, confusion, drowsiness, polyuria, polydipsia and dehydration. Symptoms may be mistaken for the underlying malignancy.

Treatment

If asymptomatic and corrected calcium less than 3mmol/L:

Check U&E and albumin.

Ensure adequate fluid intake, 2-3L per day and stop thiazide diuretics, Vitamins A, D and calcium supplements if taking.

Monitor fluid balance, corrected calcium levels and symptoms. Rehydration alone is often insufficient and most patients also need bisphosphonates. Treatment, where appropriate, should start as soon as possible, at least within 24 hours of diagnosis.

If symptomatic or corrected calcium above 3mmol/L:

Rehydrate with intravenous fluid. May require 2-4L per 24 hours. The amount and rate of rehydration depend on severity of symptoms, calcium level, cardiovascular status, urea and electrolytes.

If fluid overload give furosemide 20mg-40mg 12 hourly.

Give IV bisphosphonates. First choice is Zoledronate 4mg IV in 100mls sodium chloride 0.9% over 15 mins, then continue with rehydration. Disodium pamidronate is an alternative used in some centres. Refer to local guidelines.

Ensure adequate oral fluid intake when intravenous rehydration stops.

Note: Bisphosphonates are first line treatment for hypercalcaemia of solid tumours. Since they do not alter parathyroid hormone-related protein or renal calcium reabsorption, they may fail to control humoral hypercalcaemia of malignancy without bone metastases.

Calcium level monitoring:

Calcium levels start to fall after 48 hours with normalisation in 90% of patients in 5-10 days. Levels may respond faster than symptoms.

Urea and electrolytes should be checked regularly. When re-checking calcium levels, be aware of response time to treatment.

Once normalised check calcium two weeks after infusion, then every two weeks.

Asymptomatic hypocalcaemia may occur, but symptomatic hypocalcaemia is rare.

Treat the other symptoms associated with hypercalcaemia, e.g. bone pain, abdominal pain, constipation and nausea.

After symptoms have settled, and if appropriate, treat or review the treatment of the underlying problem causing the hypercalcaemia.

In recurrent hypercalcaemia, it may be appropriate to consider regular treatment orally or intravenously. Seek specialist advice.

Others

Corticosteroids are usually ineffective in hypercalcaemia of solid tumours, but may help in steroid responsive malignancies e.g. myeloma and lymphoma. They take several days to work.

RAISED INTRACRANIAL PRESSURE

This may be due to direct tumour pressure or surrounding cerebral inflammation. Headache, vomiting, confusion and blurred vision may occur. Steroids reduce oedema around the tumour. Dexamethasone 8mg bd may give a response within 24 hours. Apart from hydrocortisone, give oral corticosteroids no later than midday to reduce insomnia. In those with a history of gastrointestinal problems, or already on an NSAID for other reasons, provide gastroprotection with a proton pump inhibitor. After 4-5 days, reduce dose by one quarter per week to the minimum effective maintenance dose, to minimise side effects. Benefit may persist for 1-2 months. If no response after 7 days, reassess.

Patients on maintenance treatment should have a steroid card. There is no set maximum maintenance dose; some patients may progress to higher maintenance doses if symptoms return. Oral candida is common and treatable, so warn patients of possible symptoms. In practice, the oral and parenteral doses of dexamethasone are equivalent. Corticosteroid therapy should be reviewed constantly, but do not discontinue in the dying phase if it has relieved these symptoms. Dexamethasone can be given by 24hour CSCI.

If dexamethasone is contraindicated or ineffective, cyclizine is the preferred antiemetic. Positional emesis may respond to cyclizine or hyoscine hydrobromide. Headache may require analgesics in addition, e.g. codeine or strong opioids. NSAIDs increase the risk of corticosteroid gastrointestinal toxicity, so may be best avoided. Anticonvulsants may be needed for seizure control. Phenytoin or carbamazepine may reduce the effect of corticosteroids due to increased metabolism - retitrate steroid dose if necessary.

INTESTINAL OBSTRUCTION

This may be mechanical or functional or both. It can be managed medically even at home, if surgery is not indicated. Symptoms include vomiting, constant aching abdominal pain, and colic, usually occurring together, so combination therapy is required. See below for management of individual symptoms.

COLIC DUE TO INTESTINAL OBSTRUCTION

In complete obstruction, stop stimulant, osmotic and bulking laxatives, and gastrokinetic antiemetics, e.g. metoclopramide, domperidone. Prescribe hyoscine butylbromide (Buscopan) 40-60mg by 24 hour CSCI. This also reduces the volume of secretions and frequency of vomits. If there is no response after one day, increase in 40mg increments to 120mg over 24 hours. Glycopyrronium 0.6-1.2mg by 24 hour CSCI is an alternative. If symptoms are not controlled contact the Specialist Palliative Care Team for further advice.

ABDOMINAL PAIN DUE TO INTESTINAL OBSTRUCTION

Give morphine, at one half of the 24 hour oral morphine dose, or diamorphine at one third of the 24 hour oral morphine dose by 24 hour CSCI. Titrate dose if necessary.

NAUSEA AND VOMITING DUE TO INTESTINAL OBSTRUCTION

Cyclizine is often regarded as first line, and is given at 150mg by 24 hour CSCI. Some centres combine it with haloperidol 1.5-5mg (levomepromazine is an alternative to cyclizine, particularly if cyclizine would precipitate in combination with other drugs.). Partial obstruction of the large bowel without colic may benefit from a softening agent, e.g. docusate sodium 200mg twice daily. It may be difficult to distinguish between complete and partial obstruction. Severe constipation may mimic obstruction.

In resistant cases seek specialist advice. Levomepromazine or ondansetron may be of benefit. Octreotide 500 micrograms daily SC or by 24 hour CSCI may be required to reduce the volume and frequency of vomits. The dose may be increased over several days to 1mg subcutaneously daily (in divided doses) or by 24 hour CSCI. Subcutaneous injection may be painful. Dexamethasone 8mg daily for five days may help, by decreasing tumour oedema. In high obstruction, other measures may be needed if these fail, e.g. nasogastric tube or venting gastrostomy. Seek specialist advice.

If symptoms remain stable for 48hrs review medications and decrease to the lowest effective dose. Oral therapy may be resumed in some patients. If the patient is anxious about stopping the syringe driver, phase in oral replacement of each component one at a time. It may not be possible to prevent all vomiting, but occasional vomiting may be tolerated.

7. CONSTIPATION

Constipation is a major problem in patients with advanced illness and bowel management should be a routine aspect of their care. Factors which predispose to constipation in this patient group include reduced mobility, reduced fluid intake, medication including opioids and anti-muscarinics.

It is better to prevent constipation than to wait until treatment is needed. For existing constipation, assessment should rule out hypercalcaemia, ileus and intestinal obstruction. PR examination is essential, as is taking an accurate history. Passing soft stool less frequently or passing hard stool daily will both be described as constipation by some patients and clarifying what the patient sees as the problem will help in your choice of management. Patients who have hard stool in the rectum on PR examination will require either a suppository or enema to clear this.

TABLE 3: ORAL LAXATIVES

STIMULANT	
Bisacodyl	Available as tablets (suppositories also available) Starting dose 5–10mg at night - Can be increased to 10mg bd
Senna	Available as tablets, granules or syrup Starting dose 15mg at night - Can be increased to 30mg bd
SOFTENER	
Docusate	Available as capsules or oral solution Starting dose 200mg at night - Can be increased to 200mg tds
Macrogols	Available as sachet for reconstitution Starting dose 1-2 sachets at night Can be titrated incrementally to 8 sachets a day
COMBINED STIMULANT/SOFTENER	
Co-dantrusate (50/60) Co-danthrimer (25/200) Co-danthrimer strong (75/1000)	Available as capsules or suspension Starting dose 2 caps/10mls at night Can be increased to twice daily Strong formulation can be used if this is insufficient

Stimulants should be avoided if there is a tendency towards bowel obstruction or there is impacted stool that has not been cleared, as colic will be provoked.

Movicol can be highly effective, but its use can be limited by the volume of liquid the patient has to take. Patients taking movicol do not usually require a stimulant laxative as well.

Combination preparations containing dantron will turn the urine red and can also cause peri-anal irritation which can be very severe, particularly in bed bound, incontinent patients. Dantron containing preparations are only licensed for use in patients with malignant disease of limited life expectancy.

Lactulose should be avoided as it is often unpalatable, and causes bloating and flatulence. Bulking agents such as Fybogel are not recommended for use in palliative care patients. Rectal interventions in the form of suppositories or enemas are important in the management of established constipation. All patients who have not opened their bowels for a number of days should have a PR examination to exclude stool impacted in the rectum. Simple glycerine suppositories can be tried first before moving on to docusate, arachis oil (beware of peanut allergy) or phosphate enema in this order.

There are a number of opioid antagonists which are either stand alone products or in combination with opioid analgesics which are intended to specifically reverse opioid induced constipation. They should only be used by palliative care specialists.

8. DIARRHOEA

As with all cases of diarrhoea, an infective cause should be excluded first, including testing for clostridium difficile. 'Overflow' diarrhoea, where there is impacted faeces higher up in the bowel allowing liquid stool to bypass needs to be treated as the constipation guidelines indicate.

If 'overflow' and infection have been excluded, then either codeine or loperamide can be used to try and reduce the frequency of stool.

Loperamide 2mg tabs. Up to 16mg/24hrs. In acute diarrhoea, 2mg can be given after each loose stool but for chronic diarrhoea, patients may require maintenance therapy.

Higher doses may be used on the recommendation of a specialist.

Codeine 30-60 mg up to qds

Some specific causes of diarrhoea may require different management.

Pancreatic insufficiency usually requires treatment with creon supplements.

Some bowel tumours will produce copious secretions which will manifest as diarrhoea. Anti-secretory agents such as hyoscine butylbromide or octreotide can be used for these cases, but their management should be under specialist palliative care advice.

It is essential to explain clearly to the patient and their carers the concept of overflow diarrhoea so that they understand their need to comply with taking the prescribed laxatives regularly despite having diarrhoea.

9. ANOREXIA

Explanation and practical solutions can be more important than drug treatment or the use of food supplements. Dietitians can help. The family must be involved. Listen to fears of patient and family/carers; failure to eat can cause fear and conflict. Food or supplements may be more easily taken by snacking through the day.

Avoid offering excessive food and portions look less daunting on a larger plate.

Exclude treatable causes e.g. nausea, infection, sore mouth, constipation, drugs, anxiety, dyspepsia, gastric stasis, pain, malodorous tumours, hypercalcaemia, uraemia, depression. If drugs are appropriate, and there are no major contraindications, try a short course of prednisolone 15-30mg daily, or dexamethasone 2-4mg daily. They may be effective within a few days.

If there is no response after a week, stop the steroid (tapering not necessary).

Corticosteroids help only some patients, and only for a few weeks. Best used as a short-term measure for symptomatic benefit. Patients with multiple complex symptoms and limited life expectancy are more likely to benefit from them.

Watch for sore mouth from oral candida, which may contribute to anorexia, and monitor capillary blood glucose in known diabetics on insulin and oral hypoglycaemics. Alternatively, if there is a prognosis of over three months, try megestrol acetate 160mg bd.

10. BREATHLESSNESS

Breathlessness is a common symptom encountered in palliative care.

When managing a patient with breathlessness consider the following underlying causes and treat where appropriate:

- Infection
- Anaemia
- Bronchospasm
- Pleural effusion
- Heart failure
- Pulmonary embolus
- Collapse/consolidation secondary to tumour

GENERAL PRINCIPLES

Non-pharmacological Management

The use of strategies that do not involve drugs can have a significant impact on the management of breathlessness:

- Avoiding claustrophobic environments
- Well ventilated rooms
- The use of a fan on the side of the face
- Breathing control management
- Occupational therapy – adaptations, lifestyle adjustments
- Physiotherapy – breathing recovery strategies, maintaining mobility/walking aids
- Complementary therapies, including relaxation, aromatherapy, acupuncture, visualisation
- Psychological support
- Anxiety management

Pharmacological Management

Benzodiazepines

These drugs can help in breathlessness, especially if there is associated fear and anxiety:

- Lorazepam 500 microgrammes – 1 mg orally or sublingually PRN, up to a maximum dose of 2mg in 24 hours. Although not licensed to be taken sublingually, the oral tablet formulation can be administered by this route to achieve more rapid symptomatic relief.
- Alternatively, diazepam 2 mg PRN, increased if necessary up to a maximum total dose of 15 mg over 24 hours in divided doses. These doses should be halved in elderly and debilitated patients.
- If the patient is too unwell to take oral medication, midazolam 2.5mg S/C four hourly PRN can be used as an alternative. If multiple doses are required then consider administration via 24 hour CSCI at a starting dose of 5-10mg.

Opioids

- Oral morphine sulphate solution (10 mg/ 5 ml) at a starting dose of 2.5 mg four hourly PRN, titrating upwards every 48 hours according to response.
- If PRN medication is required more frequently it would be advisable to seek advice from the Specialist Palliative Care Team.
- Immediate release morphine is often more effective for control of dyspnoea than modified release morphine.
- In patients who are already taking strong opioids, such low doses of oral morphine can still be effective for dyspnoea. Some patients may need to take different doses for dyspnoea and breakthrough pain.
- Morphine is excreted renally. In renal impairment use a lower dose initially & reduce the frequency of administration. In established renal failure alternative opioids may be more appropriate – seek specialist palliative care advice.

Oxygen

The use of oxygen in hypoxic patients should be under specialist supervision (for use in end- stage chronic respiratory disease see following section). In exceptional circumstances, some patients do get benefit from having oxygen available at home but this should follow discussion with a palliative care specialist.

Other agents

Nebulised bronchodilators can be useful if there is an element of reversible airways obstruction. Nebulised sodium chloride can also be useful if thick secretions are present. Dexamethasone may be beneficial in certain situations including large airway obstruction, SVCO and lymphangitis. Specialist advice should be sought in these situations.

For cough see page 44.

MANAGEMENT OF END-STAGE CHRONIC RESPIRATORY DISEASE

Guidance for the management of COPD in adults in primary and secondary care has been produced by the National Institute for Clinical Excellence (NICE 2010) and by the British Thoracic Society (BTS) (available at www.brit-thoracic.org.uk).

Local and national guidelines are available for the management of other diseases such as asthma and diffuse parenchymal disease (BTS Guidelines available at www.brit-thoracic.org.uk).

- Regardless of the underlying diagnosis, by the time end-stage is reached, symptom control will be essentially the same. Where appropriate, disease-specific treatment should continue alongside symptom control. In the case of the less common respiratory diseases, close liaison with Specialist Respiratory teams is recommended, to ensure that appropriate, active management is optimised.

Referral to Specialist palliative care services

Appropriate timing of referrals to palliative care services for patients with non-malignant disease can be harder to judge than for cancer patients. Referral criteria vary so check with local services before referring the patient.

The following guidelines may be helpful:

- The patient has had a diagnosis of chronic respiratory disease confirmed at some stage of their disease trajectory by a specialist respiratory physician, and attempts to optimise therapy, including pulmonary rehabilitation where appropriate, have been made.
- The patient has knowledge and understanding of their disease, is aware of the reason for referral to Specialist Palliative Care and agrees to this.
- Two or more of the following should also apply:
- The patient has uncontrolled physical or psychological symptoms despite optimal tolerated therapy.
- The patient makes increasing use of emergency treatment for infection and/or respiratory failure.
- The patient has an anticipated life expectancy of 12 months or less.

Ideally, if a patient is being referred to hospice services, they should be aware that, dependent on local policy, resuscitation facilities are limited and such treatments as intravenous aminophylline, intravenous antibiotics and blood gas interpretation are generally not provided within the hospice setting.

SYMPTOM CONTROL

The management of specific symptoms e.g. constipation, nausea and vomiting is applicable to both cancer and non-cancer patients. Please see relevant chapters for details. The information covered in the 'Breathlessness' chapter regarding non-pharmacological interventions, benzodiazepines and opioids is equally appropriate in the management of end-stage respiratory disease from whatever cause. The use of bronchodilators and oxygen specific to end-stage chronic respiratory disease will now be covered in more detail. Advice on cough and sputum management may be applicable to palliative care patients without end-stage respiratory disease.

BRONCHODILATORS

- Inhaled or nebulised
- β agonists e.g. salbutamol, terbutaline
- Antimuscarinic bronchodilators e.g. ipratropium bromide, tiotropium bromide
- Combination preparations

Bronchodilator therapy should be optimised in accordance with NICE guidance. Optimal doses include:

	Inhaled	Nebulised
Salbutamol	100 – 200 micrograms QDS +/- or PRN	2.5 – 5 mg QDS +/- or PRN
Terbutaline	500 micrograms QDS +/- or PRN	5 - 10 mg QDS +/- or PRN
Ipratropium*	20 – 40 micrograms 3 - 4 times daily Max QDS	250 – 500 micrograms 3 -4 times daily Max QDS
Tiotropium*	18 micrograms OD (Handihaler) 5micrograms OD (Respimat)	Not available

Please note: Tiotropium should be discontinued if patients are commenced on Combivent® or ipratropium. British National Formulary Volume 55, March 2009

- Higher doses can be used out of licence.
- See also local guidelines for management of COPD.
- Bronchodilators may not be effective in some diseases, eg pulmonary fibrosis. However a trial of inhaled, or occasionally nebulised, bronchodilators may be still be worthwhile in such conditions.
- Prescriptions for inhaled long-acting 2 bronchodilators (LAB) eg. Formoterol or Salmeterol or combination LAB/ corticosteroid inhalers should be continued. Use of a spacer device should be considered.

Consider possible causes of breathlessness other than end-stage respiratory disease such as coexistent heart failure, pleural effusion, pneumothorax, pulmonary embolus.

OXYGEN IN END-STAGE RESPIRATORY DISEASE

Almost all patients with end stage respiratory disease will previously have been found to require long-term oxygen therapy (LTOT). The guidelines for requirement for LTOT are well documented for both COPD and pulmonary fibrosis.

Oxygen should only be considered if there is evidence of hypoxia or improvement in physical function after a trial. It should be remembered that use of oxygen may lead to dependence, reduced mobility and reduced quality of life for some patients.

Oxygen for palliation can be ordered from primary or secondary care. Formal assessment, including measurement of blood gases, or follow up, may not be required in patients who are in the terminal phase of their illness. When ordering oxygen (using a Home Oxygen Order Form – HOOF), two decisions need to be made:

- 1. or how many hours per day does the oxygen need to be used?**
- 2. What flow rate (Litres/minute) is required?**

There are no strict criteria to be met as far as the flow rate is concerned. In COPD patients, care must be taken to avoid carbon dioxide retention if at all possible, although in patients who are terminally ill this consideration is overridden by the need to palliate symptoms. If pulse oximetry is available, it is reasonable to provide oxygen at a flow rate sufficient to keep the SaO₂ is around 92% (88-92% in patients who retain CO₂), or as near to this as possible without causing significant side effects (such as dry upper airways due to high flow rates, or headaches due to carbon dioxide retention).

Patients with pulmonary fibrosis often have very low oxygen saturations and desaturate still further on exertion. They frequently require high flows of oxygen.

COUGH AND SPUTUM MANAGEMENT

If sputum increases in amount or changes colour, exclude infection and consider antibiotics. Ensure adequate oral fluid intake, where appropriate, to liquefy secretions.

Mucolytics

- Carbocysteine capsules at starting dose of 750 mg tds reducing to maintenance dose of 750mg bd or carbocysteine oral liquid (250 mg/5 ml) at initial dose of 750 mg tds reducing to 750mg bd.
- Mucysteine hydrochloride 200mg qds for 2 days then 200mg tds for 6 weeks, then 200mg twice daily.

These should both be reviewed 4 to 8 weeks after initiation and reduced to the maintenance dose. If the patient feels no benefit, then it should be stopped.

Sodium Chloride 0.9% nebulas 2.5–5 ml PRN, which anecdotally may ease expectoration.

Antitussives

Symptomatic relief of tickly cough Simple linctus 5-10 ml PRN up to qds.

Codeine linctus 5-10 ml PRN up to qds.

Oral morphine solution (10 mg/5 ml) starting dose 2.5 mg 4 hourly PRN. This may also help dyspnoea & pain.

Methadone linctus (2 mg/5 ml) 2 mg initially nocte, increasing to bd if necessary.

In the event of acute infection it may not be advisable to use cough suppressants (see NICE guidance).

Physiotherapy, positioning and acupuncture.

TERMINAL RESPIRATORY FAILURE – THE LAST FEW DAYS OF LIFE

- There needs to be agreement within the team about the patient's condition.
- It is important to recognise patients who appear to be approaching the terminal phase of their illness. It is often more difficult to diagnose the dying phase in patients with end-stage respiratory disease than in terminal cancer patients.
- In patients with end-stage respiratory disease, improvement may be achieved with medication – a reversible precipitant such as a chest infection may be present.
- If recovery is uncertain, this needs to be shared with patient & family.
- It is important to establish the inappropriateness of ventilation, including non-invasive ventilation, & cardiopulmonary resuscitation.
- Once the dying phase has been identified management should follow the guidance for the terminal stage (See chapter 23 on page 63), including the use of the end of life tools.

Adapted from: The Merseyside and Cheshire cancer network palliative care clinical network group.

11. MOUTH PROBLEMS

DRY MOUTH

Mouth problems are common among palliative care patients. Many patients will admit that they have a sensation of dryness in the mouth if asked; they rarely volunteer this symptom spontaneously.

It can cause problems with discomfort, impaired taste and difficulties with chewing, swallowing and speaking. This may lead to secondary complications of poor oral hygiene, caries and infection.

These symptoms can adversely affect appetite and mood.

Drug therapy is a major cause of dry mouth and saliva production is affected. The saliva produced is of very poor quality and quantity.

Management is focused on treating the cause, using saliva stimulants and the use of saliva substitutes.

Saliva stimulants are more effective than substitutes and patients prefer them. Prevention of secondary complications is often easier than treating them.

Poorly fitting dentures can aggravate the problem.

Preventative treatment:

Teeth and tongue should be cleaned at least twice daily with a small or medium head toothbrush and fluoride toothpaste. The mouth should be rinsed thoroughly with water after cleaning.

Dentures should be removed twice daily, cleaned with a brush and rinsed with water. They should be soaked overnight in water or in the patient's usual solution and cleaned with a brush.

Adequate oral fluid intake should be encouraged.

Lips should be moisturised with lip balm or tasteless oil, e.g. olive oil.

Management:

Consider if drug therapy can be stopped or an alternative prescribed. Diagnose and manage secondary oral infection.

Temporary relief can be provided by stimulating saliva production with regular small drinks, chewing sugar-free gum.

Artificial saliva sprays, pastilles or tablets are of limited use but may enhance comfort. Many artificial saliva products are acidic and can accelerate the development of dental caries. Some patients benefit from the use of parasympathomimetics and are prepared to use them despite side effects as the sensation of dry mouth is so unacceptable. Side effects include blurred vision and sweating. Topical pilocarpine 4% eyedrops to the oral cavity is the cheapest option. Topical administration is most likely to increase lacrimation compared with PO administration. Bethanechol 25mg PO tds or pilocarpine tablet PO 5mg tds are alternatives.

ORAL MUCOSITIS

Oral mucositis refers to inflammation of the oral mucous membrane. This is a common side effect of chemotherapy and local radiotherapy.

The amount of damage varies from the absence of symptoms and signs, through the presence of ulcers, causing pain and requiring soft diet, to marked haemorrhage and necrosis with a need for parenteral or enteral nutritional support.

Management is focused on improving comfort and maintaining good oral hygiene. A stepwise approach can be adopted, initially using a topical anti-inflammatory. If this provides inadequate relief try a topical anaesthetic. In some cases topical morphine is required.

TABLE 4: MANAGEMENT OF SPECIFIC ORAL PROBLEMS

Problem	Management
Prevention	Chlorhexidine mouthwash (may discolour teeth)
Apthous ulcers:	Diffiam oral spray, corlan pellets, antiseptic - mouthwash (Chlorhexidine), topical anti-inflammatory gel (bonjela), local anaesthetic (lidocaine), see BNF 12.3.1 Aloe vera toothpaste can be soothing
Viral ulcers:	aciclovir 200mg 5 times a day for 5 days topical gels (see above)
Malignant ulcers:	consider antibiotic
Mucositis:	benzydamine (Diffiam) mouthwash or spray paracetamol mucilage 1gm 4-6 hourly opioid analgesics if above inadequate. Gelclair sachets. Caphosol
Gingivitis:	metronidazole 200mg PO tds for 3 days. Consider metronidazole suspension topically or rectal administration if not tolerated orally. Antiseptic mouthwash – e.g povidone-iodine or chlorhexidine, gluconate mouthwash
Dry mouth:	review medications (opioids, antimuscarinics), increase oral intake, saliva stimulants, (pilocarpine tablets / eye drops – seek specialist advice), saliva substitutes – saliva orthana, oralbalance gel, see BNF 12.3.5 pilocarpine tablets / eye drops – seek specialist advice
Coated tongue:	chewing pineapple chunks, brushing tongue with a soft toothbrush
Fungal infection:	nystatin suspension 5ml qds, fluconazole 50-100mg daily for minimum of 7 days or 150mg stat if appropriate. Soak dentures overnight in weak chlorine solution (Milton). Use a new toothbrush and have 2 brushes in use so that the heads can dry out

12. HICCUP

May be due to gastric distension, enlarged liver, toxicity from metabolic disorders or infection, phrenic nerve irritation or tumours of the central nervous system both primary and secondary.

If due to gastric distension, try an antacid with a defoaming antifatulent (dimethicone), e.g. Asilone suspension 10 ml qds.

Metoclopramide or domperidone will reduce gastric distension. Peppermint water may help, but less desirable than a defoamer. Metoclopramide or domperidone and peppermint water should not be used concurrently because of their opposing actions.

If due to diaphragmatic or phrenic nerve irritation baclofen 5-10 mg b.d. or t.d.s. (effective within 48 hours, but may be issues with unacceptable side-effects), or an anticonvulsant such as gabapentin 300 mg t.d.s. may help.

If due to toxicity, consider haloperidol 1.5-3 mg b.d. or chlorpromazine 10-25 mg t.d.s.
If due to CNS tumour, an anticonvulsant such as gabapentin or sodium valproate may help.
In intractable cases or in the terminal stages midazolam can be used 5 mg SC initially then by continuous subcutaneous infusion over 24 hours in a syringe driver, titrated as necessary, range 10-60 mg. Sedation is likely, so this may not be appropriate in non-terminal patients.

An acute episode may respond to nebulised saline 2-5 mls over 5 minutes using mouthpiece. Its onset of effect is within minutes and may last 3-4 hours. It acts by causing pharyngeal stimulation and may be used every 2 hours for prophylaxis.

13. DEPRESSION

Depression is two to three times more common in patients with a chronic physical health problem. Assessment and management are similar to that in the general population with some additional considerations. See www.nice.org.uk/cg91 for detailed information on assessment, diagnosis and management.

Management

Moderate or Severe Depression

For patients who present with moderate or severe depression or who are at risk of harm to themselves or others, seek advice from specialist mental health services.

Sub threshold depressive symptoms or mild depression

Initial management when diagnosed as per NICE Guidance.

- Advice on sleep hygiene.
- Active monitoring and further assessment.

Consider

- o A physical activity programme (modified for the physical health problem).
- o A peer support programme with patients with shared physical problems.
- o Individual guided self-help based on cognitive behavioural therapy.

Pharmacological Management

- Do not use antidepressants routinely to treat sub-threshold depressive symptoms or mild depression but consider them for patients with:
 - o A past history of moderate or severe depression or
 - o Mild depression that complicates the care of the physical health problem
 - o Initial presentation of sub-threshold depressive symptoms for at least two years or
 - o Sub-threshold depressive symptoms or mild depression persisting after other interventions
- Do not prescribe or advise use of St John's Wort

Choice of Antidepressants

- Consider side effects on the physical health problems and drug interactions. Seek specialist advice if any uncertainty.
- Consider a selective serotonin reuptake inhibitor (SSRI) – citalopram or sertraline. See table for drug interactions.
- Explore any concerns the patient has about taking medication.
- Do not prescribe antidepressants at sub-therapeutic doses.
- Review regularly.

In patients who have persistent sub-threshold depressive symptoms or mild depression despite the above treatment, refer to www.nice.org.uk/cg90 and www.nice.org.uk/cg91

Interactions of SSRI's with other medications

Medication for chronic physical health problem	Recommended antidepressant(s)
Non-steroidal anti-inflammatory drugs (NSAIDs)	<ul style="list-style-type: none"> • Do not normally offer SSRI's – but if no suitable alternatives can be identified, offer gastroprotective medicines (for example, proton pump inhibitors) together with the SSRI. • Consider mianserin, mirtazapine, moclobemide, reboxetine or trazodone.
Warfarin and heparin	<ul style="list-style-type: none"> • Do not normally offer SSRI's. • Consider mirtazapine (note that when taken with warfarin, the international normalised ration (INR) may increase slightly).
Aspirin	<ul style="list-style-type: none"> • Use SSRI's with caution – if no suitable alternatives can be identified, offer gastroprotective medicines together with the SSRI. • When aspirin is used as a single agent, consider trazodone, mianserin or reboxetine. • Consider mirtazapine.
'Triptan' drugs for migraine	<ul style="list-style-type: none"> • Do not offer SSRI's. • Offer mirtazapine, trazodone, mianserin or reboxetine.
MAO-B inhibitors (for example selegiline and resagiline)	<ul style="list-style-type: none"> • Do not normally offer SSRI's. • Offer mirtazapine, trazodone, mianserin or reboxetine.
Theophylline, clozapine, methadone or tizamide	<ul style="list-style-type: none"> • Do not normally offer fluvoxamine. • Offer sertraline or citalopram.
Flecainide or propafenone	<ul style="list-style-type: none"> • Offer sertraline as the preferred antidepressant • Mirtazapine and moclobemide may also be used.
Atomoxetine	<ul style="list-style-type: none"> • Do not offer fluoxetine or paroxetine. • Offer a different SSRI.

14. ANXIETY IN ADVANCED ILLNESS

Anxiety is a state of apprehension or fear, which may be appropriate to a particular situation. Morbid anxiety occurs with individuals who are unable to banish their worries.

- Anxiety tends to aggravate the severity of other symptoms.
- In life-limiting illnesses, anxiety or panic may be associated with uncertainty about the future, job and social worries, future separation from loved ones; as well as unrelieved symptoms.
- Co-existing depression is common.

Anxiety disorders can be divided into the following:-

Generalised anxiety disorder

- Over arousal, irritability, poor concentration, poor sleeping and worry about several areas, most of the time.

Panic disorder

- Intermittent episodes of panic or anxiety and taking avoiding action to prevent these feelings.
- Agoraphobia or social phobia – not covered by this guideline.

Assessment

- Full medical history and examination.
- Signs and symptoms of anxiety may also be due to organic disorders such as hypoxia, sepsis, medication, metabolic causes, poorly controlled pain.
- Elicit patient's specific fears and understanding.
- Note language, culture or other characteristics that may be important.
- Gather information from those close to the patient, e.g. family, GP.
- Assess for depression and risk of self harm.

General Management

The severity of the underlying disease and the overall prognosis guides treatment decisions.

- Treat organic disorders.
- Acknowledge and discuss anxiety and specific fears.
- Share decision making with patient. Involve family.
- Consider referral to Specialist Palliative Care services for additional psychological support and access to therapy such as Hospice Day Care, relaxation techniques, etc.
- If severe anxiety, marked functional impairment, risk of self harm or failure to respond to therapy, consider referral to Specialist Mental Health services.

Specific Management

Generalised anxiety disorder

- As for general management.
- In addition, consider referral for psychological therapy or pharmacological therapy.
- SSRI's may be considered.
- Benzodiazepines are only recommended for short-term use of not more than two to four weeks.
- Pregabalin is licenced for use in generalised anxiety disorder and may be worth considering, particularly where there is co-existing neuropathic pain

Panic Disorder

- As for general management.
- Consider referral for psychological therapy.
- SSRI's may be considered.
- Benzodiazepines, sedating anti-histamines or anti-psychotics are not recommended for the treatment of panic disorder.

15. CONFUSION

Confusion is common in patients with advanced illness, particularly in older people and those with chronic cognitive impairment.

Principles of Management: Treat reversible causes
 Manage the patient in a suitable, quiet environment
 Make the patient safe
 Acknowledge the distress and fears of the patient and carers and give clear explanations and reassurances where possible.

Potentially reversible causes of confusion:

Biochemical	Hypercalcaemia Hyponatraemia/SIADH Uraemia Hyper- and hypoglycaemia Dehydration
Infection	Urine Chest Cellulitis
Drugs	Opioids Benzodiazepines Antidepressants Anticonvulsants Steroids Antimuscarinics/anticholinergics (chlorpheniramine, cyclizine, hyoscine, glycopyrrolate, levomepromazine)
Deficiency or Drug withdrawal	Thiamine Nicotine Alcohol Benzodiazepine Opioid Adrenal steroid
Hypoxia	
Hypotension	
Extreme anxiety	
Severe pain	
Constipation	
GI bleed in patient with liver failure	
Brain metastases	

Management

Consider the role of investigation to identify reversible causes. If drug induced, reduce dose or stop as appropriate. Medication should only be part of the treatment plan, and may not be needed in those who are “happily muddled” without distress. It will not reverse confusion and may sometimes worsen it.

If specific treatment does not help consider one of the following:

Haloperidol – used where minimal sedation is required.

Start with 0.5mg nocte in the elderly or with 1.5mg nocte for other patients and titrate to a maximum of 10mg daily. Higher starting doses may be used patients who are hallucinating.

Haloperidol can also be given subcutaneously in a syringe driver or as a stat injection. Use half the oral dose.

Levomepromazine – sedative. An oral dose of 6.25-12.5mg can be given daily increasing to a maximum of 25mg a day as necessary. Parenterally, a stat sc dose of 6.25mg should be given initially and a continuous infusion via a syringe driver of 6.25-25mg thereafter over 24 hours.

Admission to hospital or hospice may be required.

16. CONVULSIONS

May occur with primary or secondary brain tumours, uraemia or other metabolic disorders e.g. hypercalcaemia. The following advice refers to palliative care patients with a diagnosed cause for fitting.

Dexamethasone is used to reduce oedema around brain tumours (see Nausea & Vomiting: Raised Intracranial Pressure, page 35). Anticonvulsants are used for prophylaxis; consider oral phenytoin, sodium valproate, carbamazepine or levetiracetam but seek specialist advice and check interactions (phenytoin and carbamazepine decrease effect of dexamethasone, so consider doubling steroid dose if clinically significant).

Patients with a history of epilepsy and receiving treatment for it, will still need prophylaxis when the oral route is not possible.

Benzodiazepines, including diazepam and midazolam, can be used as either prophylaxis or for emergency treatment of convulsions. Caution is suggested with diazepam because of its prolonged sedative effect. Typical ranges are quoted below.

Midazolam:

Emergency: 5-15mg, subcutaneously, intravenously, intramuscularly, buccally or intranasally, repeated after 5-15 minutes if necessary.

Prophylaxis: 10-60mg by 24 hour subcutaneous infusion.

Midazolam is 3 times more potent than diazepam in single doses for sedation but as an anti-epileptic it is twice as potent as diazepam.

Diazepam:

Emergency: 5-10mg as rectal solution, repeated if not settled after 5-15 minutes .

Never give subcutaneously.

Lorazepam:

Emergency: 4mg intravenously (diluted 1:1 with sodium chloride 0.9%) as a single bolus into a large vein.

When oral therapy is not possible, an alternative prophylaxis is phenobarbital (phenobarbitone) 200-400 mg by subcutaneous infusion over 24hrs in a separate driver but only on the advice of a palliative care specialist (See section on drug compatibility in a syringe driver page 60). A loading dose of 100-200mg by intramuscular injection can be given if necessary. It is not first line - for difficult cases only. Beware drug interactions with oxycodone, fentanyl and alfentanil; Phenobarbital decreases opioid effect after 4-5 days.

17. MUSCLE SPASM AND MYOCLONIC JERKS

Muscle spasm

Usually due to pressure on, or irritation of, a nerve. The pain is not helped by opioids.

Diazepam:	Oral, 5-10mg up to three times daily.
Baclofen:	Oral. Increase slowly from 5mg every 8 hours after food. Max 100mg daily. Nausea and sedation common.

Smooth muscle spasm

Buscopan:	Hyoscine butylbromide. Oral, 20mg four times daily. Subcutaneous, 10-20mg four times daily or 60-120mg by subcutaneous infusion over 24 hours.
Nifedipine:	Oral, initial dose 5mg three times daily with food, increase as necessary to maximum 20mg three times daily. Modified release, initial dose 20mg daily, increase to maximum 60mg daily.
GTN:	Glyceryl trinitrate. If oesophageal spasm on eating: Sublingual, 400-500mcg 5-15mins before food. If symptoms constant: Transdermal patch, 5mg / 24 hours, increase to maximum 15mg / 24 hours.

Myoclonic jerks

Exacerbated by escalating doses of opioids, sepsis and metabolic disorders e.g. renal failure, hepatic failure. Common in the last 48hrs of life. Multifocal myoclonic jerks are considered pre-epileptiform.

Midazolam:	5-10mg by subcutaneous injection. 10-60mg by subcutaneous infusion over 24 hours.
Diazepam:	Orally or rectal solution, 5-10mg repeated every hour if necessary. Do not use in syringe driver.

18. PRURITIS

Diagnose and treat reversible causes of pruritis:

- Skin disorders: dry skin, atopic dermatitis, contact dermatitis, urticaria, psoriasis, Lichen Planus
- Skin infections: candidiasis, scabies, fungal infection, lice, flea or other insect bite
- Systemic disease: uraemia, cholestasis, lymphoma, leukaemia, myeloma, iron-deficiency anaemia, polycythemia, hyper & hypothyroidism, carcinoid, diabetes, paraneoplastic syndrome
- Drugs: opioids (especially morphine & diamorphine), cephalosporins, penicillins, phenytoin, allopurinol, sulphonamides

Management:

<p>Step 1 Treat underlying cause</p>	<p>Including medication review</p>
<p>Step 2 Good skin care</p>	<p>Emollient to bath water and aqueous cream as a soap substitute Avoid hot baths; dry skin by gently patting rather than rough rubbing Wear loose-fitting cotton clothing; avoid rough underclothing Avoid lanolin-based and perfumed products Avoid alcohol/spicy foods/avoid vigorous scratching</p>
<p>Step 3 Topical treatments</p>	<p>Emollient as a moisturiser Apply after washing morning and evening Avoid topical antihistamines – can cause contact dermatitis. Topical steroids can be used with caution for in dermatitis or eczema. Use in lowest dose concentration and for short course.</p>
<p>Step 4 Systemic treatments (often not necessary if skin care is improved)</p>	<p>Antihistamines (stop if no benefit after a few days)</p> <ul style="list-style-type: none"> • Sedating: Chlorphenamine, Promethazine, Hydroxyzine or Trimeprazine - may help sleep too • Non-sedating: Certirizine or Loratadine - can be useful for histamine mediated itch, eg drug reactions, urticaria or insect bites <p>Antidepressants</p> <ul style="list-style-type: none"> • Paroxetine can help in paraneoplastic itch Mirtazepine can be useful in lymphoma or Uraemia Systemic corticosteroids (if skin inflamed, but not if infected) • Dexamethasone 2-4mg once daily <p>Anticonvulsants</p> <ul style="list-style-type: none"> • Pregabalin and Gabapentin have some effect in uraemic
<p>Specific treatments</p>	<p>Cutaneous malignant disease: NSAIDs Systemic Lymphoma: Cimetidine 400mg twice daily (beware drug interactions) Cholestasis: Biliary stenting; Ondansetron 4mg twice daily; Stanazol 5mg daily; Rifampicin 150mg twice daily; Colestyramine not recommended as ineffective; Rifampicin can be useful in itch due to intra-hepatic cholestasis; Ranitidine can be useful in Urticaria and Hodgkin's Lymphoma</p>

19. FUNGATING TUMOURS

BLEEDING

These tumours may be friable and bleed during dressing change. Soak dressings with sodium chloride to ease removal. If the wound needs cleansing, irrigation with sodium chloride or water is preferred, because some antiseptics interfere with healing, and mechanical cleansing with swabs may be painful and disturb granulation tissue. Pressure applied over a bleeding point may reduce or stop bleeding.

Tranexamic acid can be used orally as prophylaxis against but should be used with caution in those patients with a history of thromboembolic disease. To avoid this it can be used topically by either dissolving the tablets in normal saline and applying directly with cover of non-adherent dressing or use gauze soaked in this solution, or use gauze soaked in tranexamic acid for injection.

Other options include alginate dressings (e.g. Kaltostat) or topical adrenaline (epinephrine) 1 in 1000 to bleeding points. An alternative is to use sucralfate paste; crush a 1g tablet and mix with 5 ml KY jelly or Intrasite gel to appropriate consistency. Gauze soaked in sucralfate suspension has also been used. These topical applications may be used as often as necessary and they are more effective and longer lasting than adrenaline. Infection of the area can increase bleeding therefore give consideration to treating infection or colonisation of the lesion.

If the tumour is near a major blood vessel, make plans to deal with major haemorrhage (see section on Major Haemorrhage, page 57)
Reconsider referral for embolic procedure. Reconsider referral for radiotherapy.

TUMOUR BULK

Discuss reduction of tumour bulk with a clinical oncologist.

ODOURS

Anaerobic organisms cause offensive smells which distress the patient and may cause nausea. Oral metronidazole, 200-400mg 8-12 hourly, can be used. There are also gel formulations, e.g. metronidazole gels for topical application. However the concentration of metronidazole is low and if a higher concentration is required then metronidazole tablets can be crushed and applied to the lesion or the injection preparation used mixed with an appropriate carrier. Charcoal cloth dressing placed over the main dressing may help. Not all dressings are available on prescription in the community.

WOUND CARE

For further advice on wound care, contact your Tissue Viability Nurse or other specialist nurse, e.g. community/hospital Clinical Nurse Specialist in Palliative Care or Hospice Inpatient Unit. Useful dressings include hydrophilic foam sheets or cavity dressings, alginates, and semi-permeable films (to contain odour and exudate).

PAIN

This may be difficult to control, requiring regular drugs for neuropathic pain as well as opioids and NSAIDs* (*these may also control itch). Dressings changes may require a short-acting analgesic 30 minutes prior to changing the dressing, or irrigation with 20ml of 1% topical lidocaine (lignocaine) solution. Opioids can also be used as a topical analgesia directly onto wound; seek specialist advice.

20. SWEATING AND FLUSHING

Profuse sweating, often worse at night, may occur in malignancies such as lymphoma and other cancers, carcinoid syndrome and liver secondaries. Fluid loss may be significant. Exclude treatable causes such as infection, anxiety, thyrotoxicosis, menopause. Drug causes include tricyclic antidepressants, opioids, anti-oestrogens, anti-androgens and alcohol. Reduce or stop unnecessary diuretics.

General measures are most important, including skin cooling, attention to clothing and environment, and oral fluids. Drugs alone may be insufficient.

- Regular paracetamol 1g qds or prn.
- NSAIDs, e.g. ibuprofen 200-400mg tds or naproxen 250-500mg bd even in afebrile patients.
- Hyoscine hydrobromide patch 1mg/72hours.

If antimuscarinics are ineffective other potential treatments include propranolol 10-20mg tds which may reduce sweating, but observe usual contraindications, e.g. asthma history. For hot flushes as a result of hormonal manipulation venlafaxine, gabapentin and clonidine have all been used with varying degrees of success. Megestrol acetate, 40mg daily for 4 weeks, has been used successfully for treatment of hot flushes following surgical or chemical castration. Seek specialist advice.

For carcinoid syndrome octreotide has a specific action. Seek specialist advice. For localised sweating of palms, soles, axillae, apply an aluminium chloride 20% antiperspirant preparation.

21. MAJOR HAEMORRHAGE

This section deals only with prescribing for major haemorrhage occurring as a terminal event, when death may result within minutes. The management of chronic bleeding is not covered here. Please seek specialist advice.

Major haemorrhage may occur as a consequence of:

- Fungating lesion which erodes a major blood vessel
- Internal tumour which erodes a major blood vessel
- Systemic coagulation disorder

Major haemorrhage may:

- have been heralded by “warning bleeds”
- or may occur without warning.

If there have been warning bleeds or there is a strong likelihood of major haemorrhage:

- It is important to ensure that staff are aware of the management plan.
- It may be appropriate to discuss with the patient and/or their family re the risks, and how to respond to such a bleed. (This will be an individualised decision for each patient)
- It is imperative to make sure that appropriate drugs have been prescribed “as required” on the community drug prescription sheet, and are available in the patient’s home.

If a bleed occurs:

- It is best to give medication via the intravenous route, however if the patient is hypovolaemic or peripherally shut down, IV access may not be possible and then give by deep intramuscular injection (subcutaneous drugs will be poorly absorbed in circulatory shut down).
- Red or green towels will mask the evidence of a bleed.
- Stay with the patient; explain what is happening, what treatments are being given and supporting them and their family.
- The intention is to relieve anxiety and distress, creating amnesia if necessary. Midazolam provides prompt relief of distress.
- Provide support and de-briefing for the professionals involved.

Medication Options:

- Midazolam 5mg to 10mg intravenously, titrated slowly to desired effect. Can be repeated if necessary
- OR midazolam 5mg to 10mg by deep intramuscular injection. Avoid oedematous sites. Repeat if necessary after 5 minutes if inadequate control.
- OR diazepam rectal solution 10mg.
- For surface bleeding; Application of pressure, 1 in 100 adrenaline soaked gauze or other dressing, Kaltostat dressings can minimise bleeding. However, they will not stop a torrential haemorrhage.
- Hypotension arising from these drugs or the bleeding itself, may arrest the bleeding temporarily. If blood pressure rises again, bleeding may re-start, so do not leave the patient alone.

Not all major haemorrhage is fatal. In the event of survival:

- Reassess the patient and institute appropriate symptom management. Consider the use of prophylactic treatments such as tranexamic acid or local measures if appropriate. The bleed may recur.
- Provide explanation and support for the patient and their family.
- Provide support and de-briefing for the professionals involved.

22. SYRINGE DRIVERS

GENERAL GUIDANCE

The syringe driver is an infusion pump used to give medication subcutaneously, usually over 24 hours. A number of machines are available, please refer to local policies.

For most drugs, this method of administration is unlicensed.

Other routes of administration may be useful and limit the need for a syringe driver, e.g. rectal, transdermal and sublingual.

Some drugs may be given as a once daily injection (dexamethasone, haloperidol, levomepromazine and octreotide). It is best to avoid giving several 'once daily' injections SC. However, consider this as an alternative or if it is the patients choice.

Drugs are generally more bioavailable by injection than PO. This means that the dose of drug given by syringe driver is likely to be lower than the dose previously given PO.

Although infusion pumps can take a variety of syringe sizes the minimum recommended size is 20mls. Dilute the mixture to the maximum volume the syringe driver will take to minimise problems with site irritation. See local policies for recommendations relating to the volumes that can be accommodated in different size syringes.

It takes a few hours before the drugs are sufficiently absorbed for an effect to be seen. If symptoms are controlled start the syringe driver 1-2hr before the effect of medications are due to wear off. If symptoms are uncontrolled, set up the syringe driver immediately. It may be necessary to cover the 'lag time' with a stat subcutaneous dose of the relevant drug if a delay would be unacceptable for symptom control.

Protect the contents from light with a holster.

Pain control is no better via the subcutaneous route than the oral route if the patient is able to swallow or absorb the drugs.

If a patient is well symptom controlled using other routes of administration and these can be maintained in the dying phase, a syringe driver does not have to be set up as a matter of routine.

Transdermal fentanyl or buprenorphine patches should remain in situ in most cases when the need for a syringe driver is short-term, e.g. in the last days of life. It is more straight-forward to titrate additional analgesic requirements with parenteral opioids (e.g. SC morphine) when necessary, rather than to convert to a single alternative opioid.

USES

A continuous subcutaneous infusion is a useful method of administration when the oral route is inappropriate e.g. persistent nausea, vomiting, malabsorption, dysphagia and unconsciousness.

CAUTIONS

Avoid oedematous tissue.
Care in restless/confused patient. Bleeding diathesis.

ADVANTAGES

Round the clock comfort because plasma concentrations are maintained, avoiding peaks and troughs.
Avoids repeated injections.
Generally needs to be loaded once daily.
Independence and mobility maintained because device is light-weight and can be worn in a holster.
Control of multiple symptoms with a combination of drugs.

DISADVANTAGES

Irritation or erythema and swelling at the site interfere with the rate and absorption.
May be seen as a terminal care event by the patient and carers.
Training necessary for staff.
Lack of flexibility.
Lack of reliable compatibility data for some mixtures.
Infection.
Psychological.

DRUG COMPATABILITY

It is common practice to administer 2 – 3 drugs in the same syringe. It is not recommended to mix more than 3 drugs without specialist palliative care advice.

A predictor of drug compatibility is pH. The majority of drugs given by syringe driver are acidic with only dexamethasone, diclofenac, ketorolac and phenobarbitone being alkaline. Consequently, combinations involving these drugs tend to be incompatible and separate infusions are usually recommended.

For most drug combinations, water for injection is the suggested diluent, as there is less chance of precipitation. Generally, incompatible drugs cause precipitation and thus cloudiness in the syringe. Do not use if this happens. Change the syringe and the giving set. For more information on drugs used via this route access www.palliativedrugs.com or www.prodigy.nhs.uk

Some drugs are not suitable for SC injection as they are irritant to the skin; e.g. diazepam, prochlorperazine, chlorpromazine.

GOOD PRACTICE

Before setting up the syringe driver explain to the patient and family:

- The reason for using this route and method
- How the device works
- Advantages and possible disadvantages

When prescribing the drugs to be placed in the syringe driver ensure that the correct SC rescue doses are prescribed (i.e. for analgesia 1/6th of the total 24 hour dose of opioid). All staff should ensure they are familiar with their local syringe driver before using. Follow local protocol for use.

All syringe drivers in use should be serviced regularly.
After use all syringe drivers should be cleaned and decontaminated as per local guidelines.

Label the syringe with the list of drugs, date and time.

Use of a syringe driver chart can prompt checks that the syringe driver is functioning properly. Checks should include the remaining volume, site condition, rate setting and appearance of the contents of the syringe.

If the site becomes inflamed or painful resite using a fresh cannula.

Site irritation may be reduced by diluting the drugs in a greater volume of diluent or using sodium chloride 0.9% as the diluent or substituting a plastic cannula.

Assess symptom control and adjust the prescription at appropriate intervals.

Some patients are able to revert from a syringe driver to PO medication. When this seems possible, convert the drugs sequentially rather than all at once.

TABLE 5: COMMON SYRINGE DRIVER DRUGS

DRUG	24HR RANGE	INDICATION	COMMENTS
Haloperidol	2.5 – 5mg	Anti-emetic	Antipsychotic with less sedative effects than levomepromazine. Higher doses may be used on specialist advice
Cyclizine	75 – 150mg	Anti-emetic	Irritant Mild sedative
Levomepromazine	5 – 12.5mg 5 - 25mg	Broad spectrum anti-emetic terminal restlessness	Higher doses may be used on specialist advice (more sedating)
Metoclopramide	30 – 60mg	Antiemetic	Irritation at site extrapyramidal effects non-sedating avoid in obstruction
Midazolam	5 – 30mg	Terminal restlessness anticonvulsant anxiolytic	Higher doses may be used on specialist advice
Glycopyrronium	600 – 1200micrograms	Terminal secretions, intestinal obstruction	Non-sedative
Hyoscine Hydrobromide	800 – 2400micrograms	Terminal secretions Intestinal obstruction Anti-emetic	Although sedative, it may cause agitation and confusion at the higher doses
Hyoscine Butylbromide (Buscopan)	40 – 120mg	Terminal secretions Intestinal obstruction	Non-sedative
Diamorphine	No ceiling doses	Analgesic	May precipitate with cyclizine at concentrations greater than 15mg/mL
Morphine	No ceiling dose, although solubility may be dose limiting (max solubility is 30 mg/mL).	Analgesic	
Oxycodone	No ceiling dose	Analgesic	Avoid using cyclizine with oxycodone doses >150mg in 24 hour

SPECIFIC SYMPTOMS - (also refer to respective chapters)

PAIN

If a continuous subcutaneous infusion (CSCI) of analgesia is appropriate, use the information in Chapter 3 Pain and Guidance on opioid conversion on page 22 to calculate the dose for the syringe driver and the breakthrough doses.

If the patient is opioid naive use as required doses of analgesia subcutaneously for the first 24 hours. If three or more doses of analgesia are required in 24 hours, consider starting a syringe driver based on the doses required in the previous 24 hours.

If the patient is in pain when a syringe driver is being set up, the first "breakthrough" dose can be given at the same time the syringe driver is started to cover the time it will take for the infusion to reach steady state.

In impaired renal function toxicity may occur. Consider giving a reduced dose if using morphine, diamorphine or oxycodone or switching opioids to one more appropriate in renal failure - seek Specialist Palliative Care advice before prescribing.

Switching between other analgesic presentations and a syringe driver

IMPORTANT : This covers timing only. Check appropriate sections for dose conversions.

- **Changing from twice daily MR morphine (e.g. MST) to the syringe driver.**
The syringe driver can be started when the next MST dose is due.
However, individual subcutaneous doses may be needed for pain control.
- **Changing from once daily MR morphine (e.g. MXL) to the syringe driver.**
MXL lasts for 24 hours, so diamorphine will not be needed in the syringe driver until the patient cannot swallow the next MXL dose when due.
- If the MXL dose has been taken but the syringe driver is needed for other symptoms, omit the diamorphine from the first syringe. When the next MXL dose is due, change the syringe and include the diamorphine with the other drugs.
- **Changing from a syringe driver to once daily MR morphine (e.g. MXL).**
Ideally, start MXL at least four hours before the syringe driver is discontinued. If the driver is taken down earlier, monitor the patient's need for breakthrough analgesia.
- **Changing from a Fentanyl patch to a syringe driver.**
Seek specialist advice.

OTHER ANALGESICS

Ketorolac (non-steroidal anti-inflammatory drug); clonazepam, ketamine and methadone (for neuropathic pain) should only be used under Specialist Palliative Care advice or in a Specialist Palliative Care unit.

NAUSEA AND VOMITING - See Chapter 6 page 29.

FOR USE OF SYRINGE DRIVERS IN THE TERMINAL PHASE

See chapter 23 page 63.

23. THE TERMINAL STAGE

The terminal stage is when death is imminent, within hours or days.

Common terminal symptoms include:

- Noisy breathing
- Pain (may be several simultaneously)
- Restlessness and agitation
- Urinary incontinence/retention
- Breathlessness
- Dry/sore mouth
- Sweating
- Nausea and vomiting
- Jerking, twitching, plucking
- Confusion
- Extreme fatigue

During this stage, symptom control alone forms only part of the care necessary for dying people and their carers. Advance planning for medications is critical, because medicines are the mainstay of therapy. Frequent symptom review is essential; if the situation is unstable, at least every 4 hours. There is no evidence that the appropriate use of opioids for symptom control in this setting shortens life.

Use of supportive guidance such as the 'Liverpool Care Pathway for the Dying Patient' or its equivalent is strongly recommended. Tailored versions also exist for different disease groups such as renal patients and patients on intensive care. **See www.mcpcil.org.uk**

Remember the potentially reversible causes of distress:

- Constipation
- Urine retention
- Infection
- Hypercalcaemia
- Gastric dilatation
- Fear
- Opioid toxicity

The three important steps in medication planning are:

1. Rationalising regular medication
2. Anticipating the drug administration route
3. Ensuring availability of parenteral medicines

RATIONALISING REGULAR MEDICATION

Only medicines which will control or prevent distressing symptoms should be prescribed regularly at this time. It will require considerable skill, tact and sensitivity when explaining this to relatives.

Many medications previously regarded as essential need to be reviewed and some may need to be discontinued.

Prescribe medication for new symptoms, which may arise. Write a treatment plan for any breakthrough of symptoms.

ROUTE OF ADMINISTRATION

Oral administration, even liquids, may become more difficult to administer. Consider alternative routes e.g. subcutaneous, iv, rectal.

If subcutaneous infusion is a likely option, discuss this with carers. If this is overlooked, families may blame the syringe driver for rapid deterioration. Explain that using the syringe driver is just switching to an alternative route of administration when a patient cannot swallow and is not a way of escalating the dose.

Not all dying patients need a syringe driver. If a patient is deteriorating rapidly and is within one or two hours of death, intermittent injections may be sufficient.

AVAILABILITY OF PARENTERAL MEDICINES

It is necessary to anticipate the possible use of a small number of drugs which are commonly used in the terminal phase. Drugs commonly used in this setting include diamorphine, morphine, oxynorm, cyclizine, haloperidol, levomepromazine, midazolam, hyoscine hydrobromide and hyoscine butylbromide (buscopan) and glycopyrronium. Specific details are given in the relevant symptom section and/or syringe driver section of this booklet.

In the home, make sure these are prescribed and obtained in good time, to avoid difficulties out-of-hours or at weekends. In case of unforeseen symptoms, find out what arrangements are in place locally before you need to use them.

The medication must be prescribed on an appropriate administration sheet so that the district nurses or ward staff can administer these drugs appropriately. With adequate training and discussion amongst team members, it is usually possible for doctors to write appropriate dose ranges for particular drugs to allow for changing circumstances.

IMPORTANT POINTS TO CONSIDER AT THE END OF LIFE

STEROIDS

Continue with steroids if they are considered essential for symptom control. Otherwise reduce and discontinue. Steroids should be given in a separate syringe driver or as a single daily s/c dose. (The oral dose of Dexamethasone is the same as by injection).

ANITCONVULSANTS

If no longer able to take oral anticonvulsants consider midazolam 10mg via syringe driver over 24 hours (increasing if necessary to a maximum of 60mg). Make available prn benzodiazepines for ictal activity (e.g. midazolam 5mg s/c) or diazemuls 5-10mg prn.

BOWEL OBSTRUCTION

Total cessation of nausea/vomiting may be impossible in complete obstruction. Consider Hyoscine butylbromide (Buscopan) 60-120mg in 24 hours via syringe driver to maximise antispasmodic and antisecretory actions. Make available Hyoscine butylbromide 20mg s/c 6 hourly prn stat doses.

If you require further advice regarding any of the above or if symptoms persist contact the Palliative Care Service for advice

GUIDANCE ON USE OF FENTANYL PATCHES AT THE END OF LIFE

The options listed below provide general guidance only. The patient should always have a pain assessment.

If in doubt regarding pain management then seek advice from Specialist Palliative Care.

It is usual practice to leave the fentanyl patch in place.

To calculate the breakthrough dose of diamorphine/morphine s/c prn for a fentanyl patch see the opioid conversion table or the manufacturers guidance.

If the patient develops unstable pain diamorphine/morphine s/c stats may be used in addition to the patch.

If more than two breakthrough doses of s/c diamorphine/morphine are required in 24 hours diamorphine/morphine can be put in the driver. The total number of breakthrough doses of s/c diamorphine/morphine needed in a 24 hours period is placed in a syringe driver and run alongside the fentanyl patch.

If the syringe driver containing diamorphine/morphine is started continue to make available prn diamorphine/morphine.

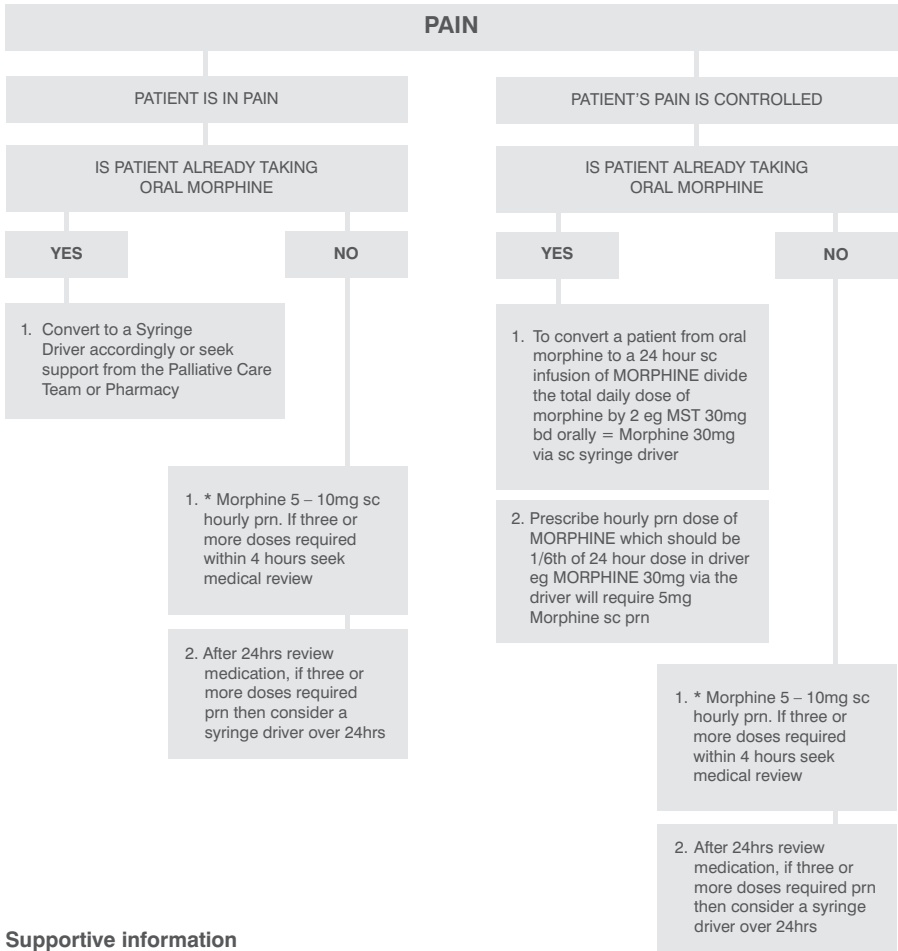
TERMINAL RESTLESSNESS AND AGITATION

This involves restlessness, anguish, agitated delirium, myoclonic jerks, confusion, crying out or moaning, in the last hours or days of life. Urgent management is essential for the sake of the patient and carers. A calm environment is important.

Restlessness and agitation can be mistaken for pain, leading to inappropriately escalating doses of strong opioids. This may lead to further agitation and confusion in the dying person. Opioid-induced myoclonic jerks may be mistaken for "jumping with pain". Consider dose reduction or an alternative opioid. Explanation to the relatives is very important. Other drug causes of restlessness include hyoscine hydrobromide, drugs with antimuscarinic properties and corticosteroids, even if previously tolerated; nicotine withdrawal (consider nicotine patch); alcohol withdrawal.

Exclude potentially reversible causes of distress such as pain, urine retention, constipation, gastric stasis, fear.

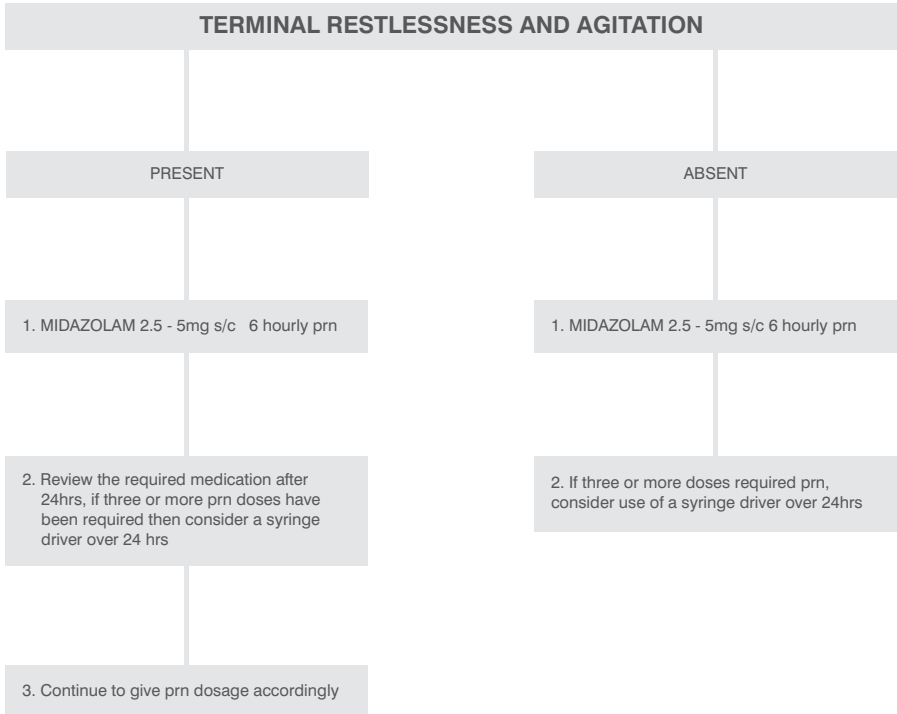
PAIN CONTROL AT THE END OF LIFE



Supportive information

- * Diamorphine 2.5mg – 5mg sc hourly prn may be utilized as an alternative.
- To convert other strong opioids (e.g. oxycodone or fentanyl) to subcutaneous route contact Palliative Care Team/Pharmacy for further advice & support on conversion ratios. Also see Palliative Care Guidance on opioid dose conversion and fentanyl prescribing notes, see chapter on Opioid Conversions starting on page 20.
- If symptoms persist contact the Palliative Care Team.
- Anticipatory prescribing in this manner will ensure that in the last hours/days of life there is no delay responding to a symptom if it occurs.
- If patient has impaired renal function consider reducing doses or alternative opioid.**

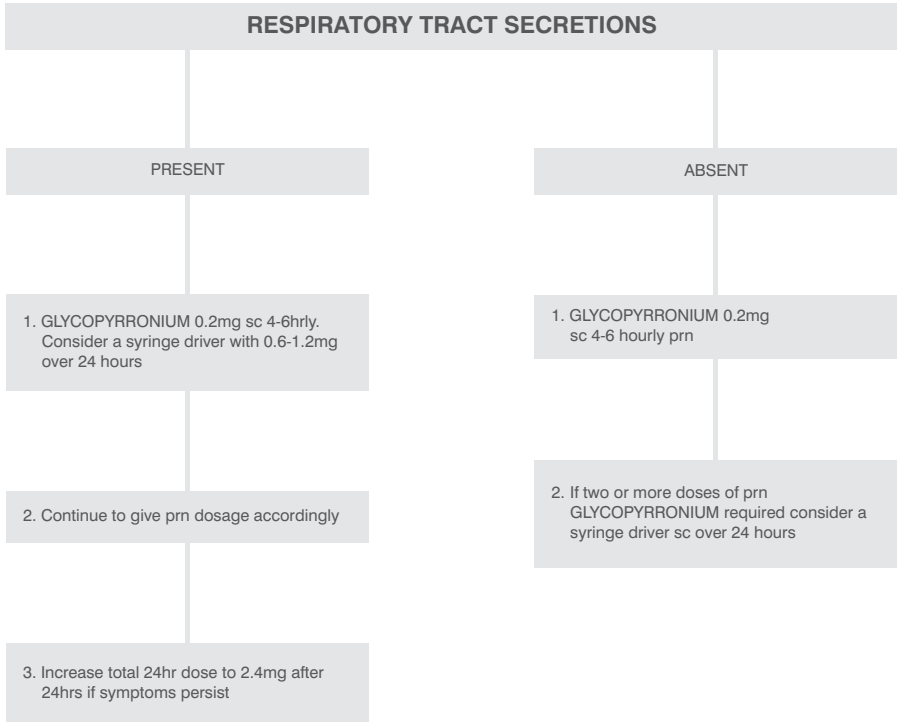
TERMINAL RESTLESSNESS AND AGITATION



Supportive information:

- Exclude reversible causes e.g. urinary retention, constipation, pain.
- If symptoms persist contact the Palliative Care Team
- Anticipatory prescribing in this manner will ensure that in the last hours / days of life there is no delay responding to a symptom if it occurs.

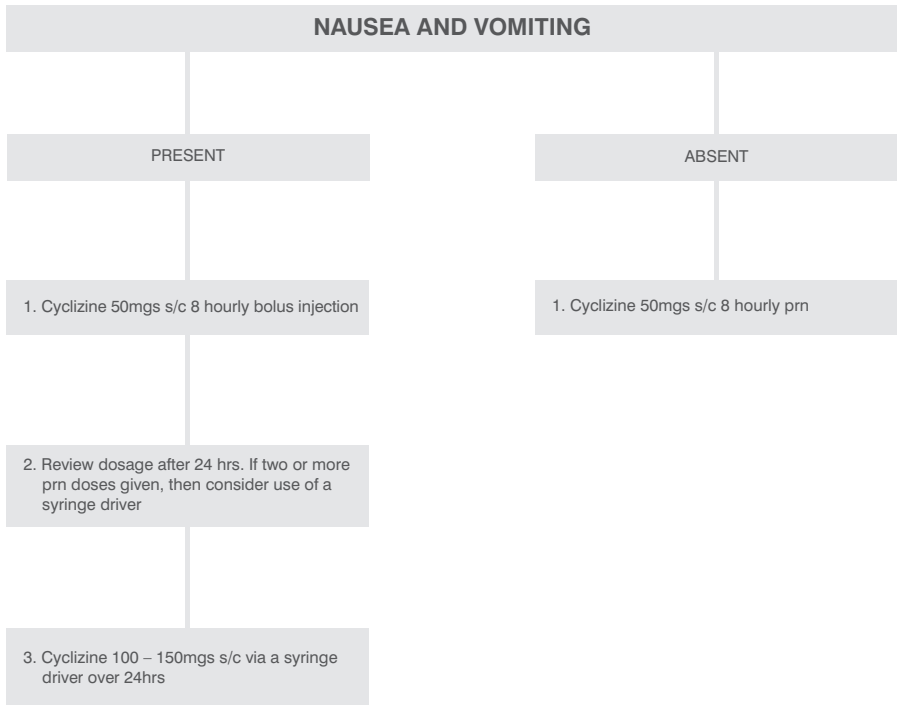
RESPIRATORY TRACT SECRETIONS AT THE END OF LIFE



Supportive information:

- Consider turning patient.
- If symptoms persist contact the Palliative Care Team
- Anticipatory prescribing in this manner will ensure that in the last hours / days of life there is no delay responding to a symptom if it occurs.
- Other antisecretory medication include hyoscine butylbromide 20mg sc 4-6hourly or hyoscine hydrobromide 0.4mg sc 4-6hourly.

NAUSEA AND VOMITING AT THE END OF LIFE



Supportive information:

- N.B Always use water for injection when making up Cyclizine.
- If symptoms persist contact the palliative Care Team.
- Cyclizine is not recommended in patients with heart failure.
- Alternative antiemetics according to local policy & procedure may be prescribed

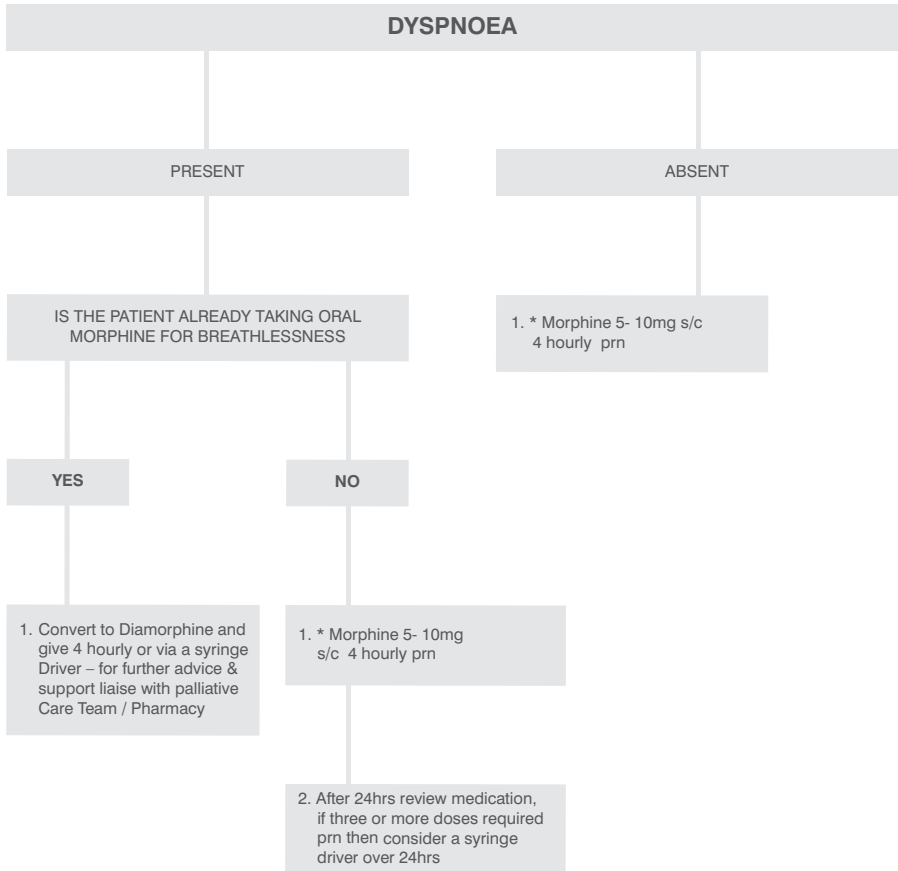
e.g.

**Haloperidol 1mg – 2.5mg sc 8 hourly
(up to 10mg in a syringe driver over 24 hours)**

**Levomepromazine 6.25mg sc 6 hourly
(up to 25mg in a syringe driver over 24hours)**

- Anticipatory prescribing in this manner will ensure that in the last hours /days of life there is no delay responding to a symptom if it occurs.

DYSPNOEA AT THE END OF LIFE



Supportive information:

- * Diamorphine 2.5-5mg s/c 4 hourly prn may be utilized as an alternative
- If the patient is breathless and anxious consider Midazolam 2.5mg s/c 4 hourly prn. This can also be added to the syringe driver.
- If symptoms persist contact the Palliative Care Team.
- Anticipatory prescribing in this manner will ensure that in the last hours / days of life there is no delay responding to a symptom if it occurs.
- These guidelines are produced according to local policy & procedure and you may want to alter them for local use and reference accordingly.

24. REFERENCES AND RESOURCES

GENERAL

British National Formulary: Guidance on prescribing: Prescribing in Palliative Care.

Changing Gear – Guidelines for managing the last days of life in Adults 1997.

National Council for Hospice and specialist palliative Care Services. 1st Floor, 34-44 Britannia St, London WC1X 9JG.

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Back I, Hoy A, Lucas C, Watson M. Oxford: Oxford Handbook of Palliative Care. Oxford Medical Publications 1st Ed 2005.

Faull C, Carter Y, Woof R. Handbook of Palliative Care. Oxford: Blackwell Science Ltd, 1998.

Mersey Palliative Care Audit Group: Standards & Guidelines, Jan 2000. Published by Liverpool Marie Curie Centre, Speke Rd, Woolton, Liverpool L25 8QA (contact Personal Assistant to Medical Director).

Wigan Borough Palliative Care Pain & Symptom Control Guidelines Version 1, 2007.

Palliative Care Prescribing January 2001, North West Medicines Information Service and Aintree Hospitals NHS Trust, 2001.

Regnard C F B, Tempest S. A Guide to Symptom Relief in Advanced Disease. Manchester: Hochland & Hochland, 1998.

Thorns A, Sykes N. Opioid use in last week of life and implications for end-of-life decision making. Lancet 2000: 356 : 398.

Twycross R Wilcock A. Palliative care Formulary 4. Oxford Radcliffe Medical press 2011 (PCF5 to be published Autumn 2014).

Merseyside and Cheshire Palliative Care Network Respiratory Guidelines

Lancashire Teaching Hospitals Foundation Trust Guidelines. "Hypercalcaemia-2007", "Status Epilepticus CM 09.09.07".

Dickman A Schneider J. The Syringe driver: continuous subcutaneous infusions in palliative care. Third edition Oxford University press 2011

Dickman A. Drugs in Palliative Care. Second edition. Oxford University press 2012.

WEB SITES

Macmillan Cancer Services www.macmillan.org.uk

PCF3 Palliativedrugs.com, Dr Robert Twycross, Dr Andrew Wilcock www.palliativedrugs.com

Palliative Medicine Matters, Dr Ian Back. www.pallcare.info.

Together for Short Lives www.togetherforshortlives.org.uk

INFORMATION SOURCES AND SPECIALIST ADVICE

Specialist Palliative Care advice may be sought from a number of hospital Palliative Care Teams, hospices and community Clinical Nurse Specialists in Palliative Care, throughout the region.

For details:

Barrow in Furness Macmillan Service	01229 402567	
East Lancashire Teaching Hospitals NHS Trust	01254 732316	www.elht.nhs.uk
East Lancashire Hospice, Blackburn	01254 733400	www.eastlancshospice.org.uk
Furness General Hospital	01229 870870	www.uhmb.nhs.uk
Hospice of St Mary of Furness	01229 580305	www.stmaryshospice.org.uk
Lancashire Teaching Hospitals NHS Foundation Trust		www.lancsteachinghospitals.nhs.uk
Preston site	01772 522055	
Chorley Site	01257 245356	
Macmillan Service, Kendal	01539 738650	
Pendleside Hospice, Burnley and Pendle	01282 440100	www.pendlesidehospice.org.uk
Rosendale Hospice, Rosendale	01706 253633	www.rosendalehospice.org
Royal Lancaster Infirmary	01524 65944	www.uhmb.nhs.uk
St Catherine's Hospice, Preston	01772 629171	www.stcatherines.co.uk
St John's Hospice, Lancaster	01524 382538	www.sjhospice.org.uk
Trinity Hospice & Palliative Care Services, Blackpool	01253 359379	www.trinityhospice.co.uk
Blackpool Teaching Hospitals		
NHS Foundation Trust	01253 300000	www.bfw hospitals.nhs.uk

For advice around children please seek specialist advice:

Derian House Children's Hospice	01257 271271	www.derianhouse.co.uk
Brian House Children's Hospice	01253 358881	www.trinityhospice.co.uk

INFORMATION AND SPECIALIST ADVICE FOR GREATER MANCHESTER

Bolton Hospice www.boltonhospice.org.uk	01204 663066
Bury Hospice www.buryhospice.co.uk	0161 725 9800
Dr Kershaw's Hospice (Oldham) www.drkershawshospice.org.uk/	0161 624 2727
Springhill Hospice (Rochdale) www.springhill.org.uk	01706 649920
St Ann's Hospice (Heald Green) www.sah.org.uk	0161 437 8136
St Ann's Hospice (Little Hulton) www.sah.org.uk	0161 702 8181
Wigan & Leigh Hospice www.wlh.org.uk	01942 525566
Willow Wood Hospice (Ashton) www.willowwood.info	0161 330 1100
Central Manchester University Hospitals NHS Foundation Trust www.cmft.nhs.uk	0161 276 1234 (switchboard)
The Christie NHS Foundation Trust www.christie.nhs.uk	0161 446 3000 (switchboard)
Pennine Acute Hospital NHS Trust www.pat.nhs.uk	0161 624 0420 (switchboard)
Salford Royal NHS Foundation Trust www.srft.nhs.uk	0161 789 7373 (switchboard)
Stockport NHS Foundation Trust www.stockport.nhs.uk	0161 483 1010 (switchboard)
University Hospitals of South Manchester NHS Foundation Trust www.uhsm.nhs.uk	0161 998 7070 (switchboard)

FOR ADVICE AROUND CHILDREN PLEASE SEEK SPECIALIST ADVICE

Derian House Children's Hospice www.derianhouse.co.uk	01257 233 300
Francis House Children's Hospice www.franchishouse.org.uk	0161 434 4118

INDEX OF MEDICATIONS USED IN THE GUIDANCE

Please note this is only for guidance.

Please read the relevant symptom control section for guidance of medication choice.

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