FRIMLEY ICS
ADULT PALLIATIVE CARE SYMPTOM CONTROL GUIDELINES

Key points

- Guidance for management of symptoms for adult patients in the last year of life
- Guidance for the management of patients in the last days of life
- Adapted from Berkshire Adult Symptom Control Guidelines in Palliative Care

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- Symptom Management
- End of Life

POLICY DEVELOPMENT

ADULT PALLIATIVE CARE GUIDELINES

Section 1: Pain
Section 2: Other Symptoms
Section 3: Last Days of Life Guidance

History	These guidelines were originally developed through Thames Valley Cancer Network Palliative Care Group to cover all services in Berkshire. In November 2021 minor amendments made to enable use in Frimley Park Hospital. Reviewed September 2022 to enable the guidance to be used throughout the Frimley ICS – East Berkshire, Surrey and N Hampshire. To be read in conjunction with Organisational Policies on Medicines Management, Prescribing and administration of medicines and use of Oxygen appropriate to each organization.
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Key to symbols:

† = unlicensed route/indication
# = non formulary – requires approval and continuation from secondary care.

Section 3. Last Days of Life

For staff working in FHFT Acute Hospitals Trust specific guidance is found on the Guidelines App

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Who are these guidelines intended for?

Which patients?
These palliative care guidelines are intended to help alleviate symptoms in adults with advanced life-limiting illnesses, including both malignant and non-malignant conditions. Whilst some of the principles of symptom control presented here are applicable to adults with potentially curable illnesses, there are often important differences. The likely causes, underlying pathophysiology and therapeutic aims may differ, making these guidelines inappropriate for use in the non-palliative setting.
For patients 16 years – 18 years in transition to adult palliative care services care should be taken to ensure that medication use is individualised to the patient and that treatment plans are appropriate for the physiology and disease state of the young person.

Paediatric Formulary is available from Association of Paediatric Palliative Care Medicine

https://www.appm.org.uk/guidelines-resources/appm-master-formulary/

Which healthcare professionals?
These guidelines are aimed at all members of the multi-disciplinary healthcare team, regardless of specialty and profession, providing palliative care wherever it is required (in hospitals, care homes or the patient's own home). They are designed to aid decision-making by experienced professionals without specialist palliation training.

They are not intended to discourage professionals from seeking specialist advice if they are uncertain or outside of their usual experience.

What knowledge, on the part of the professional, is assumed?
It is assumed that the professional using these guidelines has sufficient skills in clinical assessment to answer the clinical questions posed in the guidelines and to understand the overall clinical context (for example, whether care is aimed at palliation or cure, and the degree of urgency with which to act).

Where medication is recommended, the usual skills of a prescriber are assumed, including that:

•They are familiar with disease states (e.g. renal impairment) and other concurrent medication that might affect the use or dose of the suggested medication. Details of these drug- and disease-interactions are found in the British National Formulary or Summary of Product Characteristics and not replicated here. It is assumed that prescribers are able to make appropriate adjustments to the doses suggested in these guidelines in the light of such circumstances. If in doubt, discuss with a pharmacist or Specialist Palliative Care Team

•They practice a shared decision making (patient centred) approach to making treatment decisions, combining their own experience and clinical knowledge with the patient's priorities and wishes.

In palliative care, medications are often used outside of their marketing authorisation (product licence). These guidelines are intended to give a clear indication of where such use is "generally accepted" (†) and where use should be overseen by a specialist. Guidance on the specialist support for use of these drugs is detailed at the end of each section. N.B. # next to a medication indicates that it is an unlicensed product.

The drugs included in this guideline have been considered by local formulary and medicines management committees. These are "accepted uses" and may be initiated by non-specialists for the indications described**.**
The standard text in palliative care is the Palliative Care Formulary (PCF), which may be accessed (with a subscription) via Medicines Complete. A print version is also available (PCF7 Pharmaceutical Press).
NICE guidance NG 142 (End of Life Care for Adults), NG31 (Care of Dying Adults in the last days of life), and CG140 (Palliative Care for Adults: strong opioids for pain relief) also inform this guideline.

Where to get advice, make referrals and get further information

Patients' location	Daytime weekdays advice	Out of hours advice
Frimley Park Hospital	All referrals to be made on EPIC 08:30 - 16:30, 7 days a week, on ext 136755 or bleep 5799.	Out of hours (16:30 - 08:30) contact the duty SHO. If issue has not been resolved, contact the duty palliative medicine consultant for FPH via switchboard.
Wexham Park Hospital	All referrals to be made on EPIC 8.30 to 16.30, 7 days a week, on ext 154879 or, for urgent clinical advice, on call mobile through switchboard.	Out of hours (16:30 to 08:30, Mon to Sun) switchboard has access to the on call Consultant for telephone advice to a Registrar or Consultant.
East Berkshire Community setting Thames Hospice	Single point of Access Thames Hospice **01753 848 925**	Single point of Access Thames Hospice 01753 848 925
Surrey and N Hampshire Community setting Phyllis Tuckwell Hospice	ART (advice and referral team) 01252 729440 email pth.adviceandreferral@nhs.net	ART 01252 729440
Royal Berkshire Hospital NHS Foundation Trust	**I**nternal ext. 7826 External Tel. 0118 322 7826 Referrals taken by phone 0800 – 1600 7 DAY SERVICE Team Lead Jacquie Batchford Nurse Consultant Elizabeth Flannery	A specialist nurse is available 7 days a week 0800 - 1600 A Palliative Care Consultant is on-call 24 hrs a day if needed via switchboard

1. INTRODUCTION TO PAIN MANAGEMENT

1.1. Pain assessment: how and why?

Pain assessment is essential because:

i. It is important to identify treatable underlying contributors, such as
   - Constipation, infection, pathological fractures
   - Unaddressed fear, depression or sleep disturbance

i. Some drugs are effective for some pain types and not others

ii. Fears and beliefs about the pain, its significance and its treatment can affect the pain's severity and the patient's willingness to accept suggested treatments.

The key stages of pain assessment

Where is/are the pain(s)? It can be helpful to use a body diagram (see below).

For each pain, establish:

i. Site, exacerbating and relieving factors, radiation, etc (i.e. traditional clinical assessment). This is helpful in identifying likely underlying causes

ii. Severity. Use a number (e.g. "If zero is pain free and 10 is the most severe pain you can imagine, how severe is the left arm pain?") or words (mild, moderate or severe)

iii. What's already been tried, how helpful was it, and were there any adverse effects. Consider also non pharmacological interventions such as heat or massage.

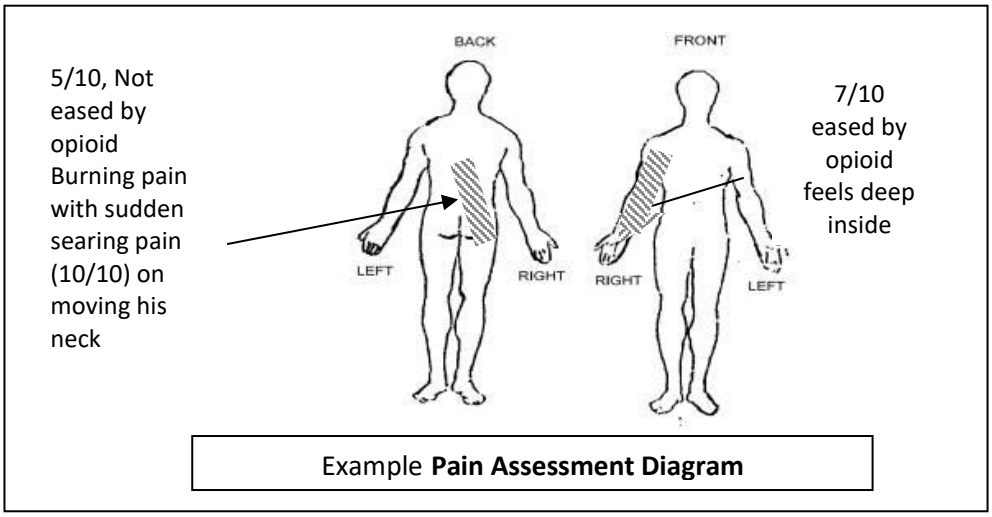
Enquire about:

i. The effect of the pain on the patient (their sleep, mood, mobility and independence)

ii. What they think might be causing the pain.

iii. For patients with dementia or learning difficulties consider use of specialised pain assessment tools eg abbey pain scale, and other verbal cues.

Review the medical history, including previous investigations, looking for potential explanations for the pain.



Example **Pain Assessment Diagram**

1.2 Pain treatment: The WHO ladder versus problem-specific approaches

Pain treatments fall into two groups:

i. **Broad-spectrum analgesics** that work for many different pain situations. Examples include paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. They are usually added in a step-wise fashion (the World Health Organisation Pain Ladder or 'WHO ladder'). This is described in section 2.1.

ii. **Approaches for pain in specific situations** (usually unhelpful for other pain types). They either affect the cause of the pain or a specific part of the pain system. Situations amenable to specific approaches include:

- Neuropathic pain (section 3.1)
- Skeletal muscle spasm (section 3.2)
- Smooth muscle spasm (colic) (section 3.3)
- Malignant bone pain (section 3.4)
- Incident pain and other episodic pains (section 3.5)

Specific approaches may also be required for secondary effects of the pain (e.g. depression, sleep disturbance, loss of independence).

It is helpful to divide pain problems into three groups:

i. Acute (short-term) pain
ii. Cancer pain
iii. Chronic (long-standing) non-cancer pain.

Type	General approach	Where to get advice
Acute	Generally requires broad-spectrum analgesics (paracetamol, NSAIDs, opioids) while the underlying cause is addressed.	Acute Pain Team FPH 03006134571 WPH 03006154435
Cancer	Usually of mixed cause and therefore initially treated with broad-spectrum analgesics (paracetamol, NSAIDs, opioids) Treating the underlying cancer is also an important aspect of pain management (e.g. with radiotherapy, surgery or chemotherapy) Additional specific approaches are added where pain is not responding completely to broad-spectrum analgesics (e.g. targeted at neuropathic pain, muscle spasm and bone pain).	Palliative Care Team contact numbers
Chronic	Often amenable to specific approaches (e.g. targeted at neuropathic pain or muscle spasm) plus non-opioid broad-spectrum analgesics (paracetamol, NSAIDs). The WHO ladder approach is often less effective for chronic non-cancer pain. Opioids are generally avoided in chronic pain because of uncertainties about their long-term adverse effects (see section 2.3). Inexperienced clinicians are advised to seek advice early. https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware	Chronic Pain Team FPH 03006134571 WPH 03006154435

2. BROAD-SPECTRUM ANALGESICS

2.1 Commencing and titrating broad-spectrum analgesics in palliative care

This section describes:

i. Dosing and titration of these agents
ii. Use of concurrent medication. e.g. (for opioids: antiemetics and laxatives)
iii. NSAIDs: gastroduodenal protection
iv. Dealing with common concerns about morphine
v. The use of parenteral NSAIDs

Subsequent sections describe:

i. Managing opioid adverse effects (section 2.2)
ii. Switching between opioids and conversion ratios (section 2.2)
iii. Long term use of opioids (including non-cancer pain) (section 2.3)

Overview

2.1.1 Paracetamol
2.1.2 Codeine
2.1.3 Starting morphine (doses, preparations and information to give patients)
2.1.4 Morphine titration
2.1.5 NSAIDs (and gastro-intestinal protection)
2.1.6 Parenteral NSAIDs

2.1.1 Paracetamol

Paracetamol 1g PO q.d.s. is the 1st line broad-spectrum analgesic based on tolerability profile. Consider reducing the dose in low body weight and/or the patient has impaired liver or renal function. If patients have found paracetamol ineffective for previous (different) pains, explain that:

- paracetamol is often more effective taken regularly than intermittently
- different pains respond differently to the same types of painkiller
- you will offer alternatives if ineffective, but that paracetamol is the safest 1st option

If patients struggle with the tablet load:

- consider caplet ('torpedo' shaped tablets), soluble or liquid preparations
- if other analgesics are subsequently added, consider a trial discontinuation of paracetamol to assess contribution to overall analgesia

2.1.2 Codeine (codeine phosphate)

If paracetamol is insufficient, **codeine** 30-60mg PO q.d.s. may be added, along with a laxative (e.g. senna 7.5 to 15mg (1-2 tablets or 5-10ml) b.d. PO). If a liquid preparation is needed, use **codeine** (25mg/5ml) 5-10ml PO q.d.s. or dissolve the normal tablets in a small amount of water†. The dose in combination preparations (e.g. co-codamol 8/500) is often sub-therapeutic. Up to 25% of the Caucasian population are unable to metabolise codeine to morphine (its active metabolite). Careful assessment of its effectiveness is needed. It may be worth considering using morphine at low dose (see section 2.13) instead of a step 2.

Nausea or vomiting is common for the first few days when codeine is commenced. It is not an 'allergy'. Give **haloperidol** 0.5-1.5mg PO (SC if vomiting) prn t.d.s. Review whether still needed after 5 days.
Have prn immediate release **morphine** (2mg -5mg prn 2-4 hourly) available if codeine is likely to be insufficient. Morphine Sulfate Oral solution 10mg/5ml may be easier for patients to measure 2mg (1ml) than 2.5mg (1.25ml) as a starting dose.

2.1.3 Morphine (morphine sulfate)

Morphine Sulfate is the first choice strong opioid by all routes.

Morphine is available in two forms:

i. Immediate release solution or tablets (e.g. Oramorph®, Sevredol®) lasting 4 hours
ii. Modified release (e.g. Zomorph capsules, MST Continus tablets) lasting 12 hours

Morphine is prescribed both regularly (to provide a background level of analgesia) and prn (to allow top-up doses if the pain 'breaks through' the regular dose).

Morphine sulfate m/r is generally used as the regular opioid since it is only needed b.d. (12 hourly) rather than 4 hourly (as with immediate release) and does not wear off overnight.

Zomorph capsules have additional advantages over MST tablets in that the capsules can be opened and sprinkled on yogurt or other cold food to make swallowing easier (the granules should not be chewed or crunched). The capsules can also be opened for the granules to be administered via feeding tubes (See manufacturer's instructions). When prescribing please make sure that you have checked the available strengths for the preparation recommended by your local formulary.

If a smaller dose is needed, use MST Continus® 5mg tablets (**these cannot be crushed or administered via feeding tubes).**

Immediate release morphine is used as the prn opioid. It is available as:

i. Morphine solution (10mg/5ml: uncoloured): e.g. ®oral solution 10mg/5ml
ii. Concentrated morphine solution (100mg/5ml: pink in colour): e.g. Oramorph® concentrated oral solution 20mg/ml.
iii. Tablets (e.g. Sevredol® 10, 20, 50mg). The tablets are scored: i.e. can be halved.

The preferred immediate release formulation of morphine is the oral solution to facilitate dose titration and avoid confusion between MR and IR dose forms

Potentially fatal drug errors can occur if these preparations are confused.

It is essential to be clear about which units are being used when describing morphine solution since 5ml does not contain 5mg. "Mills" is ambiguous and a common source of confusion. It is recommended that the DOSE in MILLIGRAMS is prescribed NOT the volume

Common concerns about starting morphine

- Adverse effects (especially sedation, constipation and delirium): good pain relief can be achieved without troublesome side-effects by careful dose adjustment, the use of laxatives and other approaches.
- Fear of addiction: rarely occurs when used for pain (though caution is required if there is a history of prior opioid addiction: see section 4.2).
- Fear re prognosis (e.g. morphine means the 'end of the road'): morphine use depends on pain, not the severity or stage of an illness.
- Fear of tolerance (i.e. inadequate analgesia in the future): morphine does not become less effective with time, even if used over many years. If the pain changes, the dose can be altered accordingly.

Patient information leaflets for patients commencing morphine, oxycodone or fentanyl transdermal patches are available appended to this document to comply with the requirements of the NICE guidance. (NICE CG140).

Starting dose of morphine

The starting dose for regular modified release morphine is 10mg PO 12 hourly, this replaces codeine. When regular codeine has been initially effective this starting dose may not be sufficient (codeine 60mg q.d.s. is approximately equivalent to modified release morphine 15mg 12 hourly). The unpredictable response to codeine means that dose equivalence is not reliable and safe practice is to titrate slowly co-prescribing immediate release morphine for breakthrough pain. Where immediate release morphine has been used the 24-hour requirement will enable a starting dose for MR morphine to be calculated. Consider a lower dose (e.g. 5mg PO 12 hourly) for frail debilitated patients. Where a different prior opioid has been used, see section 2.2 for dose conversions.

Remember to also prescribe:

i. Regular laxatives (e.g. senna or macrogol): 90% of patients will require a laxative.
ii. As needed prn antiemetic (e.g. metoclopramide 10mg tds/ haloperidol 0.5mg – 1mg tds)
iii. A third of patients experience nausea in the first few days. This is a class effect occurring with all opioids. Treat with antiemetics: only switch to an alternative opioid if it persists >1wk with concurrent antiemetic treatment.
iv. As needed prn immediate release morphine (e.g. morphine solution [10mg/5ml] 5mg PO prn 2-4 hourly).

Alternative method to start oral morphine

Traditionally, patients were started on regular morphine solution (e.g. 5-10mg PO 4 hourly) before converting to a slow release preparation. This is still an equally effective alternative method, though 12 hourly preparations are more convenient.

When opioids are first started, 3 problems are commonly encountered:

i. Sleepiness – Give reassurance: it usually settles within the first few days (but occurs each time the dose is increased)
ii. Constipation – Countered with laxatives (usually required throughout opioid treatment and not dose dependant)
iii. Nausea – Countered with antiemetics (usually settles within the first few days and doesn't recur)

Managing other and more persistent, adverse effects is described in section 2.2

2.1.4 Morphine titration

The background opioid dose should be titrated in **increments of 25-50% every 48hrs** until:

i. effective pain control is achieved or
ii. adverse effects appear (see 'opioid adverse effects' 2.2 below) or
iii. prn opioid doesn't bring relief and/or two previous dose increases in succession haven't helped (i.e. the pain is failing to respond well to the morphine dose increases: see 'opioid poorly responsive pain' in section 2.2).

Remember to increase the prn dose as the background dose increases: the prn normal release morphine dose remains 1/6 of the total daily dose (e.g. for Zomorph 60mg 12 hourly, prescribe immediate release morphine [e.g. morphine solution] 20mg prn).

If the severity of the pain warrants more **rapid dose titration**, discuss with the Palliative Care Team or Pain Team; a non-oral approach (e.g. IV titration) may be preferable.

2.1.5. **Oxycodone**

Oxycodone is a strong opioid with similar properties to morphine. Based on morphine equivalent doses, the combination is twice as potent as morphine. It can be prescribed second line in patients experiencing side effects with morphine, such as hallucinations, pruritus. Oxycodone and its metabolites are cleared by kidneys, so accumulation can occur in renal impairment. Oxycodone is preferable to morphine in moderate renal impairment as likely to cause less toxicity. It is contraindicated in severe renal and hepatic impairment.

2.1.6 **Oxycodone titration**

The principle of titrating **oxycodone** is similar to morphine with starting dose modified release (MR) Oxycodone 5mg bd and co- prescribing immediate release (IR) Oxycodone 1- 2mg for breakthrough pain. The preferred immediate release formulation of oxycodone is the oral solution to facilitate dose titration and avoid confusion between MR and IR dose forms

2.1.7 **Fentanyl**

Transdermal fentanyl differs from titration of oral opioids and is described in section 2.2. Prescribers unfamiliar with whichever opioid preparation is being used are advised to seek advice from the Specialist Palliative Care Team, Pain Team or a Pharmacist.

2.1.8 NSAIDs (and gastro-intestinal protection)

Non-steroidal anti-inflammatory drugs (NSAIDs) are useful broad-spectrum analgesics despite a number of safety concerns:

i. Gastroduodenal ulceration
   Gastroduodenal risk factors include:
   - Increasing age
   - Previous ulcer
   - Type and dose of NSAID
   a. Concurrent antiplatelet, anticoagulants, SSRIs or corticosteroids
   b. Long term NSAID

ii. Renal: all NSAIDs (including coxibs) can exacerbate renal impairment

iii. Cardiovascular: there are two cardiovascular safety concerns with NSAIDs:
   - *Pro-thrombotic risk (e.g. myocardial infarction)*.
     a) *Exacerbation of heart failure*.

iv. Bleeding risk: in thrombocytopenia and anticoagulated patients

v. Asthma: asthmatic patients without prior exacerbations with NSAIDs or aspirin should be warned about the risk and peak flow monitored more closely. All NSAIDs should be avoided where aspirin or any other NSAID caused an exacerbation previously (it is a class effect).

Choice of NSAID

- **Ibuprofen** 400mg PO t.d.s has a good overall (especially gastrointestinal) safety profile
  - Dose may be titrated up to max 2.4mg/24hrs.
- **Naproxen** 250-500mg PO b.d. (particularly if cardiovascular risk is high and NSAID unavoidable. However, higher gastrointestinal risk than diclofenac and low dose ibuprofen)
  - **Diclofenac** MR 75mg PO b.d. is an alternative where gastrointestinal risk is high and NSAID unavoidable [combine with PPI]. However, higher cardiovascular risk than naproxen and low dose ibuprofen). Dispersible (50mg tablets) and rectal preparations (50mg and 100mg) available.

- **Celicoxib 100mg PO BD** may be required if GI risk is very high, and other NSAID have not been tolerated.

Gastroduodenal risk

If NSAIDs can't be avoided in patients with risk factors, prescribe a proton pump inhibitor (PPI) eg **omeprazole** 20mg PO o.d. or l**ansoprazole** 30mg o.d. PO. The dose and duration of treatment should still be minimised as far as possible.
Famotidine 20mg b.d. may be used in patients unable to tolerate PPIs.

2.1.9 Parenteral NSAIDs

Patients previously receiving oral NSAIDs do not generally require a parenteral NSAID when they can no longer receive oral medications (e.g. when approaching the end of life). In palliation, parenteral opioids are usually sufficient. Only consider a parenteral NSAID if subsequent opioid titration is ineffective or poorly tolerated. If in doubt, discuss with Palliative Care Team

If a parenteral NSAID is required:

- Give **diclofenac** 75mg over 24 hours via subcutaneous syringe driver, diluted in sodium chloride 0.9%†.(N.B. equivalent to 150mg orally over 24 hours). Can be increased to 150mg over 24 hours if required.
- **Ketorolac** has a substantially higher gastrointestinal risk and should only be used on the advice of a Specialist Palliative Care or Pain team.

Other off-licence, infrequently used agents should be initiated only after discussion with, or review by, a palliative medicine or pain specialist e.g. ketorolac. See section 2.2 for difficulties with opioid analgesics.

2.2 Difficulties with opioids:

Pain that responds poorly to opioids

When titrating opioids, be alert to features of poor opioid responsiveness:

- Previous opioid dose increases were of limited benefit
- PRN opioid doses bring limited relief
- Adverse effects despite ongoing pain (see below)

Managing poorly opioid responsive pain

Switching opioids is usually unhelpful (unless adverse effects have prevented titration of morphine for a pain that would normally be fully opioid-responsive).

One of the following pain types is usually present and often requires non-opioid analgesics

- Neuropathic pain (section 3.1)
- Skeletal muscle spasm (section 3.2)
- Smooth muscle spasm (section 3.3)
- Malignant bone pain (section 3.4)
- Incident pain and other episodic pains (section 3.5)
- Unaddressed fear, depression or other psychosocial distress

Common adverse effects from opioids

Managed by 1 of 3 options:

1. **Opioid dose-reduction (adding non-opioid analgesics if required)** (e.g. NSAID, specific agents from section 3). See list of *poorly opioid responsive pains above*.
2. **Switching to an alternative opioid** may improve tolerability.
   This is useful when the pain is *fully opioid-responsive*
3. **Adding counter-measures** (e.g. **haloperidol** for delirium).
   This is *short-term management* (e.g. while awaiting benefit from an opioid dose reduction).

Problem	**Management** (N.B. Also consider alternative causes of the symptom)
Constipation	**Laxatives** (see also 'Constipation 'section and Frimley ICS constipation guidelines). Switching opioids is usually unhelpful: although lower laxative doses are needed for some opioids (e.g. fentanyl). Non-opioid factors (e.g. debility) are usually responsible for intractable constipation. **Combination oxycodone-naloxone (Targinact)** is *not recommended*: for generalist initiation. PAMORA (peripherally acting mu opioid receptor antagonists) may be considered in refractory opioid induced constipation specialist advice should be sought. Naldemidine 200 mcg od. (first line choice) Naloxegol 25mg once daily – reduced to 12.5mg once daily in renal impairment or if concomitant use of CYP3A4 inhibitors (eg clarithromycin, itraconazole)
Delirium	Often multi-factorial: address other contributing causes. • If due to opioid toxicity, reduce opioid dose and consider adding non-opioid analgesics. • If pain is fully opioid responsive consider switching to alternative opioids. if marked, give **short-term** haloperidol 0.5-1.5mg o.n PO while awaiting benefit from the above changes with regular review. **Start at lowest clinically appropriate dose and titrate cautiously according to symptoms**.
Drowsiness	Mild drowsiness is common in the first few days of starting or increasing opioids. Give reassurance that it is self-limiting. If marked or persistent (e.g. >1 week): consider whether pain may be poorly responsive to opioids (eg neuropathic, spasm, bony, etc.) Reduce dose and add a non-opioid analgesic.
Itching	Opioid-induced itching is uncommon in cancer and chronic pain. Consider alternative causes. Treat dry skin with emollients. **Consider trial of sedative antihistamine e.g. chlorphenamine** (still commonly used despite limited role of histamine in opioid induced itching). **Give stat dose chlorphenamine 4mg-12mg PO. If after 2-3 hours there is benefit prescribe chlorphenamine 4mg tds PO.** If severe and persistent, consider opioid switch or **ondansetron 8mg b.d. PO'**
Myoclonus	Other drugs used in palliative care may cause this e.g. gabapentin/pregabalin. Consider also metabolic causes. • Consider whether pain may be poorly opioid responsive (list above: neuropathic, spasm, bony etc.): **reduce dose** and add a non-opioid analgesic • If pain is fully opioid responsive consider a switch to an **alternate opioid** • If marked, give **clonazepam**† 0.5mg o.n. PO/SC while awaiting benefit from the above changes.
Nausea and vomiting	Occurs in 1/3 of people within the first few days of starting an opioid. Give **haloperidol**† 0.5-1.5mg PO/SC nocte or **metoclopramide** 10mg tds PO/SC. for 5 days; then aim to discontinue. Nausea occurs with all opioids: only consider switching opioids if persistent (e.g. >1 wk) *New* nausea in someone already established on opioids usually has a different cause.

Switching opioids

Conversion errors can be fatal*:* The **Opioid Equivalence Table** below is a quick reference . Advice can be sought from Palliative Care Teams on switching*.* However, the ratios are **approximations**. Use particular care when converting between higher doses or where doses have recently required rapid titration. In such patients, consider a dose 25-33% lower than predicted by the ratios and ensure PRNs are available
Methadone is titrated differently - this must always be started by the Specialist Palliative Care Team. Seek specialist advice before changing an established dose.

New adverse effects in a person previously tolerating their opioid

Explanations include:

i. Reduction in underlying pain (e.g. following radiotherapy, bisphosphonates or other pain-modifying treatment) → Reduce opioid dose
ii. Opioid accumulation (e.g. due to renal impairment) → Reduce opioid dose and consider a non-morphine opioid if renal impairment is marked (discuss with Pain or Specialist Palliative Care Team)
iii. An unrelated alternative cause (e.g. UTI).

Indications for switching opioids

Non-oral route required (e.g. vomiting, weakness, dysphagia):

- **Subcutaneous** (e.g. **morphine or oxycodone** via 24 hr subcutaneous syringe driver): steady state is achieved more rapidly than with transdermal opioids
- **Transdermal** (e.g. transdermal **fentanyl**): may be more convenient if non-oral route is likely to be required for a long time period (e.g. ongoing dysphagia). This is not suitable for unstable pain.

Intolerance to a particular opioid. (eg persistent drowsiness, hallucinations)

- Opioid adverse effects are managed either by reducing the dose of the existing opioid and adding a non-opioid analgesic or by changing to a different opioid (see 'managing opioid adverse effects' above) Oral **oxycodone** is a useful alternative when patients are unable to tolerate morphine despite active treatment of side effects.

Using transdermal fentanyl

Knowledge of the correct use of transdermal fentanyl is often poor, even amongst clinicians regularly prescribing it. Care should be taken with opioid equivalent doses: if in doubt, seek advice. Onset of analgesia can take 12-24 hours following application of transdermal fentanyl patch (steady state can take up to 72 hours). As the time taken for the patch to work is variable, ensure adequate prn opioid is available. In opioid naïve patients commence oral or parenteral opioids and titrate dose until pain is controlled before converting to transdermal fentanyl.

Dose conversion

Convert from	Patch instruction	Breakthrough prescription
Immediate Release IR morphine/ oxycodone	APPLY patch	Continue IR 4hrly for next 12hrs i.e. x3 doses and then use PRN
Modified release MR Morphine/ oxycodone	APPLY patch at time of last dose MR given	Use IR as PRN only
CSCI morphine/ oxycodone	Apply patch	Continue infusion for next 12hrs and then STOP CSCI and use PRN

CSCI = continuous subcutaneous infusion

The patch(es) should be applied to clean, dry, hairless, non-irradiated, non-oedematous skin on the upper chest or upper arm (hair may be clipped but not shaved) and replaced every 72 hours on a new area of skin. In an inpatient setting used patches should be folded (adhesive side inwards) and placed in a sharps box as they will still contain some active drug. Patients who are at home should fold patches (adhesive side inwards) and replace in the foil envelope, ensuring that they are kept away from children. Care should be taken to avoid accidental transfer of patches either to family members or to staff applying or removing patches.

Vasodilation increases the rate of drug absorption. Patients should be advised to

- Avoid application of local heat source over patches e.g. hot water bottle.
- Monitor patients with fever for signs of opioid toxicity.

Fentanyl is less constipating than morphine: laxatives should be halved and re-titrated as needed.

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Specialist Advice

The above are "accepted uses" and may be initiated by non-specialists for the indications described.
Other off-licence, infrequently used agents should be initiated after discussion with, or review by, the Palliative Care Team:

Transdermal buprenorphine: if the transdermal route is required, transdermal fentanyl is preferred since it has a lower incidence of skin reactions and when higher doses are required titration is more straightforward.

The main advantage is in those patients who require transdermal route, but whose opioid requirement is too low for the use of fentanyl 12micrograms/hour.
Transdermal fentanyl is the preferred option if the transdermal route is required and inadequate relief is achieved with a buprenorphine 5mcg/hr patch.
There is wide inter-patient variability, making conversion ratios variable. Highlighting the need for individual titration and assessment.
The PCF7 states that fentanyl and buprenorphine transdermal patches are roughly equipotent, and that 5micrograms/hr of buprenorphine is equivalent to oral morphine 12mg in 24 hours.

- **Hydromorphone**: has a tolerability profile similar to morphine
- **Methadone** Converting to or from methadone should only be done under specialist guidance. A shared care protocol is available when methadone is used in the community.

How to switch opioids

Note the important cautions

Key principles

This conversion chart is only a guide. It does not provide definitive equivalences; individuals metabolise drugs differently and at different rates

Adjust to suit the individual situation. If in doubt, choose the lower dose for any conversion

1. **Morphine sulfate** is the strong opioid of choice. **Diamorphine** is only used if smaller volumes of opioid are required to enable use in a syringe driver

2. Renal failure
    i. Moderate renal failure: consider **Oxycodone**. If the pain is stable, consider a **Fentanyl TD** patch
    ii. Severe renal failure: consider **Alfentanil**.
    iii. This is on advice from the Specialist Palliative Care Team.
    iv. In FHFT hospitals see End of life in renal failure guidelines on the intranet.
3. Hepatic failure
    i. Weak opioids have unpredictable effects in hepatic failure and should be avoided.
    ii. Moderate hepatic failure- use morphine with caution as reduced first pass metabolism can increase bioavailability by 100%
    iii. Oxycodone absorption can increase by up to 400%, increasing half life and decreasing clearance and should be avoided.
    iv. In severe hepatic failure- Fentanyl is the drug of choice
    v. SEEK ADVICE from the Palliative Care Team.

Opioid Equivalence Table

These dose equivalences are **approximations** intended for use by experienced clinicians. Always seek specialist advice before prescribing unfamiliar opioids. Use particular care when converting between higher doses or where doses have recently required rapid titration. In such patients, consider a dose 25-33% lower than predicted by the ratios and ensure PRNs are available

Codeine		Tramadol		Oral Morphine			Subcutaneous Morphine		Oral Oxycodone			Subcutaneous Oxycodone		Subcutaneous Diamorphine*		Fentanyl Patch**
Q.D.S. dose	24 hour total dose (mg)	Q.D.S. dose	24 hour total dose (mg)	4 hour / p.r.n. dose (mg)	12 hour MR b.d. dose (mg)	24 hour total dose (mg)	4 hour / p.r.n. dose (mg)	24 hour total dose (mg)	4 hour / p.r.n. dose (mg)	12 hour MR b.d. dose (mg)	24 hour total dose (mg)	4 hour / p.r.n. dose (mg)	24 hour total dose (mg)	4 hour / p.r.n. dose (mg)	24 hour total dose (mg)	Micrograms per hour
60	240	50	200	2.5-5	10	20	2.5	10	1-2.5	5	10	1	5	1	5	½ x 12***
		100	400	5-10	20	40	2.5-5	20	2.5-5	10	20	2	10	2	10	12
				10	30	60	5	30	5	15	30	2.5	15	2.5	15	12-25
				15	45	90	7.5	45	7.5	20	40	2.5-5	20	5	30	25-37 (25+12)
				20	60	120	10	60	10	30	60	5	30	7.5	40	37 (25+12)-50
Is long term (years rather than months) opioid use anticipated? If so, seek specialist advice before titrating to the higher doses in the section below. Adverse effects (particularly endocrinopathies) are common with longer term higher dose opioids; Higher doses *are* used for opioid-responsive pains in the *palliative prognostic context (weeks to months)* since longer term effects are not relevant. Use particular care when converting between higher doses: consider a dose 25-33% lower than predicted by the ratios and ensure P.R.N.s are available.																
				30	90	180	15	90	15	45	90	7.5	45	10	60	50-75
				40	120	240	20	120	20	60	120	10	60	10-15	80	62 (50+12)-100
				50	150	300	25	150	25	75	150	10	75	15	100	75-125
				60	180	360	30	180	30	90	180	15	90	20	120	100-150
				70	210	420	35	210	35	105	210	15	105	20-25	140	125-175
				80	240	480	40	240	40	120	240	Max**** Subcut Volume	120	25	160	125-200
				90	270	540	45	270	45	135	270		135	30	180	150-225

* Where possible, morphine, oxycodone and fentanyl are recommended choices to ensure familiarity with a smaller number of opioids.

** Conversions to and from transdermal patches are especially unpredictable. Prescribers unfamiliar with such products are encouraged to seek specialist advice

*** Matrix fentanyl patches can be cut diagonally in half for smaller dose increments where a smaller patch size is unavailable (unlicensed use)

**** At usually available concentrations. If higher doses required, seek specialist advice about higher concentration preparations (50mg/ml) or alternatives.

2.3 Opioids in Chronic Pain

Opioids Aware is a national resource funded by PHE and hosted by the Faculty of Pain Medicine, Royal College of Anaesthetists. http://www.fpm.ac.uk/faculty-of-pain-medicine/opioids-aware

Key points

1. Patients who do not achieve useful pain relief from opioids within 2-4 weeks are unlikely to gain benefit in the long term.
2. Patients who may benefit from opioids in the long term will demonstrate a favourable response within 2-4 weeks.
3. Short-term efficacy does not guarantee long-term efficacy.
4. Data regarding improvement in quality of life with long-term opioid use are inconclusive.
5. There is no good evidence of dose-response with opioids, beyond doses used in clinical trials, usually up to 120mg/day morphine equivalent. There is no evidence for efficacy of high dose opioids in long-term pain

Overview of sections

2.3.1 Patient selection
2.3.2 Practical aspects of prescribing long-term opioids
2.3.3 Monitoring and features of problem drug use
2.3.4 Adverse effects from long-term use

2.3.1 Patient selection

Opioids reduce pain intensity by an average of ~30% (including neuropathic and musculoskeletal pain). However, this does not always bring corresponding improvements in functional ability individual response varies greatly and less than half of patients remain on opioids long-term.

Only Prescribe a trial of opioids if all of the following:

i. Better established treatments have been tried (e.g. antidepressants/antiepileptic drugs for neuropathic pain, non-opioid analgesics where appropriate).
ii. The underlying cause has been adequately assessed and, where possible, treated (e.g. orthopaedic review of osteoarthritic hip pain).
iii. Screening questions reveal no psychiatric co-morbid features indicating that specialist supervision of the opioid trial is desirable (e.g. prior or concurrent addiction disorder (section 4.2), severe depression, psychosis, suicidal risk).
iv. The patient understands:
   - This is a trial. Benefits and problems vary from person to person.
   - Opioids are one part of an overall plan to reduce the impact of pain on their life: other components may include help from a physiotherapist, psychologist or OT.
   - There are uncertainties about some of the long term effects (described below): if problems arise, specialist referral may be needed (e.g. to an endocrinologist).
   - Concerns about addiction, and fears about using pain medication appropriately, are very common. Mutual trust is essential: they should feel able to discuss such concerns openly both before and during opioid use.
   - Complete pain relief is rarely achievable: realistic goals and time period to review these goals should be agreed by the patient and clinician in advance (e.g. “partial pain relief sufficient to allow me to mobilise with a frame out of my house, to get to the shops independently and to have some nights uninterrupted by pain”).
   - British pain society produce a leaflet for patients in managing long term pain: https://www.britishpainsociety.org/static/uploads/resources/files/Understanding_and_Managing_Long-term_Pain_Final2015.pdf

2.3.3 Monitoring and features of problem drug use

Patients should be reviewed regularly during titration (e.g. 2 – 4 weekly), looking at the effect on pain, social and physical functioning, adverse effects and any other concerns.

If using longer term after a successful opioid trial, periodically taper the dose to confirm continuing effectiveness.

Be alert to suggestions of problem drug use [BPS 2010] (discuss promptly with a Pain Specialist):

- Early prescription seeking
- Claims of lost medication
- Intoxication or use to regulate mood rather than pain
- Frequent missed appointments
- Concurrent use of other controlled drugs.

Addiction is the compulsive 'out-of-control' use of a drug despite adverse physical or social consequences. Features include craving and a preoccupation with obtaining opioids. However, this can be confused with behaviour motivated by obtaining opioids for pain relief, **pseudoaddiction**: the features resemble addictive behaviours and can arouse suspicion in staff, but stop when pain is relieved.

Tolerance is where the dose needed to achieve the same effect increases over time with exposure to the drug. It is uncommon with opioids used for analgesia. After a period of titration (that may take several months), most patients stabilise on a long term opioid dose.

2.3.4 Adverse effects from long term use

Short term adverse effects of opioids for chronic non-cancer pain are comparable to opioids in other settings, including constipation, nausea and sleepiness (section 2.2).

Endocrine effects, clinically apparent in ~1% of patients, include altered:

- Sexual axis (affecting libido, potency, menstruation, fertility). Check endocrine function if symptomatic; seek endocrinological advice. Laboratory evidence suggests that buprenorphine may exhibit less of these effects.
- Adrenal axis
- Weight (loss or gain).

In females of childbearing age, discuss possible effects on:

- Fertility
- The developing baby (e.g. opioid withdrawal effects after birth). Seek specialist obstetric advice if a woman requiring regular opioids is planning a pregnancy.

There is some (laboratory) evidence that opioids cause some degree of immunosuppression. The clinical relevance of this is unclear.

Section 2.2 describes switching to an alternative opioid (e.g. oxycodone MR, transdermal fentanyl) as one strategy for managing persistent adverse effects. Note that:

- Pethidine is *not suitable* for long-term use [BPS 20042010]
- Methadone is only initiated by Specialists in Pain or Palliative Medicine.

Analgesia and fitness to drive: see section 4.1
https://www.gov.uk/drug-driving-law

2.4 **Opioid Induced hyperalgesia** (OIH)

This needs to be considered if there is worsening pain despite increased dose of opioids or if there is increased sensitivity to pain stimulus or if non-painful stimuli trigger pain.

Management includes:

- **Always SEEK SPECIALIST ADVICE**
- reduce the dose of the causal opioid to about 25%
- switch to an opioid with less risk of OIH, i.e. fentanyl (highest) → morphine → methadone → buprenorphine (lowest) (rarely)
- if occurring at very low doses (less than 10mg/ 24hr) discontinue the opioid completely.
- Use non opioids- paracetamol/ NSAIDs or adjuvant – eg TCA/gabapentin

3. PAIN AMENABLE TO SPECIFIC APPROACHES

3.1 Summary Neuropathic Pain: Management in Palliative care and Chronic pain

Evaluation and Diagnosis is based on the combination of:

- Known cause of nerve injury (e.g. diabetic neuropathy, malignant nerve infiltration)
- Co-existent features of nerve injury (sensory alteration, motor deficits)
- Suggestive pain descriptors (e.g. burning, tingling, sudden paroxysms).

In malignancy, re-staging may be needed if nerve injury is not explained by known disease.

Look for features of spinal cord or cauda equina compression: co-existent limb weakness, sphincter impairment, sensory level. *If in doubt, seek urgent advice.*

FIRST LINE OPTIONS

Explain that a **staged withdrawal would be considered at 6 months** (lifelong treatment not always required).

Choice of agent	Initial dose	Rate of increase / max
Amitriptyline†. Minimal tablet load; syrup available; good 1st-line choice unless antimuscarinic effects preclude use	10mg o.n. PO	10-25mg every 5-7 days Usual max[1]: 50-75mg/day
Gabapentin. Few drug interactions; good evidence base and widely used; can sprinkle capsule contents† on yogurt if swallowing problems (syrup is unlicensed and expensive: see opposite)	300mg o.n. PO (if frail: 100mg o.n. with slower titration)	300mg every 1-3 days (100mg if frail) Divide doses[3] (b.d. or t.d.s.) Usual max[1]: 1800mg/day Absolute max[2]: 3600mg/day

[1]Usual max: Benefit usually seen by this dose. Only titrate beyond this if already partly helpful

[2]Absolute max: Do not exceed this dose (except on the advice of a pain or palliation specialist)

[3]Examples of gabapentin titration are given in the full guidance below

SECOND LINE OPTIONS (1st line in specific situations)

When no benefit to a 1st drug, swap to (rather than add) a 2nd drug.

If partially responding to a 1st drug, consider combining an antidepressant with an anti-epileptic.

Do not combine 2 anti-epileptics for pain management except on specialist advice.

Choice of agent	Initial dose	Rate of increase / max
Nortriptyline†. If amitriptyline helpful but poorly tolerated (has fewer antimuscarinic adverse effects)	10mg o.n. PO	10-25mg every 5-7 days Usual max[1]: 50-75mg/day
Pregabalin. 2nd line when other options ineffective or poorly tolerated (b.d. more convenient than gabapentin). 1st line choice in **fibromyalgic pain. (due to its anxiolytic properties)**	75mg b.d. PO (if frail: 25-50mg b.d. with slower titration)	150mg every 3-4 days (25mg if frail) Absolute max[2]: 600mg/day
Lidocaine 5% plasters. 2nd line for localised pain if above options ineffective or poorly tolerated.	1 to 3 patches as needed to cover the affected area. (NB this is non formulary indication) Apply once daily and remove after 12hrs.	
Carbamazepine. 1st line for **trigeminal neuralgia** Otherwise 3rd line†: consider referral.	100-200mg MR b.d. PO	100-200mg every 1-2 wks. Divide MR doses (b.d.) Usual max: 800mg/day
Duloxetine. If both tricyclics and gabapentin ineffective, poorly tolerated or contra-indicated.	30-60mg o.d. PO	30-60mg every 2-4 wks. >60mg: divide doses (b.d.) Absolute max[2]: 120mg/day
Sodium valproate†. Single daily regimen helpful where tablet load is problematic; trial results conflicting.	200mg MR o.n. PO	200mg every 2-5 days Usual max[1] 800mg/day Absolute max[2]: 2500mg/day

Specialist-initiated options

All other anti-epileptics (e.g., **oxcarbazepine**†, **clonazepam**†) or **combinations of anti-epileptics** (e.g. **gabapentin plus carbamazepine**); **cannabinoids** (**Sativex**†); **mexiletine**†; **ketamine**†**/#**; **methadone** (**capsaicin 8% patch** (**Qutenza**) should be initiated by a Palliative Care or Pain Specialist.

Overview of sections

3.1.1 NICE guidelines on the treatment of neuropathic pain
3.1.2 1st line systemic treatments (amitriptyline, gabapentin)
3.1.3 2nd line systemic treatments (nortriptyline, pregabalin, carbamazepine, duloxetine, valproate)
3.1.4 Non-drug approaches (TENS, acupuncture)
3.1.5 Topical approaches (capsaicin, lidocaine patches)
3.1.6 Specialist referral

3.1.1 NICE guidelines on the treatment of neuropathic pain

NICE guidance (No 173) was given detailed consideration alongside the literature, local clinical experience and national and international guidelines from expert consensus groups.
This clinical guideline was prepared following discussions by local pain and palliative care specialists in liaison with the CCG Medicines Optimisation Team. It is consistent with European, Canadian and international guidance.

3.1.2 1st line systemic treatments: amitriptyline and gabapentin

No single agent is "best" in all situations. Their efficacy appears comparable. Choice is based on tablet load, tolerability, co-morbidities, cost and accepted use/licensing (key issues summarised in the 'key points' box, above). Guidance on all commonly encountered agents is given here, but restricting use to 2 or 3 familiar agents is usually sufficient and advisable (e.g. the usual 1st line agents, amitriptyline and gabapentin). The usual skills of a prescriber are assumed below (e.g. the impact of other drugs and disease states such as renal impairment on the drugs and doses recommended).

Amitriptyline

Minimal tablet load makes it a useful first line agent. It is inexpensive and available as tablets (10mg, 25mg, 50mg) and syrup (25mg/5ml, 50mg/5ml). Its main adverse effects, cautions and drug interactions relate to its sedative and antimuscarinic effects (including arrhythmogenic effects). These can go unrecognised or be misattributed to age-related changes. Simultaneous use of other sedatives/antimuscarinics and increased age are risk factors.

Commence 10mg o.n. PO and increase by 10-25mg every 5-7 days. If no benefit is seen by 50mg-75mg/day consider stopping and trying a different agent. Can increase further if well tolerated and increases are effective (up to 150mg/day can be used but is rarely tolerated).

Stopping: Small doses (e.g. ≤25mg/day) given for less than 8 weeks can be stopped abruptly. Larger or longer-standing doses should be withdrawn in stages over 4 weeks.

Use in patients with liver metastases is usually acceptable (despite contraindication in 'severe liver disease'). Be alert to increased sedation, particularly with co-existent cirrhosis or liver metastases extensive enough to cause ascites or jaundice.

Gabapentin

A widely used and well tolerated alternative 1st line agent where use of amitriptyline is precluded. Available capsule sizes: 100mg, 300mg, 400mg. Tablets (800mg) can be significantly more expensive, depending on dose 600mg tablets may be more cost effective than 2 x 300mg capsules. Capsule contents can be sprinkled† on food or dispersed† in water or fruit juice and taken immediately. Its commonest adverse effects are drowsiness and unsteadiness. It has few clinically important drug interactions.

Gabapentin: typical dose titration:

- 300mg o.n. PO for first 1 to 3 days
- 300mg b.d. PO for next 1 to 3 days
- 300mg t.d.s. PO thereafter for a stable period (usually at least a week)
- Subsequent increases of no more than 300mg per day.

In frailer patients, increase more gradually:

- 100mg o.n. PO for first 1-3 days
- 100mg b.d. PO for next 1 to 3 days
- 100mg t.d.s. PO thereafter for a stable period (usually at least a week)
- Subsequent increases of no more than 100mg per day.

If no benefit seen with 1800mg/day, consider stopping (gradually: see below) and trying a different agent. If well tolerated and increases are effective, consider increasing further (up to 3600mg/day).

Stopping: withdraw gradually (e.g. by 300mg every 1-3 days. Slower if history of seizures)

3.1.3 2nd line systemic treatments: nortriptyline, pregabalin, carbamazepine, duloxetine, valproate

Nortriptyline's dose, use and mode of action are the same as amitriptyline's (see above). However, it has fewer antimuscarinic adverse effects. Thus it may be helpful in patients not tolerating amitriptyline although is unlikely to be helpful in patients not responding to amitriptyline.

Pregabalin. Acts at the same target (neuronal N and P/Q type calcium channels) as gabapentin. It is more potent, though the clinical relevance of this is not yet determined. Pain reduction and adverse effects in trials for non-malignant pain are comparable to gabapentin. However, pregabalin is preferred in fibromyalgic pain (gabapentin lacks evidence in this group). Clinical experience also suggests that response is more rapid than with gabapentin and that it is also helpful in patients not responding to, or not tolerating, gabapentin. Pregabalin has a licence for treatment of anxiety. At present it remains unclear whether such patients should be switched to pregabalin or a mechanistically distinct agent (such as an antidepressant or carbamazepine).

Commence 75mg b.d. PO (in frailer patients: 25-50mg b.d. with slower titration) and increase by 150mg (25-50mg if frail) every 3-4 days to a maximum of 600mg/day.

Stopping: withdraw gradually (particularly if history of seizures).

Carbamazepine is rarely used except in trigeminal neuralgia (where it appears to be more effective than other agents). See CKS for advice re dosing. https://cks.nice.org.uk/topics/trigeminal-neuralgia/prescribing-information/carbamazepine/

Duloxetine is an antidepressant licensed for use in painful diabetic neuropathy. Adverse effects and mechanism appear comparable to venlafaxine. Its place relative to other agents is unclear, but it should be considered for patients in whom 1st line options are ineffective, poorly tolerated or contra-indicated. See BNF for dose and indications.

Sodium valproate†. Can be given once daily (m/r tablets) so can be helpful where tablet load/medication adherence is difficult and amitriptyline is contra-indicated/ineffective. The evidence is limited: results from clinical trials are conflicting. Counselling and baseline blood tests are required for rare but serious hepatotoxicity. Sodium Valproate is teratogenic and should not be considered for this indication in women of childbearing potential. Advice should be sought from Palliative Care before starting.
Commence 200mg m/r o.n. PO (or 100mg syrup b.d. PO) and increase by 200mg/day every 2-5 days. If no benefit is seen with 800mg/day, consider stopping (gradually: see below) and trying a different agent. If well tolerated and increases are effective, consider increasing further (up to 2500mg/day).
Stopping. Withdraw gradually (e.g. by 200mg every 1-3 days. Slower if history of seizures).

3.1.4 Non-drug approaches (TENS, acupuncture)

Non-drug approaches are useful options in those intolerant of, or averse to taking, oral medication. Physiotherapists will usually show patients or carers how to use TENS, and some are trained acupuncturists. The Pain Team and Palliative Care Team can also provide both treatments.

3.1.5 Topical approaches (capsaicin *cream**, lidocaine plasters)

**NB Capsaicin patches (Qutenza) are also available but require specific expertise:*
Capsaicin and lidocaine plasters are less effective than antidepressants and anticonvulsants, but they are useful options in those intolerant of, or averse to taking, oral medication. Where the shape/hairlessness of the affected area allows, the more rapid onset and convenience of lidocaine plasters may be preferable to capsaicin.

Lidocaine 5% plasters ('Versatis') †
These are non-formulary in Frimley ICS, except for NICE approved licensed indication, post-herpetic neuralgia.
However, it can be considered 2nd line for patients in whom 1st line treatments are ineffective or poorly tolerated, on specialist advice.

Apply to the affected area for 12 hours a day (i.e. 12 hours on, 12 hours off). They can be cut to size to fit the area of pain. Up to 3 may be used simultaneously to cover larger areas. Avoid broken/inflamed skin and mucosae. Local reactions at site of application may occur as a result of the, necessary, repeated application to the same area.
Be alert to systemic effects (confusion, seizures, hypotension, bradycardia) in those with severe cardiac, liver or renal impairment, or where unlicensed doses are required (application for 24 hours a day† in patients whose pain recurs during the 12 hour 'off' period, or simultaneous application of more than 3 patches† in more widespread pain [specialist review advised]).

Capsaicin 0.075% cream
Licensed for painful diabetic neuropathy (where manufacturer advises supervision by a hospital consultant) and post-herpetic neuralgia. Use for neuropathic pain following cancer surgery is described†. A lower concentration is licensed for osteoarthritic pain (0.025%).

It requires frequent application (t.d.s. – q.d.s.) and benefit is slow to appear. Adverse effects (coughing and localised burning) are common. Hands must be washed after application and contact with eyes/mucosae avoided.

3.1.6 Specialist referral

Where neuropathic pain fails to respond to the above measures, or where there is uncertainty about its diagnosis, investigation or their use, consider **specialist referral**:

- Pain in the context of advanced life limiting illness: referral is usually to the Palliative Care Team
- Pain in the absence of an advanced life limiting illness: referral is usually to the Chronic Pain Team (unless other issues are likely to require the involvement of the Palliative Care Team).

Other off-licence, infrequently used agents for this indication may be initiated after discussion with, or review by, the Palliative Care Team or Pain specialist:

- **Combined use of 2 or more anti-epileptic drugs**
- **Strong opioids** (e.g. morphine, oxycodone, fentanyl or buprenorphine) for neuropathic pain unrelated to cancer.
- **Anti-epileptic drugs (for pain) not specified above** e.g. **clonazepam**, **lamotrigine**, **oxcarbazepine**
- **Ketamine† (oral preparation#**; non formulary
- **Methadone**;.
- **Oral agents related to lidocaine**: **mexiletine#**
- **Cannabinoids† (Sativex†)** Only used under the direction of a palliative medicine or pain specialist
- **Systemic (IV) lidocaine and capsaicin 8% patch** (**Qutenza**). Specific experience and training is required; not for use by non-specialists.
- **Lidocaine 5% Plasters** non formulary.

3.2 **Skeletal muscle spasm**

Main options

Physiotherapy referral
Baclofen 5mg b.d.-t.d.s. PO increased as necessary (usual max 15mg t.d.s.)

Alternatives:

- Benzodiazepines (e.g. d**iazepam** 2-5mg b.d. PO increased as necessary), where other indications are present (anxiety, sleep disturbance) and use is likely to be short-term
- **Acupuncture**
- **Trigger point injections**
- **Quinine is not used** for painful spasm other than nocturnal cramps

Specialist referral

Overview of sections:

3.2.1 Recognition of muscle spasm
3.2.2 Skeletal muscle relaxants
3.2.3 Specialist referral

3.2.1 Recognition of muscle spasm

Skeletal muscle spasm occurs

- in acute musculoskeletal injury
- as a (often undesirable) protective response to bone pain or injury
- secondarily to nervous system dysfunction (**spasticity**).

Clinical features:

- Continuous pain: tender hypertonic muscle may be palpable
- Movement-induced pain (which may resemble paroxysmal neuropathic pain): tender muscle spasm often palpable with specific directions of movement
- Debility (both directly and through pain-avoidance).

3.2.2 Skeletal muscle relaxants

There is no clear evidence that any one agent is superior to any other. All agents cause drowsiness and muscle weakness (of particular concern with pre-existing weakness, especially where there is respiratory insufficiency).

Baclofen is the usual 1st line choice. Start 5mg b.d. - t.d.s. PO and increase as necessary. Usual max 15mg t.d.s. (though if further increases are helpful and tolerated, can use up to 100mg/day). Its contraindications include peptic ulceration. It can worsen seizure control. Muscle hypotonia may be worsened by concurrent tricyclic antidepressants.

Diazepam (2-5mg b.d. PO, increased as necessary) is a useful alternative where other indications are present (anxiety, sleep disturbance) and use should be short-term. Accumulates: Once daily administration may be required due to long half-life and risk of accumulation.
Clearance is reduced in the elderly and by drugs inhibiting the P450 system (e.g. omeprazole).
Quinine is confined to use in nocturnal muscle cramp. There is no evidence supporting its use in spasm due to injury, bone pain or neurological disorder.

3.2.3 Specialist referral

Where painful spasm fails to respond to the above measures, or where there is uncertainty about their use, consider referral to:

- the Rehabilitation Team – particularly where spasm is due to neurological injury or neurodegenerative disease
- the Palliative Care Team – particularly in the context of advanced life-limiting illness with other concurrent palliative care issues.

The above are "accepted uses" and may be initiated by non-specialists for the indications described.

Other agents may be used initiated after discussion with, or review by, a Palliative Medicine, Pain, Rehabilitation or Neurology specialist:

- **Tizanidine** (usually commenced by a neurologist or rehabilitation specialist)
- **Dantrolene** (several of the risk factors for fatal hepatic failure are common in palliative care patients: age>30 yrs, hepatic impairment, concomitant hepatotoxic medications). The product licence specifically advises against use in acute muscle spasm
- The **cannabinoid**, **Sativex** [non formulary]**,** is licensed for refractory spasticity in multiple sclerosis.

Specialist Only drugs

- **Botulinum toxin** can be helpful for localised areas of spasm where the above agents are poorly tolerated.

3.3 Smooth muscle spasm (colic)

Key points

Colic in the context of **constipation**: add/increase **stool softeners**

Intestinal or bladder spasm

- 1st line: **antimuscarinics** (e.g. hyoscine butylbromide [Buscopan] 20mg q.d.s. PO/SC)
- 2nd line: NSAIDs, nitrates†, nifedipine† (see text)

Biliary or renal/ureteric colic

- 1st line: **NSAIDs and/or opioids** (section 2.1)
- 2nd line: antimuscarinics, nitrates†, nifedipine† (see text)

Overview of sections:

3.3.1. Antimuscarinics
3.3.2. Nitrates
3.3.3. Nifedipine
3.3.4. Specialist referral

3.3.1. Antimuscarinics

Option		Example
Minimal psychotropic adverse effects (doesn't penetrate blood brain barrier)		**Hyoscine butylbromide (Buscopan)** • licensed for gastro-intestinal and genito-urinary smooth muscle spasm • Give 20mg q.d.s. PO, IM, IV or SC† (though only ~10% of oral dose absorbed, so may be ineffective via this route) • Alternatively, give 40-120mg/24hrs via SC syringe driver
Additional direct relaxant effect on smooth muscle	Bladder	**Oxybutynin** • Licensed for genito-urinary spasm • Give 2.5-5mg b.d. - t.d.s. PO (max 20mg/24hrs) • If undesirable effects occur, switch to an alternative
	Intestine	**Mebeverine** • Licensed for gastro-intestinal spasm • Give 135mg t.d.s. 20-30 minutes before meals PO
Transdermal patch		**Hyoscine hydrobromide (Scopoderm TTS 1.5mg)** † • 1mg/24 hours changed every 72 hours (1 patch) • Consider where other routes impractical • Monitor for psychotropic effects (e.g. delirium, memory impairment)

3.3.2. Nitrates†

These are 2nd line agents used where antimuscarinics or NSAIDs/opioids (see key points box above) are ineffective. Their use is based primarily on case reports. If in doubt about the presence or absence of smooth muscle spasm, discuss with the Palliative Care Team.

- Give **glyceryl trinitrate** 1-2 sprays (400-800 micrograms) prn SL
- If effective, consider a regular nitrate (e.g. **isosorbide mononitrate MR** 30-60mg o.m. PO)

3.3.3. Nifedipine†

Nifedipine is a 2nd line agent, used where antimuscarinics or NSAIDs/opioids (see key points box above) are ineffective. Its use is based primarily on case reports.

If in doubt about the presence or absence of smooth muscle spasm discuss with the Palliative Care Team.

- Give **nifedipine MR** 10-20mg b.d. PO
- Normal release/short-acting nifedipine (including sublingual nifedipine†) is not recommended for spasmodic pain. It may cause large variations in blood pressure and reflex tachycardia

3.3.4. Specialist referral

The above are "accepted uses" for initiation by non-specialists; consider referral to the Specialist Palliative Care Team when smooth muscle spasm fails to respond to the above measures.

3.4 Malignant Bone Pain

Evaluation

Assess fracture risk. Risk factors prompting discussion with an orthopaedic surgeon include:
Site: Lower limb/peri-trochanteric
Pain severity (especially if exacerbated by movement/weight bearing)
Degree of cortical destruction on plain X ray (especially if lytic)
If vertebral, look for **spinal cord compression/cauda equina syndrome**
Look for **co-existent neuropathic pain** (treated differently: section 3.1)

Analgesic options

Radiotherapy: Usually the treatment of choice (d/w oncologists)
Benefit seen in 1 to 4 weeks; if sedation/confusion occurs, consider opioid dose reduction
Broad-spectrum analgesics (section 2.1) in addition to, or while awaiting radiotherapy
Drugs: NSAIDs (+/- paracetamol) are usually extremely helpful
Opioids. Effectiveness varies: assess opioid responsiveness carefully when titrating
Dexamethasone 4-8mg/24hrs**,** particularly short term use whilst awaiting radiotherapy
Orthopaedic surgery
Especially if bony instability (e.g. movement-induced pain) +/or high fracture risk
Bisphosphonate (d/w oncologists, haematologists or palliative care physicians)
They have an established place in the prevention of pain and other skeletal events from bone metastases. They may be initiated (by specialists only) if other methods are ineffective for the treatment of established bone pain.

Overview of sections:

3.4.1. Assessing fracture risk
3.4.2. Specialist referral

3.4.1. Assessing fracture risk (i.e. is prophylactic fixation required prior to radiotherapy?)

>50% cortical destruction on plain X-rays makes pathological fracture almost inevitable, but the risk can still be considerable with <50% destruction. Mirels' scoring system is a more reliable indicator.

Mirels' score	**Score**		
	1	**2**	**3**
Site	Upper limb	Lower limb	Peri-trochanteric
Pain	Mild	Moderate	↑ by weight-bearing
Lesion	Sclerotic	Mixed	Lytic
Cortical destruction (plain films, any view)	<1/3	1/3 to 2/3	>2/3
Maximum possible score is 12 Score ≥8: discuss prophylactic fixation with an orthopaedic surgeon			

3.4.2. Specialist referral

The above are "accepted uses" and may be initiated by non-specialists for the indications described.
Where bone pain fails to respond to the above measures, or where there is uncertainty about their use, consider referral to the Specialist Palliative Care Team.

Specialist Drugs:

- **Intravenous bisphosphonate**. Helpful for malignant bone pain in around half of patients. Benefit usually occurs within 14 days and lasts around 8 weeks
- **Denosumab** May be prescribed by hospital specialists in line with NICE guidance (NICE TA 265) for the prevention of skeletal – related events in adults with solid tumours

3.5 Incident pain and other episodic pains

Episodic (intermittent) pain is a *transient* increase in pain level e.g.:

Incident pain: predictable response to movement, coughing, defecation etc.
Procedural pain: result of a procedure such as a dressing change
Spontaneous pain: i.e. unpredictable

Approach differs from conventional use of analgesia (e.g. Morphine Sulphate oral solution):
The action of conventional prn analgesia (e.g. Morphine Sulphate oral solution) is sometimes too slow and too prolonged (i.e. can result in persistent drowsiness after the pain episode has passed)
It is difficult to control episodic pain with regular opioids (e.g. Zomorph) – doses sufficient to control the 'peak' of the pain episode often cause drowsiness/toxicity in the 'trough' in-between

Treatment options:
Address causes (e.g. bony instability → orthopaedics, vertebroplasty, radiotherapy, splints)
Optimise background analgesia (regular opioids, NSAIDs, paracetamol)
Target specific pains (e.g. measures for neuropathic pain, skeletal muscle spasm)
Referral as Specialist options include:
- *Interventional anaesthesia*
- *Topical analgesia* for painful dressing changes (topical morphine or local anaesthetics)
- *Episodic analgesia* (e.g. specialist initiated rapid onset opioids

Overview of sections:

3.5.1. Background analgesia – differences from use in other settings
3.5.2. Identifying and treating specific pains
3.5.3. Specialist referral
Topical opioids† and local anaesthetics†
Rapid onset opioids
- buccal and intranasal fentanyl
- Preparations include: Abstral, Effentora, Actiq, Instanyl (non formulary)
- **NB these products are not interchangeable**

3.5.1. Background analgesia – differences from use in other settings

Around half of patients with episodic pain will achieve satisfactory pain control through conventional use of opioids and adjuvants. Some patients find **pre-emptive Morphine Sulfate oral solution** ~30 minutes before painful movement/procedure helpful without unacceptable drowsiness afterwards.

However:
- Be alert to drowsiness or cognitive impairment developing in-between painful episodes, indicating possible opioid toxicity. Dose reduce and discuss with a specialist
- Pre-emptive **Morphine Sulfate oral solution** doses attempt to *transiently* increase opioid levels to reflect the transient increase in pain. Such pre-emptive doses are not usually 'added in' to the regular Zomorph dose.

3.5.2 Identify and treat specific pains

- *Neuropathic pain* (can cause incident and/or spontaneous pain). (section 3.1)
- *Skeletal muscle spasm* (section 3.2)
- *Bony instability* (see also section 3.4) Look for pathological fracture and nerve compression (e.g. spinal cord or cauda equina compression). Options include orthopaedic advice or vertebroplasty.
- *Painful dressing changes* and other procedures. If pre-emptive Morphine Sulphate oral solution (above) is ineffective, discuss with the Palliative Care Team.

3.5.3. Specialist referral

The above are "accepted uses" and may be initiated by non-specialists for the indications described
Where episodic pain fails to respond to the above measures, or where there is uncertainty about their use, consider referral to the Specialist Palliative Care Team.

The following should only be used after seeking Specialist advice:

i. **Morphine (10mg/1ml) for injection applied topically in a carrier suitable for the wound type eg: Intrasite, Purilon, Granugel, Hydrogel, Aquagel†** for painful ulcers and dressing changes.
Systemic absorption is negligible in all but large ulcers.
The effect on healing and long-term safety (esp. incidence of hypersensitivity) is uncertain.
Prescribe as morphine 0.1% (may be increased to 0.3%) in Intrasite (or alternative – as per formulary)
i.e. for 0.1%: mix 8mg morphine in 8g Intrasite (or 15mg in 15g) immediately before applying to wound.

This would be made up immediately prior to application by nursing staff. In a community setting components prescribed on FP10 individually. Advice from palliative care team available.

ii. **Morphine mouthwash**

iii. **Topical local anaesthetic agents (e.g. EMLA†)**. Effective for debridement pain in 5 of 6 short-term RCTs. EMLA (5%) was applied beneath an occlusive dressing (e.g. cling film) for 30-45 minutes prior to debridement. The incidence of hypersensitivity is unclear. The effect on wound healing and continuous ulcer pain was not addressed. Ulcers larger than 50cm^2 were excluded (of relevance to toxicity from systemic absorption)

iv. **Sublingual /Intranasal fentanyl [Instanyl, Abstral, Effentora]**. Although absorbed quickly (T_{max} ~15mins.) the duration of action can be up to 4hrs, hence oral morphine sulfate solution is still the drug of first choice.

v. **Related preparations offering limited or no advantage in episodic pain:**
Fentanyl lozenges (Actiq). Rate of onset only marginally faster than oral morphine. Absorption is often hindered by dry mouth.

DIFFICULT CIRCUMSTANCES

4.1 Driving and analgesia

Key points

Doctors have a duty of care to inform patients of the risks of treatment, including that of impaired ability to drive, but the impact of ceasing to drive can be considerable. For information on the impact of the diagnosis itself on fitness to drive (not covered here) www.gov.uk/government/publications/assessing-fitness-to-drive-a-guide-for-medical-professionals

Driving impairment is maximal when first commencing central-acting analgesics and when doses are titrated.
Once doses are stable and patients no longer feel drowsy, they can usually consider re-starting driving (benzodiazepines are a possible exception, where some degree of impairment may persist indefinitely)

This advice can be supported with the patient information leaflet below.
Patients should be advised to carry a copy of their prescription for opioids when driving as per leaflet.

4.1.1. Centrally acting analgesics and ability to drive

Opioids, antidepressants and antiepileptic drugs for pain control

Once patients are on stable doses, and no longer feel drowsy (often a period of ~5 days or a few weeks), their road accident risk may be no different to that of people not receiving such medication. P.r.n. 'rescue' doses of opioids may continue to cause transient impairment.

Benzodiazepines:

- Risk is associated with longer half-life, higher dose and concurrent alcohol.
- It only partially decreases with time
- The risk from night-time short-acting hypnotic benzodiazepines is unclear. Zopiclone may not be a safer alternative

Underlying illness

See https://www.gov.uk/health-conditions-and-driving for further information for patients on the effect of underlying illness on fitness to drive (and requirement to notify the DVLA).
https://www.gov.uk/government/publications/drug-driving-and-medicine-advice-for-healthcare-professionals

4.1.2. Painkillers and driving: Patient Information leaflet – SEE NEXT PAGE

Patient Information Leaflet

Painkillers and Driving information for Patients

The medicines you are taking do not automatically stop you driving in the United Kingdom[1]. However, some painkillers can affect the speed of your reactions or general alertness. Both the label and information leaflet will warn you that drowsiness can occur[2]. From March 2015 is an offence to drive with certain controlled drugs in your bloodstream; this includes strong painkillers such as morphine and oxycodone. There is a statutory "medical defence" for people taking the drugs as prescribed by a healthcare professional, **if their driving was not impaired.** If you have followed the advice below and feel safe to do so, it is recommended that you carry a copy of your prescription to provide documentary evidence at the time you are requested to do so by the police.

If receiving such medication, or other sedative drugs, it is important that you take the following precautions:

Do not drive:

unless you feel 100% safe to do so
if you feel sleepy
after taking other sedative drugs, whether or not recommended by your doctor, or after drinking alcohol
after taking extra 'rescue' doses of a sedative painkiller, e.g. for at least 3 hours after an extra dose of morphine
after starting or increasing the dose of a sedative painkiller. Wait until any sleepiness wears off, generally about 5 days, but sometimes longer, before driving again.

Restarting driving

You may try driving when you feel 100% safe to do so and you no longer feel sleepy. Begin by making a short trip:

on roads that are quiet and familiar
at a quiet time of day when the light is good
with a companion who may take over driving if required.

If you and your companion are happy with your attentiveness, reactions and general ability, then you may start to drive. Do not exhaust yourself by driving long distances. If you are in any doubt, discuss with your doctor or other health professional.
It remains an offence of driving whilst impaired through drugs (whether due to non-medical use of drugs or due to legitimate use of medicines) in section 4 of the Road Traffic Act 1988 and you can still be found guilty of a driving offence

Who to inform

Your doctor. Please ensure that your doctor is aware if you are planning to drive. He/she can warn you about medication that might affect the speed of your reactions or general alertness
Your insurance company. Each company is different. It is best to discuss your circumstances with your insurance company to be sure that you are covered, and possibly to send the company a copy of this leaflet.

Although you do not necessarily need to inform the DVLA that you are taking regular painkillers, in practice insurance companies generally advise this. However, the DVLA do need to be informed about certain illnesses. *If in doubt, discuss with your doctor or the DVLA medical advisory helpline* (0870 600 0301; with your driving licence number ready).

4.2 Pain with concurrent drug misuse

Based on consensus guidance from the British Pain Society, the Royal College of Psychiatrists, the Royal College of General Practitioners and the Advisory Council on the Misuse of Drugs [BPS 2007] (under review at time of writing See also :https://fpm.ac.uk/opioids-aware-opioids-addiction/patients-substance-misuse-general-considerations

Key points

The principles of pain management, including the use of opioids, remain the same
However, it is difficult to balance the avoidance of mistrust on all sides with the avoidance of morbidity from misuse and prescription diversion. Clinicians not experienced in managing pain in such patients are advised to contact the Pain or Palliative Care Team
Inadequate pain management risks self-discharge, further illicit self-medication and great distress (which can in itself precipitate relapse of addiction disorders.
(http://www.fpm.ac.uk/faculty-of-pain-medicine/opioids-aware)

Prescribing opioids for affected patients
If the underlying cause would normally require opioid analgesia, it is just as likely to in a patient with a drug misuse history
Prior opioid misuse causes tolerance. Such patients may require higher than normal doses.
Start at the higher end of the usual starting dose ranges
Maintenance treatments
Maintenance methadone or buprenorphine should not be titrated to manage pain.
The same dose is continued (though will not provide an analgesic benefit).
Analgesics, including opioids if indicated, are added alongside
Maintenance opioid antagonists (e.g. naltrexone) will render opioid analgesia ineffective.
If paracetamol and NSAIDs are insufficient, seek advice from the Pain or Palliative Care Teams. Also consider nefopam and specific measures for the type of pain (see text).
For patients outside hospital, take precautions to avoid prescription-diversion: agree a single prescriber [usually the GP]; do not replace lost prescriptions
For patients being admitted to an inpatient unit, ensure maintenance methadone/buprenorphine dose is verified with the prescriber. If in doubt seek advice from a clinical pharmacist.

Overview of sections

4.2.1. When should opioids be used?
4.2.2. Are there any differences from using opioids in other patients?
4.2.3. Patients using maintenance methadone, buprenorphine, or opioid antagonists
4.2.4. Responding to demands for opioid dose increases

4.2.1. When should opioids be used?

The general principles of pain management, including the use of non-opioids (paracetamol, NSAIDs) and adjuvants targeted at specific pain types (e.g. antidepressants and anticonvulsants for neuropathic pain) are the same as for other patients.

If the pain's underlying cause would normally require opioid analgesia in other patients, it is just as likely to in a patient with a concurrent or prior drug misuse history.

4.2.2. Are there any differences from using opioids in other patients?

- The general principles of use are the same as with other patients (described in section 2.1) and should include empathic communication with the patient and reassurance that pain will be managed optimally.

. However:

i. **Higher doses are often required**: Start at the higher end of the usual starting dose ranges. When titrating, be aware that higher doses may well be needed. Requests for more analgesia can be difficult to distinguish from addiction behaviour (see 4.2.4 below)
   - Opioid-users exhibit tolerance to the effects of opioids
   - Pain threshold is often lower (both a pharmacological effect of opioid misuse and presence of other exacerbants of severity)

ii. **Sustained release preparations are preferred** to immediate release where possible because the risk of misuse is thought to be lower. However, immediate release preparations can be difficult to avoid, especially where rapid titration for acute pain is required

iii. **Discuss concerns and limits of acceptable behaviour openly** with the patient at the outset. Consider giving them a written summary. In the outpatient setting, discuss prescriptions from one prescriber only, not replacing lost prescriptions etc. The GP is usually best placed to prescribe. If out-of-hours supply (e.g. by A+E or a deputising GP) cannot be avoided, ensure the GP is informed

iv. **Adherence**: Some patients will have frequently self-medicated with over-the-counter and illicit medication previously. Enquire about what else they are using, including over-the-counter analgesics.

Clinicians not experienced in managing pain in such patients are advised to contact the Pain or Palliative Care Team

4.2.3. Patients using maintenance methadone, buprenorphine, or opioid antagonists

Maintenance methadone or buprenorphine should not be titrated to manage pain. They are continued at the same dose, though will not provide an analgesic benefit. If opioids are indicated for pain, they are added alongside. However, higher than usual doses will usually be required, particularly with buprenorphine (an opioid partial agonist). If in doubt, discuss with the Palliative Care or Pain Team.

Maintenance opioid antagonists (e.g. naltrexone) will render opioid analgesia ineffective.
If paracetamol and NSAIDs are insufficient, seek advice from the Pain or Palliative Care Teams.
In the interim, consider:
Non-opioid adjuvants targeted against specific pain types (e.g. **antispasmodics** for colicky pain, **antidepressants/antiepileptic** drugs for neuropathic pain: described in section 3).

4.2.4. Responding to demands for opioid dose increases

It can be difficult to decide whether requests for more opioids are due to pain or addiction. Mistrust on all sides can lead to such demands becoming confrontational. Consider:

i. Is the increase in pain understandable in terms of disease progression or co-morbidities?

ii. Is it opioid responsive? There should be a fall in prn use when an effective regular dose is found just as with other patients (although higher opioid doses will be required on average)

iii. Are there features of misuse or prescription diversion?
   - Early prescription seeking, prescriptions forged or frequently reported lost
   - Repeated visits to other clinicians for prescriptions
   - Stealing or borrowing drugs from others
   - Intoxication or concurrent use of other controlled drugs
   - Frequent missed appointments
   - Resistance to changes in analgesia despite adverse effects

iv. Seeking advice from the Pain, Specialist Palliative Care or Addiction Teams

4.3 Pain Assessment in the Cognitively Impaired Patient

Based on a report from the British Geriatrics Society, Royal College of Physicians and British Pain Society [BGS 2007]

Key points

Cognitive impairment can alter pain behaviour, with patients being slower to express pain, less able to localise it or expressing it differently (e.g. aggression towards themselves or others). Always involve a relative or carer who may notice a change in behaviour and help clinicians assess pain response. No behaviour is unique to pain.

If numerical ('0-10') scales aren't understood, switch to a **verbal scales** ('mild, moderate or severe')

If cognitive impairment is too severe to use a verbal scale, switch to an **observational scale** to assess pain severity and the response to trials of analgesia.
The **Abbey scale** is a straightforward observational scale, with good agreement between different observers.
In Frimley Heath the recommended pain assessment tool for patients with cognitive impairment is the **Bolton Pain Scale**. This can be found on the FHFT intranet.

BOLTON PAIN ASSESSMENT TOOL

(For patients with communication problems)

NHS
Frimley Health
NHS Foundation Trust

Surname.....

First name..... Male / Female

Date of birth			Hospital No:	
D	M	Y	NHS No:	

Use for initial assessment and then as a prompt for ongoing assessment

	NO PAIN 0	MILD 1	MODERATE 2	SEVERE 3	SCORE
VOCALISATION	None	Occasional moan or groan	Low level speech with a negative or disapproving quality	Repeatedly crying out, loud moaning or crying	
FACIAL EXPRESSION		Looking tense	Sad, Frowning	Grimacing and looks frightened	
CHANGE IN BODY LANGUAGE	None	Tense, fidgeting	Guarding part of the body	Withdrawn, rigid, fists clenched. Knees pulled up	
BEHAVIOURAL CHANGE	None	Increased confusion	Refusing to eat, alterations in usual pattern	Pulling or pushing away, striking out	
PHYSIOLOGICAL CHANGE	Normal	Occasional laboured breath, increased heart rate	Hyperventilation, increased heart rate and BP	Change in pulse BP, respiratory rate and perspiring, flushed or pallor	
PHYSICAL CHANGES	None	Skin tears	Pressure sores, arthritis	Post surgery, trauma	
				TOTAL SCORE:	

Please transpose pain score onto NEWs observation chart.
(Equivalent numbers to FHFT standard verbal descriptor scale are given in brackets)

0-2 = NO PAIN (0)	3-8 = MILD PAIN (1)	9-13= MODERATE PAIN (2)	14+ = SEVERE PAIN (3)

Date:	Time:	Designation of person completing:	Signature:
Comments by family or usual care givers			
Pain on movement / physiotherapy			

V1: Inpatient Pain Team, May 2017- Modified and reproduced with permission from copyright owner J. Gregory, Royal Bolton Hospital NHS Foundation Trust. - Filing location: Nursing Record (21).

Pain Assessment Tools

Scales based on observation have good agreement with the subjective impressions of experienced clinicians. Examples include Abbey, Bolton, PAINAD, , Doloplus-2 DISDAT, The latter is a scale assess for the presence of distress which can be emotional, physical or psychological.

The Abbey pain scale is a six item observational scale developed for use with patients in residential care who are unable to respond verbally due to advanced dementia [Abbey 2004]. Subsequent work has found good inter-rater reliability allowing consistency between different peoples' observations (e.g. a change of shift)

The six items on the score sheet (below) are scored as absent (0), mild (1), moderate (2) or severe (3).
The change in score may be the most useful measure (e.g. as an outcome for trials of analgesia)

Abbey [2004] suggested that total score indicated:

- No pain (≤2)
- Mild pain (3-7)
- Moderate pain (8-13)
- Severe pain (≥14)

The following items are scored as: • Absent (**0**) • Mild (**1**) • Moderate (**2**) • Severe (**3**)	The total implies: • No pain (≤ 2) • Mild pain (3-7) • Moderate pain (8-13) • Severe pain (≥ 14)													
Date and time														
Pre- or post- prn analgesia														
Vocalisation (e.g. whimpering, groaning, crying)														
Facial expression (e.g. looking tense, frowning, grimacing, looking frightened)														
Change in body language (e.g. fidgeting, rocking, guarding part of body, withdrawn)														
Behavioural change (e.g. increased confusion, refusing to eat, alteration in usual patterns)														
Physiological change (e.g. perspiring, flushing or pallor, pulse or BP outside normal limits)														
Physical changes (e.g. skin tears, pressure areas, arthritis, bone secondaries)														
Total														

4.4 Checklist for analgesic-resistant pain

This checklist is intended to help experienced clinicians faced with challenging pain problems. It summarises potential approaches to many of the common reasons for difficult pain. *It is not intended to dissuade people from seeking advice early*, particularly when facing challenges outside of their usual practice/experience.

Is the underlying cause remediable?

- E.g. movement-related pain from an unstable bone metastasis: Orthopaedic surgery and radiotherapy may be more effective than drug-approaches

Could the pain be targeted by more specific approaches?

- Non-opioid approaches (e.g. TENS, Entonox, nerve blocks and other regional approaches)
- The following pains often respond incompletely to opioids. Specific approaches often help
    - Neuropathic pain (see section 3.1)
    - Skeletal muscle spasm (see section 3.2
    - Smooth muscle spasm (colic) (see section 3.3)
    - Malignant bone pain (see section 3.4)
    - Episodic pain (e.g. movement-induced or procedural) (see section 3.5)

Is there co-existent depression or other psychosocial distress?

Depression, anxiety and other psychosocial distress commonly co-exist with pain, worsening pain severity and reducing the effectiveness of analgesia. Addressing these helps to break this 'vicious cycle' Consider screening patient using validated scales such as PHQ9 and GAD7 (https://serenemindsllc.com/wp-content/uploads/2022/04/PHQ-9-and-GAD-7-Form.pdf)

Fears, losses and spiritual distress: These all affect how pain is experienced, contributing to the distressing and aversive nature of pain. Exploring fears and helping patients adjust to changing circumstances is an important component of pain management

How is the pain affecting daily functioning?

- The relationship between pain severity and disability is not straightforward. It is influenced by multiple factors including the person's beliefs about the pain (e.g. its threat-value) and how they respond to it (e.g. pain avoidance by minimising movement)
- Asking about the pain's impact on daily life rather than just pain intensity therefore becomes even more important where pain is incompletely responsive to analgesia
- Information giving and exploring patients own beliefs about their pain can have important effects on both pain intensity and pain-related disability
- Setting realistic goals and targeting daily functioning directly to optimise independence (e.g. with help from physio- and occupational therapists) can impact greatly on quality of life
- Encourage self-management of pain where possible (e.g. challenging maladaptive pain beliefs, optimising independence in daily functioning, adopting analgesic modalities with a greater degree of self-control such as patient controlled analgesia systems and TENS)

Minimising harm: Can the medication be rationalised?

- Simultaneous use of different analgesics sometimes achieves the best balance between benefits and adverse effects
- However, it is important to reassess the benefits from multiple analgesics and discuss trial dose reductions/discontinuations where benefit is in doubt
- The risk of such ineffective combinations building up can be minimised by good analgesic prescribing practices:
    i. Adding/changing one medication at a time
    ii. Optimising existing medications before adding new ones
    iii. Discussing the desired outcome (e.g. reduced pain severity, improved mobility),

iv. Discontinuing the medication if ineffective
v. Simultaneous use of the non-drug approaches outlined above
vi. Discussing trial dose reductions of analgesics taken for a period of time
vii. Ensuring changes are communicated effectively to other clinicians (particularly the general practitioner)

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RESPIRATORY SECTION

1.1 Breathlessness

BREATHLESSNESS

Key points

Treating the underlying cause offers the best relief

In patients with good performance status (e.g. walking, but with exertional breathlessness)

Optimise underlying disease control and concurrent contributors (e.g. anaemia)
Rehabilitation (attention to nutrition, encouraging exercise and coping strategies, use of formal programs such as the pulmonary rehabilitation program for COPD)
Treat co-existent depression, anxiety or panic disorders (e.g. with **SSRIs** or **benzodiazepines**)

In less fit patients (e.g. breathless at rest or on minimal exertion):

Opioids are helpful
Co-existent depression, anxiety and panic requires separate treatment

Main options

Opioids: effective for breathlessness at rest or on minimal exertion. They do not improve exercise tolerance in fitter patients with exertional breathlessness

Anxiolytics: effective for co-existent anxiety and panic

Benzodiazepines where rapid onset needed (e.g. short prognosis or for prn treatment of panicky breathless attacks)

SSRIs where prognosis sufficient (delayed onset, but avoids the cognitive and falls risks of benzodiazepines)

Oxygen: helpful for hypoxic patients (not appropriate for non-hypoxic patients who usually obtain the same relief from increased airflow; advice to use electric fans/open windows in conjunction with breathing exercises. Refer BTS guidelines 2017.

Physiotherapy referral: particularly facilitating rehabilitation in good performance patients or for breathlessness management techniques.

Psycho-spiritual support: consider counselling or clinical psychology referral for patients with underlying severe anxiety or depression

1.1.1. Treatable Causes

Comprehensive assessment and examination alongside investigations, if appropriate (e.g. full blood count, chest X ray), may reveal treatable underlying contributors:

Consider **multiple pulmonary emboli** in patients with breathlessness disproportionate or unexplained by underlying disease, chest examination and X ray; consider discussion with specialist and if out of hospital: consider hospital investigation, in hospital: request a CT Pulmonary Angiogram.

Consider Covid 19 infection in presence of rapid deterioration in respiratory function or silent hypoxia

Treatable Causes of Breathlessness

In any patient	In patients with malignancy
Anaemia	Pleural effusion – consider drainage +/- pleurodesis if well enough – d/w oncology/respiratory colleagues
Bronchoconstriction	Consider s/c furosemide if IV access a problem
Hypoxia	Superior Vena Cava Obstruction (section 4.3)
Heart Failure	Lymphangitis carcinomatosa (d/w oncology)
Pulmonary Embolism	Bronchial obstruction (section 4.4)
Sepsis	Pericardial effusion (d/w cardiology)
Anxiety/depression	Ascites

1.1.2. Non-pharmacological / General measures

Breathlessness may respond to careful explanation and simple advice aimed at improving self-management

Breathing exercises (nurse specialist or physiotherapy referral)

Increased airflow (opening windows, electric fans, hand held fans)

Encourage exercise and good nutrition if appropriate: In fitter patients, where muscular deconditioning is a contributor, advise gentle exercise until mildly tired and breathless with a view to gradually increasing exercise capacity over time

Optimising independence by providing appropriate aids/assistance at home (e.g. by involving an **occupational therapist**)

Counselling and psycho-spiritual support for patients and families, cognitive behavioural therapy and self-management techniques

1.1.3. Drug therapies

i. Opioids for breathlessness

Opioids are effective for breathlessness at rest in both cancer and advanced non-cancer conditions (COPD, pulmonary fibrosis and heart failure). They can generally be used without detrimental effects on carbon dioxide levels or length of life. Additional caution is required in patients already retaining carbon dioxide: consider seeking advice from a respiratory or palliative care specialist.

In all cases opioids should be titrated to the lowest effective dose. Doses required are generally significantly lower than for pain and titration should be done more slowly.

- The evidence for opioids for exertional breathlessness or improvement in exercise capacity is very limited at present so they cannot be recommended for this use.

For the palliation of breathlessness at rest:

- The best evidence supports the use of low dose modified release morphine eg 5mg BD
- The dose can be titrated if necessary every 7 days up to usual maximum 15mg BD
- If symptoms are intermittent consider use of PRN opioids- eg morphine sulfate oral solution 2mg (whole number doses are easier for patients to measure) PRN 4hrly

- If already on opioids, an increase of 25% in the PRN dose may provide some benefit

If unable to manage oral opioids (e.g. breathlessness at End of Life):

- If opioid naïve: give Morphine Sulfate 5-10mg over 24 hours via SC syringe pump plus 1.25mg - 2.5mg prn 2 SC
- If already on opioids, and not toxic, increase dose of opioid by 25% and review response.
- Add Midazolam 5-10mg/24hours to the syringe pump if anxious/panicky, or if not responding to opioids alone.
- Doses may need titrating upwards depending on response. Eg End of Life Management of Covid 19 may require significantly higher doses of opioids and benzodiazepines to manage distressing breathlessness. (seek specialist palliative care advice)

- Consider concomitant use of antiemetic, particularly in opioid naïve patients started on SC preparations.

Medication for secondary anxiety and panic

Benzodiazepines are used to treat anxiety and panic, and there is no evidence for their beneficial effect in the relief or prevention of dyspnoea. Therefore, they should not be the first line treatment, particularly in the patients with respiratory failure.

Where prognosis likely to be weeks: benzodiazepines (dependence risk is not relevant and prognosis is too short for benefit from SSRI):

- **Lorazepam** 0.5mg b.d. PO and/or prn SL. Titrate as required
- **Diazepam** 2-5mg ON may be more appropriate for chronic anxiety

- Where the oral route is unavailable, consider **midazolam** 5-10mg over 24 hours via CSCI/ SC syringe pump plus 2.5-5mg prn SC 2-4 hourly. In patients with anxiety/panic and breathlessness, combine midazolam and morphine sulfate in a CSCI/ syringe pump.

Where prognosis likely to be months: **SSRI** (palliative care patients are vulnerable to the cognitive and sedative problems of longer term benzodiazepine use)

- SSRI eg. **Citalopram** 10mg o.m. PO for 7 days then increase to 20mg o.m, or Sertraline 50mg om.
- Short term regular lorazepam may be helpful while awaiting onset of effects of SSRI
- **Lorazepam†** 0.5mg prn SL may be a useful adjunct for panicky, breathless 'attacks'

ii. **Oxygen therapy in the palliative management of breathlessness**

Like any treatment, oxygen can have adverse effects (worsening dry mouth/nostrils, reinforced 'sick role', barrier to close contact with loved ones, hindering mobility) and may create unnecessary psychological dependence. It should therefore be reserved for patients most likely to benefit (especially hypoxic patients) https://www.brit-thoracic.org.uk/quality-improvement/guidelines/emergency-oxygen/

In hypoxic patients (oxygen saturation <92% [or presence of cyanosis if oximetry unavailable]):

- Oxygen therapy is often helpful and should usually be tried
- Start 24% or 2l/min and titrate until oxygen saturation >92% (unless target oxygen sats 88-92% eg in some patients with COPD and chronic hypoxaemia/hypercapnia) before deciding it's unhelpful
- Safety aspects need to be discussed with patient and family (oxygen is not supplied to patients who are current smokers).
- Blood gas estimation is not usually required for optimising symptom control unless severe COPD is present (needed to detect CO_2 accumulation secondary to hypoxic drive)- involve respiratory team

In non-hypoxic patients (oxygen saturation >92%):
Oxygen is generally not used in non-hypoxic patients.

For breathlessness at rest use:

- Simple measures (hand-held fan, opening windows).
- Non-pharmacological measures such as physiotherapy referral for breathlessness management
- Opioids (combine with anxiolytics if concomitant anxiety/panic)

Ambulatory oxygen (i.e. portable oxygen for use during exercise and activities of daily living) is helpful for selected patients: it is accessed by referral to the respiratory team.
Consider referring patients who desaturate during exercise (i.e. oxygen saturation fall of ≥4% to a value <90%). However, it is unhelpful for patients who do not desaturate or are confined to the house (conventional home oxygen equipment may be more appropriate)

Obtaining oxygen
All health care professionals can request a static oxygen concentrator or static cylinder by c0mpleting Form (HOOF) to the oxygen supplier, Dolby Vivisol, : Email to hoof.dv@nhs.net
For further advice:

- *East Berks;* the Home Oxygen Service is based at King Edward VII Hospital on 01753 636459 fhft.air.team@nhs.net. referrals of HOS via Air team should be made on ICE.
-
- Frimley ICS (South): Community respiratory team contactable via fhft.respiratorycare@nhs.net 03000030050

iii. **Nebulisers in the palliative management of breathlessness**

- Main place is for bronchodilators (though inhalers with good technique or spacers are more portable and less expensive)

- Nebulised Salbutamol 2.5mg up to QDS can be used where dyspnoea is associated with wheeze (exclude partial airway obstruction caused by tumour and amenable to stenting, palliative radiotherapy or steroids)

- Nebulised sodium chloride 0.9% 5ml q.d.s. is sometimes helpful for breathlessness or to aid expectoration: limited evidence, but minimal risk other than financial cost and medicalisation

- A number of other nebulised drugs have been tried without success (opioids, lidocaine, furosemide) and have no place in the routine palliative management of breathlessness.

1.1.4 Refractory symptoms/ Specialist referral

When symptoms are intractable and fail to respond to the above measures and are associated with poor quality of life, consider referral to specialist palliative care team as a multidisciplinary approach is often needed.

1.2 Cough and Respiratory secretions

COUGH

Key points

Treat the underlying cause wherever possible

Tumour-related: consider corticosteroids or discussion with an oncologist
Other common causes: infection, oesophageal reflux, aspiration, post-nasal drip

Main options

Dry cough

FIRST line: **simple linctus** 5-10ml q.d.s.
SECOND line: **codeine linctus** 15-30mg (5-10ml) q.d.s. PO (go straight to THIRD line if already receiving opioids.)
THIRD line: **morphine** 2mg -5mg 4 hourly PO if opioid naïve or 5-10mg 4 hourly PO if switching from codeine.

Productive cough

Aid expectoration with 'huffing' and **sodium chloride 0.9% nebulisers** 10ml q.d.s.
Consider a **physiotherapy** referral to teach 'huffing' and other techniques.
For viscous sputum refractory to these measures, consider **carbocisteine**
If dying and too weak to expectorate, treat as retained respiratory secretions (aim to dry secretions with hyoscine butylbromide: see EOLC section)

1.2.1. Treatable Causes:

Cancer related

Discuss with an oncologist options for radiotherapy or other anti-cancer treatments
The commonest cancer cause is large airway irritation from mediastinal or hilar deposits.

Consider a trial of **dexamethasone** 8mg o.m. PO for 5 days (or SC (6.6mg) if oral route unavailable).
If effective, reduce by 2mg weekly down to minimum effective dose.
If ineffective, give for 5 days then stop, unless this is a repeated course.

Other cancer causes include:

- Lymphangitis carcinomatosa (discuss with oncology team)
- Pleural effusion (if well enough to consider drainage +/- pleurodesis, discuss with Respiratory Team)
- Haemoptysis (section 4.6)

Other

- Respiratory tract infection
- Bronchoconstriction: e.g. asthma, COPD
- Pulmonary oedema
- Recurrent aspiration
- Gastro-oesophageal reflux: may be worse in recumbent position/at night. Consider proton pump inhibitor (higher doses are generally used e.g. **omeprazole** 40mg o.d. PO).
  Benefit may take several weeks. If no improvement, consider adding a prokinetic (e.g. **metoclopramide** 10mg t.d.s. PO) or referral to gastroenterology.
  If improvement, consider reducing to minimum effective dose after 4-8 weeks. See also NICE CG 184 guidance.
- Post-nasal drip: consider trial of a nasal corticosteroid spray, e.g. **mometasone** 100 micrograms (2 sprays) into each nostril o.d.

1.2.2 Non Drug/ General Measures

- Humidify room air or oxygen if in use (for dry cough)
- Involvement from a specialist physiotherapist is often helpful as 'huffing' and other techniques can be taught to improve symptom control.

1.2.3 Drug therapies

Dry cough

First line: simple linctus 5-10ml q.d.s.
Second line: codeine linctus 15-30mg q.d.s. (5-10ml) PO or go to third line if already on opioids
Third line: morphine 2.5-5mg 4 hourly PO if opioid naïve or 5-10mg 4 hourly PO if switching from codeine.

Wet cough

Aid expectoration with 'huffing' and **sodium chloride 0.9% nebulisers** 10ml q.d.s.
Consider a **physiotherapy** referral to teach 'huffing' and other techniques.

Carbocisteine can be used to reduce sputum viscosity.

Contra-indications: active peptic ulceration (mucolytics can disrupt gastric mucosal barrier)

Dose: 750mg t.d.s PO (subsequently reducing to b.d.). Available as capsules or liquid.

End of life care: If dying and too weak to expectorate sputum, appropriate positioning and explanation/ reassurance to relatives may be key. Treat as retained respiratory secretions (aim to dry secretions with antimuscarinic such as hyoscine butylbromide.) Treat associated distress/ anxiety with sc midazolam if necessary.

1.2.4 Refractory cough and secretions and Specialist referral

Where cough or copious respiratory secretions (bronchorrhoea) fail to respond to the above measures, or where there is uncertainty about their use, consider referral to the Specialist Palliative Care Team.

Other off-licence, infrequently used agents can be initiated after discussion with, or review by the Specialist Palliative Care Team.

Cromoglicate sodium† inhaled (cough)
Gabapentin† (cough)
Nebulised lidocaine† (cough)
Nebulised furosemide† (bronchorrhoea)
Octreotide† (bronchorrhoea)

† = unlicensed route/dose
# = non formulary use.

1.3 Hiccup

HICCUP

Key points

Gastric distension +/- Gastro-oesophageal reflux are the commonest treatable causes.
Other treatable causes:
Metabolic disturbance (e.g. uraemia, uncontrolled diabetes, hypokalaemia, hyponatraemia)
Drugs

Main options

FIRST line options for persistent hiccup either:
Metoclopramide† 10mg t.d.s. PO (**gastric distension is the commonest treatable cause** in palliative care patients (**domperidone 10mg t.d.s. PO** is an alternative if metoclopramide is contraindicated or if extrapyramidal side effect is a risk)
PPI (Omeprazole 20mg or Lansoprazole 30mg once daily) or antacid if required

SECOND line:
Baclofen† 5mg b.d. PO, increasing as required to a maximum of 10mg t.d.s. (effective in case reports and a small clinical trial

1.3.1 Causes of Hiccups

Gastrointestinal Causes:

- **Gastric distension** is the commonest treatable cause:
  Clinical features: hiccup, bloating, early satiety, nausea, vomiting
  Predispositions: constipation, antimuscarinic or opioid drugs, Ca pancreas, nerve dysfunction (diabetes, spinal cord compression, retroperitoneal disease)
  - **Gastro-oesophageal reflux disease (GORD)**

Central Causes:

- Cerebral tumour, stroke, Multiple sclerosis, Parkinson's disease

Other causes:

Metabolic disturbance (e.g. uraemia, uncontrolled diabetes, hypokalaemia, hyponatraemia, hypocalcaemia)

Drug-induced (benzodiazepines and corticosteroids are most commonly implicated, also opioids, dopamine agonists and some chemotherapy agents.

Alcohol
Infections
Psychogenic causes eg anxiety

1.3.2 Non-drug / general measures

Review regular medications and stop any causative drugs if possible

For hiccups of short duration consider:

- Nasopharyngeal stimulation (e.g. touching the uvula with a cotton bud)
- Respiratory interruption (e.g. breathing into a paper bag, breath holding or Valsalva manoeuvre): contra-indicated in patients with respiratory compromise
- Acupuncture may be helpful.

1.3.3 Drug therapies

Treat gastrointestinal causes e.g.
Gastric distension or gastroparesis- metoclopramide 10mg tds or domperidone 10mg tds
GORD- treat with PPI e.g. omeprazole 20mg od or lansoprazole 30mg od

Symptomatic approach if not clear GI cause or the above fails:

Baclofen† 5mg b.d. PO, increasing as required to a maximum of 10mg t.d.s. (effective in case reports and a small clinical trial.
Gabapentin† 100mg – 300mg TDS

1.3.4 Refractory hiccup and Specialist referral

Where hiccup fails to respond to the above measures, or where there is uncertainty about their use, consider referral to the Specialist Palliative care team
Other off-licence drugs to consider after discussion with, or review by, the Specialist Palliative Care Team:

Haloperidol†
Midazolam †(usually only at end of life)
Chlorpromazine
Nifedipine†

2.GASTROINTESTINAL SECTION

2.1 Nausea and Vomiting

NAUSEA AND VOMITING

Key Points

Always attempt to identify cause

- Check biochemistry to exclude hypercalcaemia or uraemia
- Exclude constipation
- Consider cough, acid reflux, gastritis
- Consider raised intracranial pressure
- Review drugs e.g. NSAID, opioids, SSRIs, iron, etc.

Consider impact of anxiety and psychological distress

Main options

First line treatment for symptoms due to:

Gastric stasis - consider metoclopramide
Chemical/toxic causes - consider haloperidol
Other causes - consider cyclizine

Second line drug therapies consider:

Levomepromazine
Dexamethasone
Ondansetron

Refer to Specialist Palliative Care when symptoms fail to resolve

2.1.1. Treatable Causes

Always attempt to identify cause:

- Check biochemistry to exclude hypercalcaemia or uraemia
- Exclude constipation
- Consider cough, acid reflux, gastritis
- Consider raised intracranial pressure
- Review drugs e.g. NSAID, opioids, SSRIs, iron, etc.

The three main groups of nausea/vomiting problems are:

i. **Gastric stasis**

Address underlying causes where possible. These include constipation or drugs which affect gastric emptying, e.g. cyclizine, hyoscine, opioids, ondansetron, as reversing the reversible will avoid need for medication. Avoid using metoclopramide in COMPLETE bowel obstruction.

ii. **Chemical/toxic cause**

Address underlying causes where possible (e.g. hypercalcaemia, uraemia, drugs such as opioids).

iii. **Other situations**

Address underlying cause where possible, e.g. vestibular irritation, raised intracranial pressure, gastritis, reflux.

2.1.2 Non drug/ General measures

Psychosocial distress? Fear and anxiety can exacerbate nausea as well as pain.

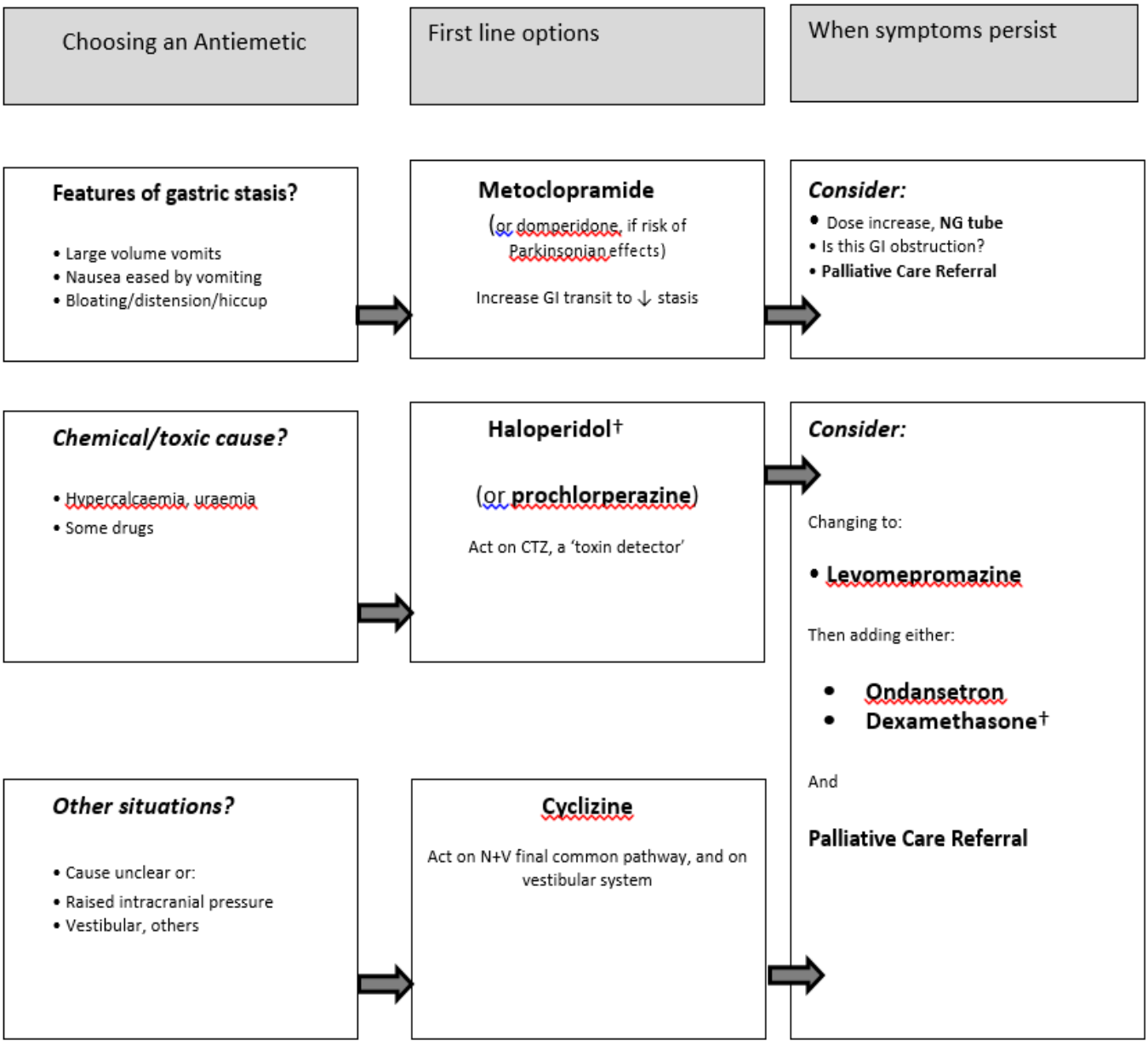
Anticipatory component? Commonly seen with protracted nausea. Consider relaxation therapies or lorazepam.

2.1.3 Drug therapies

Current consensus guidelines are largely derived from basic pharmacology. However, open-label audit suggests that this approach is effective, and some controlled studies lend support to selection based on mechanism.

Nausea and vomiting: Choosing an Antiemetic

Always ask 'Can the underlying cause be addressed?' and target drug therapy at cause.



Antiemetic Dose and Indication	Oral dose		24hr syringe pump dose	
	Starting	Usual max	Starting	Usual max
FIRST Line Agents				
Cyclizine	50mg bd-tds	50mg tds	75mg	150mg
Domperidone	10mg bd	20mg tds	n/a	n/a
Metoclopramide	10mg bd	20mg tds	30 mg	80mg†
Haloperidol† (licensing varies) Licensed alternatives (e.g. prochlorperazine) not tolerated SC Acts on CTZ (chemo-receptor trigger zone), a 'toxin detector', so helpful for chemical/toxic causes	0.5-1.5mg o.d.	5mg od	0.5-1.5mg	5mg
SECOND Line Agents				
Levomepromazine† Broad spectrum second line agent helpful in many situations Sedation and postural hypotension problematic at higher doses	6.25mg on	25mg on	6.25mg	50mg
Ondansetron Helpful for chemical/toxic or gastrointestinal irritation/distension (e.g. obstruction). Only licensed for post-op and chemotherapy	4mg bd	8mg tds	8mg	16mg
THIRD Line Agents				
Dexamethasone† Broad spectrum third line agent Reduce slowly if helpful, quickly if no benefit	8mg	16mg	3.3-6.6mg o.m. (or morning and lunch)	
Lorazepam† For anticipatory nausea or if anxiety a contributor	0.5mg prn	1mg bd	Replace with **midazolam** 5-10mg	

i. Gastric stasis

Give a prokinetic antiemetic

- **Metoclopramide** 10mg t.d.s. PO (*or* 30-40mg/24hrs via CSCI/ SC syringe pump if marked vomiting or unable to manage oral route)
- Prescribe additional metoclopramide 10mg p.r.n. PO or SC (up to 3 extra in 24 hours)

Cautions:

- For **metoclopramide**, there is a risk of extra-pyramidal disorders and tardive dyskinesia and recommendations are for a reduced daily dose and duration of treatment. In the palliative population, where its use is off label, its use can continue longer term, but patients should be closely monitored.
- For **domperidone**, there is a small increased risk of serious cardiac events. The recommended dose has been reduced and it should be avoided in patients with cardiac conditions, severe hepatic impairment, or if on drugs that cause QT prolongation.

Ongoing symptoms:
If vomiting continues and ongoing gastric stasis pattern (large vomits with nausea relief post-vomits): consider if intestinal obstruction present? (section 2.2)

If the metoclopramide is PO, change to 30-40mg/24hrs via CSCI/ SC **syringe pump**

If there is no colic and no evidence of extrapyramidal adverse effects, increase the metoclopramide to 60mg/24hrs (†) and monitor for side effects.

Alternatively, offer an **NG (nasogastric) tube** to allow aspiration of vomitus and discuss with the Specialist Palliative Care Team.

ii. Chemical/ Toxic causes

Give an anti-dopaminergic antiemetic:

- **Haloperidol**† (licensing varies) 0.5-1.5mg nocte and p.r.n. (up to 3 extra in 24 hours) PO (or SC if marked vomiting or unable to manage oral route).
  Start with 500microgram – 1.5mg PO stat and at bedtime, typical maintenance dose 1.5 – 3mg at bedtime (or 500mcg – 1.5mg b.d.).
  Doses above 5mg are rarely needed for nausea. If this is ineffective review underlying cause and consider switching.
  Caution re risk of cerebrovascular events in elderly.
  Caution re risk of extra-pyramidal side effects – use lowest dose for shortest duration possible.

- Alternatives include buccal **prochlorperazine** (Buccastem) 3-6mg p.r.n. b.d. CI with bone marrow suppression, epilepsy. Risk of extra-pyridamidal side effects. Can cause photosensitivity.

iii. Other Causes

Give an anti-histaminergic antiemetic:

- **Cyclizine** 50mg bd- t.d.s. PO (or 75-150mg/24hrs via SC syringe pump if marked vomiting or unable to manage oral route).
- Cyclizine is also the anti-emetic of choice if raised intra cranial pressure is suspected. Treatment should also include dexamethasone and referral to oncology or palliative care should be considered.
- If additional prn option desired give **haloperidol**† (licensing varies) 0.5-1.5mg p.r.n. (up to 3 doses in 24 hours): haloperidol and cyclizine have complementary sites of action.

Anti-emetics for patients with parkinsonism

Many anti-emetics are anti-dopaminergics with the potential to exacerbate parkinsonism:

- Likely to be a problem with haloperidol, metoclopramide, prochlorperazine, levomepromazine
- Less likely to be a problem, although can occasionally occur: domperidone, cyclizine

Alternative anti-emetics are advised: first line domperidone, second line cyclizine.

Usual management of nausea and vomiting with **concurrent parkinsonism**		
CAUSE	**FIRST line**	**SECOND line**
Gastric stasis	Domperidone	d/w Palliative Care Team
Chemical/toxic	Domperidone	Ondansetron or dexamethasone
Other	Cyclizine	Ondansetron or dexamethasone

2.1.5 Refractory symptoms/ Specialist referral

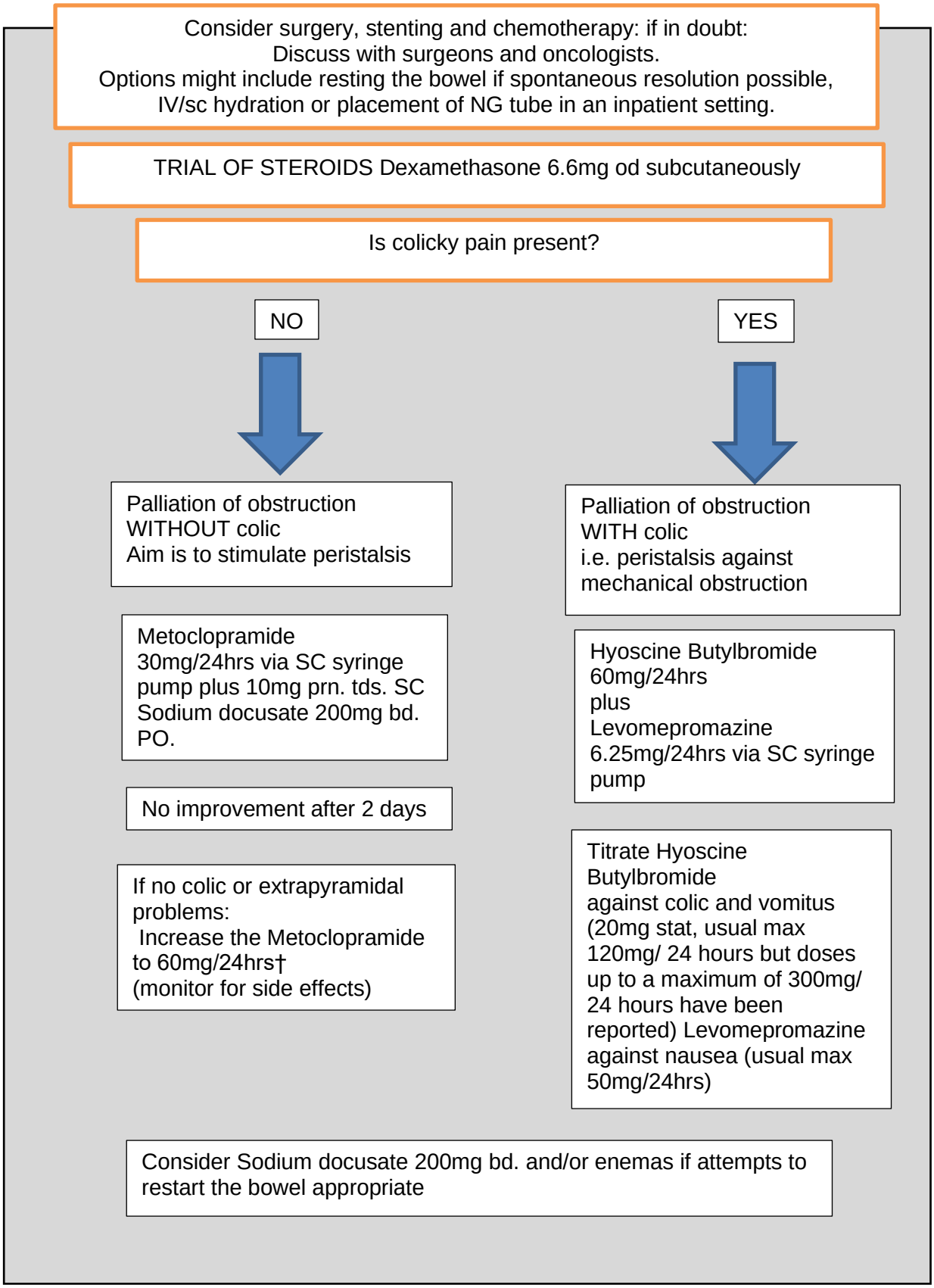
- Has gastric stasis or a treatable underlying cause been missed?

If gastritis or reflux are suspected, commence PPI (omeprazole 20mg o.d. PO or lansoprazole 15mg)

Intestinal obstruction

The palliation of obstruction is particularly difficult. Patients with disseminated intra-abdominal cancer commonly have multiple sites of obstruction involving both small and large bowel. At each level the obstruction can be functional or mechanical or both. It can also be partial or complete, transient or persistent.

2.2 Gastrointestinal obstruction:



2.2.1 Treatable causes

Consider reversible causes and disease modification

- Options include surgery, chemotherapy and stenting.
- Constipation
- Biochemical abnormalities (hypokalaemia or hypomagnesaemia)
- Where disease modification is not possible, proceed to the options described below

2.2.2 Non drug/ General measures

Consider surgical referral in all patients. Symptoms of high obstruction can be difficult to control pharmacologically. Options include bypass surgery and stenting. Where there is doubt about the place of active treatment, discuss with surgeons and/or oncologists. It may be helpful to characterize the nature of the obstruction with imaging, if clinically appropriate. When distress is associated with vomiting, offer a **nasogastric tube,** to allow aspiration during trial of medication. Consider requirements for hydration by intravenous or subcutaneous route if appropriate.

i. Drug therapies: Steroids

Steroids:
Consider a trial of steroids. **Dexamethasone** improves nausea and reduces peri-tumour oedema increasing resolution rates from one third to a half of patients.
Commence dexamethasone 8mg OM oral or 6.6mg OM subcutaneously (assuming 3.3mg/ml vial)
If no benefit after 5-7 days, then stop.

2.2.4 Drug Therapies: Managing pain

Distinguish colic from continuous background pain which should be treated with opioids.

No colicky pain: the aim is to 're-start' the bowel by stimulating peristalsis:

- Stop/minimise anti-motility drugs (e.g. anti-muscarinics, ondansetron)
- Commence metoclopramide†, sodium docusate and consider rectal measures (enemas), as described in flow diagram above:
  Metoclopramide† aim is to stimulate peristalsis. Its use is acceptable in obstruction where the aim is palliation. Discontinue if colic occurs
  Sodium docusate aims to soften stool allowing movement through a narrowed lumen. Other softeners are avoided: they increase stool volume via osmosis and so worsen intestinal distension.
- If nauseated add **levomepromazine** 6.25 mg o.d. SC or **Haloperidol** 0.5-1.5mg OD sc.

Colicky pain present: the aim is to 'rest' the bowel (colic implies peristalsis against an immovable obstruction. Stimulating further peristalsis would be ineffective and worsen the colic)

- **Hyoscine Butylbromide** reduces *colicky pain* (by suppressing peristalsis). Start hyoscine butylbromide and **Levomepromazine/Haloperidol** as in the flow diagram and titrate according to symptoms
- Add **sodium docusate**: the aim is to reverse obstruction using a softening laxative e.g. docusate.

It is important to distinguish nausea from vomiting:

Nausea in between vomits is controlled by antiemetics: haloperidol, cyclizine or levomepromazine.

Vomiting can be controlled with **hyoscine butylbromide.**
Hyoscine Butylbromide is as effective as **octreotide** after 4 – 6 days in allowing good symptom control without the need for a nasogastric tube. Neither reduces the vomiting of ingested food or drink: this can only be removed mechanically (i.e. by a nasogastric tube).
Centrally acting antiemetics (e.g. cyclizine, levomepromazine, ondansetron) are unhelpful for the mechanical vomiting in this situation.

2.2.4 Refractory symptoms/ Specialist referral

Octreotide† has an anti-secretory effect throughout the alimentary tract. It achieves a benefit faster than hyoscine butylbromide. A reduction in intestinal contents reduces distension and the likelihood of colic and vomiting**.** It can provide rapid improvements in nausea and vomiting.
Venting gastrostomy: gastrostomies and jejunostomies can perform a similar function to a nasogastric tube. Successful palliation is described (though in teams with particular expertise in their placement and use).

2.3 Mouth Problems

MOUTH PROBLEMS

Key points

Patients rate mouth problems as one of the most distressing of symptoms
Good dental hygiene and regular review of the mouth is of paramount importance

Common symptoms are **pain, dry mouth and drooling**

Main options

Soreness / pain / ulcers:

Candidiasis: (redness +/or white plaques): **nystatin** 5ml q.d.s. or **fluconazole** 50mg - 10mg o.d. PO for 7 – 14 days

Mucositis: (due to chemo/radiotherapy/haematopoietic stem cell transplantation):
If mild, antiseptic mouthwash may prevent problems.
Gelclair™ sachets can provide protection if painful
If painful, give **oxetacaine** (antacid and oxetacaine suspension#) topically 10ml Q.D.S. (use before meals and at bedtime) plus **opioid** analgesia
Note: steroids are not part of the management of Mucositis

Ulcers (e.g. Recurrent Apthous ulceration): treat pain
FIRST line with topical anaesthetics e.g. **Bonjela**
SECOND line with topical steroids e.g. hydrocortisone oral muco-adhesive buccal tablets 2.5mg q.d.s. Allow to dissolve slowly in contact with the ulcer.
Avoid in oral infections.
Check for abnormal haematinics and neutropenia. If persistent, consider oral malignancy

Dry mouth:
Consider causes e.g. drugs: antimuscarinics, tricyclic antidepressants and opioids.
Look for oral candidiasis
Support oral hydration
Offer ice chips/cubes, sucking pineapple cubes, chewing sugar-free gum
Offer trial of saliva replacements e.g. **Oral balance gel or Saliveze spray** topically before meals and PRN.
For dry lips use **Oral balance gel** or yellow soft paraffin. Ensure oxygen not used concurrently If YSP.
If too weak to self-care, offer to involve carers in mouth care
If severe, consider referral: parasympathomimetic saliva stimulants (e.g. **pilocarpine**) are used in refractory cases

Drooling
Dentist if dentures ill-fitting
Consider a barrier (e.g. Proshield, yellow soft paraffin) to maintain surrounding skin integrity
Use antimuscarinic to reduce saliva production
Amitriptyline 10-25mg o.n. PO *or*
Transdermal hyoscine hydrobromide 1mg changed every 72 hrs

Specialist advice
Glycopyrronium oral solution #(unlicensed special) 1mg up to qds
Atropine eye drops 1%† (unlicensed route) orally 1 – 2 drop up to qds

Oral candidiasis

2.3.1 Treatable causes

Prevention

Careful attention to risk factors (e.g. dry mouth, denture hygiene). Inhaled corticosteroids should be taken prior to brushing teeth or followed by mouthwash.

Oncologists/haematologists may use antifungals prophylactically in higher risk patients receiving chemotherapy or radiotherapy.

2.3.2 Non drug measures

Ill-fitting dentures due to weight-loss: soft denture linings provide cushioning and reduce rubbing. Consider dentistry referral and give good mouth care.

2.3.3 Drug therapies

Nystatin† 5 ml q.d.s. for 7 days then review

Needs to be used appropriately in those with dentures:

- Remove dentures and hold nystatin in mouth for as long as possible
- Scrub dentures with toothpaste and soak in appropriate antiseptic e.g. chlorhexidine or dilute sodium hypochlorite. The latter should not be used for dentures with metal parts. Thoroughly rinse dentures before reinsertion.

Fluconazole 100mg daily for 7 – 14 days.

Use where:

- Nystatin is ineffective or impractical
- Co-existent oesophageal candidiasis is suspected (e.g. painful swallowing).

If tablet load is burdensome, give one-off fluconazole 150mg† (licensed for genital, but not oral, candida infection).

2.3.4 Refractory symptoms / Specialist referral

Where mouth problems fail to respond to the above measures, or where there is uncertainty, consider referral to Specialist Palliative Care Team.

For severe pain, especially post radiotherapy, Antacid with oxetacaine (unlicensed special) may be recommended by palliative or oncology teams

2.4 Constipation

CONSTIPATION

Key Points

Patients commencing opioids should routinely be offered laxatives as all opioids may cause constipation

Major differences from usual care in debilitated patients:

- Lifestyle advice alone (e.g. diet, fluid) is usually inadequate: laxatives are generally required
- Bulk forming agents (e.g. ispaghula husk "Fybogel") are avoided because they become constipating without adequate fluid intake (a common feature in such patients)
- Patients may assume that reduced dietary intake will reduce frequency of defaecation. Whilst volumes may alter, the aim is still to maintain a regular bowel habit

Main Options

There are 2 broad classes of laxative:

- **Softeners** tend to increase faecal mass and hence stimulate the bowel
  e.g. docusate sodium 200mg b.d. PO
- **Bowel stimulants**: which, by reducing water absorption, also become softeners
  e.g. senna 7.5-15mg (1-2 tablets or 5-10ml) b.d. PO

Cost may influence physician's choice of laxative, but ultimately patient preference & drug tolerability has to be taken into account to improve compliance.
If a patient is constipated and is already taking a laxative, they may prefer to adjust the laxative dose rather than changing to another.
Start with a stimulant laxative alone and titrate upwards as needed
Consider adding a faecal softener after a week

- If colic occurs, add a softener or reduce the dose of stimulant
- If anal leakage occurs, reduce or stop the softener

Rectal measures may be required in specific circumstances (see below)
Constipation with colic or vomiting requires specific treatment (see below)

2.4.1 Treatable Causes

Patients commencing opioids should also routinely be offered laxatives

Opioid induced constipation:

- All opioids will cause constipation (methadone, fentanyl and buprenorphine are possibly less constipating)
- Tolerance to this effect does not develop
- Constipation in palliative patients is multifactorial and an opioid alone is seldom the only cause, hence switching to a 'less constipating opioid' does not make therapeutic sense
- **If not constipated:** start with senna 15mg at bedtime and titrate upwards to maximum 30mg t.d.s. and add a softener if there is colic or hard stool
- **If already constipated:** start with senna 15mg at bedtime and in the morning. Consider a third day time dose if this is ineffective or increase the laxative the patient is already using if the patient wishes.

Key differences from usual care in debilitated patients:

- Lifestyle advice alone (e.g. diet, fluid) is usually inadequate: laxatives are generally required
- Bulk forming agents (e.g. ispaghula husk "Fybogel") are avoided because they become constipating without adequate fluid intake (a common feature in such patients)
- Patients may assume that reduced dietary intake will reduce frequency of defaecation. Whilst volumes may alter, the aim is still to maintain a regular bowel habit

2.4.2 Non-drug/general measures

N.B. Always consider whether diet, exercise and fluid measures might be contributing factors and can be influenced.

Rectal measures are sometimes appropriate:

- If patient has not opened bowels > 3 days or reports rectal discomfort or has diarrhoea suggestive of faecal impaction; perform a rectal examination.
- The evidence for rectal measures in palliative care is limited to clinical experience and retrospective studies.
- N.B. arachis oil enema contains peanut oil (**contra-indicated in peanut allergy**)
- Glycerol suppositories 4g are used to soften and lubricate
- Bisacodyl suppositories 10mg act to stimulate the bowel
- If Glycerol and Bisacodyl suppositories are ineffective, administer a phosphate enema.

2.4.3 Drug Therapies

General principles

There are 3 broad classes of laxative:

Softeners: tend to increase faecal mass and hence stimulate the bowel

e.g. docusate sodium 200mg b.d. PO. Arachis oil enema (check peanut allergy)

Bowel stimulants: which, by reducing water absorption, also become softeners

e.g. senna 7.5-15mg (1-2 tablets or 5-10ml) b.d. PO, Bisacodyl 5mg – 10mg once daily.

Osmotic agents: act by an osmotic effect on the bowel e.g. macrogols, magnesium salts,sodium picosulphate

Two Cochrane reviews concluded there is not enough evidence to guide treatment of constipation with laxatives in palliative patients. Cost may influence physician's choice of laxative, but ultimately patient preference and drug tolerability has to be taken into account to improve compliance. If a patient is constipated and is already taking a laxative they may prefer to adjust the laxative rather than changing to another.

It is reasonable to:

- Start with, and titrate upwards, a stimulant laxative alone
- Consider adding a faecal softener after a week.
- Add a softener or reduce the dose of stimulant if colic occurs
- Reduce or stop the softener if anal leakage occurs.

Laxative choices

Senna (stimulant)

Dose: 7.5-15mg (1-2 tablets or 5-10ml) b.d. PO

if the stool is hard or cramps occur, add a softener like docusate capsules or lactulose liquid

i. **Macrogols e.g. Laxido, Movicol, Cosmocol (softener)**

Not shown to be superior to lactulose in opioid-induced constipation, but may cause less bloating.

- Each sachet must be made up with 125ml water
- If made to a more dilute solution, it is still effective but can cause hyponatraemia
- Dose: start with 1 sachet daily
- For **faecal impaction:** start with 8 sachets on day 1. The contents of the 8 sachets should be dissolved in 1L of water and the whole amount taken within 6 hrs. The made-up solution should be kept in fridge and consumed within 6 hrs. (**In heart failure**, the maximum rate of consumption should be 250ml/hr).
- Macrogols can interact with starch based thickening agents -causing thin solution which may result in aspiration.

ii. **Docusate sodium (softener with some stimulant action)**

- Dose: start with 100mg b.d. and increase to 200mg b.d. if needed
- Takes 1-2 days to work

iii. Rectal preparations (see section 2.4.2 Non-drug/general measures)

Constipation with colic

- This is caused by peristalsis against stool that won't move
- Unless the patient is obstructed (see section 2.2) the cause is hard stool
- The aim is, therefore, to soften the stool
- Temporarily reducing peristalsis will ease pain
- Reduce or divide stimulant laxatives e.g. change senna 20ml nocte to 10ml b.d.
- Increase softeners, using rectal softeners initially, if required

If colic is severe: discontinue stimulants and use **a softener** alone

- Give **hyoscine butylbromide** 20mg prn q.d.s. SC or PO (or 60mg/24hrs via SC syringe pump) for 48hrs while the softeners take effect
- Use rectal measures: softeners initially e.g. glycerol suppositories, micralax enema or arachis oil enema (**N.B.** ask about peanut allergy)

Constipation with vomiting

- Consider obstruction (see section 2.2)
- Use rectal intervention and concurrent antiemetics (see section 2.1 and 2.2)
- If refractory to these, and if opioid induced, consider use of a Peripherally acting mu opioid antagonist (PAMORA) (see below).
- Gastrointestinal obstruction: sodium docusate (200mg b.d. PO) is the laxative of choice because it softens without substantially increasing stool volume, causing a smaller increase in bowel distension than osmotic laxatives. (See also section 2.2)

Refractory Symptoms/Specialist referral: If opioid induced constipation is not resolved by use of conventional laxatives consider use of a Peripherally acting mu opioid antagonist (PAMORA); First line: Naldemidine 200micrograms daily or Naloxogol 25mg once daily – reduced to 12.5mg once daily in renal impairment or if concomitant use of CYP450 inhibitors (eg clarithromycin, itraconazole).

Drugs not currently recommended for routine use in palliative care: Combined naloxone-oxycodone (Targinact); restricted use or non-formulary use only

2.5 Diarrhoea

DIARRHOEA

Key points

Non-specific treatment should only be used after considering specific treatable causes:

- In any patient group (e.g. clostridium difficile, drug-induced, overflow [i.e. constipation]
- In malignancy (e.g. steatorrhoea, carcinoid syndrome, radiation-induced)

Main options

For non-specific palliation of diarrhoea:

- **FIRST line** options:
  Loperamide 2-4mg p.r.n. PO (less systemic effects; more potent than codeine)
  Consider b.d. regimen thereafter, with dose based on prn requirement.
  Usual maximum 16mg/24hrs (up to 32mg/24hrs occasionally used under specialist direction)

Specialist referral

Specialist options include:
Octreotide† 250- 500micrograms/day via CSCI
Hyoscine butylbromide† 60mg/24hrs via subcutaneous syringe pump
Colostomy formation may be considered in intractable circumstances

2.5.1 Treatable causes

Specific causes	Identification	Comments / Treatment
Clostridium difficile-induced	**Risk factors** • antibiotic treatment (especially multiple agents or prolonged) • increasing age • prolonged hospital stay • anti-ulcer medications • NG tubes • severe underlying illness **Symptoms**: mild diarrhoea to severe bloody diarrhoea **Diagnosis**: stool sample (request 'CDT')	Where symptoms are severe, start while awaiting stool results. Treat as per local infection control and treatment guidelines (e.g. **metronidazole** 400mg t.d.s. PO for 10 days) Where rapid control is required *in the dying* give **dexamethasone** 6.6mg o.m. SC
Drug-induced	Review treatment (including nutritional supplementation) and consider excess laxative use Sugar free liquid drug preparations in large volumes. Side effects of some drugs, e.g. chemotherapy, antibiotics, PPIs, NSAIDs	Discontinuation, where possible Where nutritional supplements implicated, consider d/w dietician
Overflow diarrhoea	Loaded or ballooned rectum Watery motion with pieces of hard faeces Abdominal X-ray in cases of doubt	Treat as constipation (ensuring patient understands the rationale)
Bacterial overgrowth / Blind loop	Consider if past history of bowel surgery	Treatment is based on empirical courses of broad spectrum antibiotics. For choice and length of antibiotic treatment consult with local specialist team
Other	Inflammatory bowel disease, secondary lactose/ gluten intolerance, autonomic neuropathy (diabetes, paraneoplastic)	

2.5.1 Treatable causes

Malignancy related problem		
Steatorrhoea	Loose offensive yellow stool (sometimes likened to 'butterscotch whip'), floating/difficult to flush away Occurs with biliary and pancreatic cancers	Start **Creon 25,000 units capsules** 1-2 with each meal and 2 – 3 with each full meal PO and titrate against symptomatic response (consider involving a dietician). If ineffective, add **omeprazole** 20mg o.m. PO (enzymes inactivated by acid
Carcinoid syndrome	**Symptoms**: intermittent release of vasoactive substances (typically serotonin) causes: • bronchoconstriction • diarrhoea • facial/skin flushing **Diagnosis**: Urinary metabolites (d/w clinical biochemistry)	Not all carcinoid tumours cause the syndrome Seek advice from an oncologist (usually treated with **octreotide** or a long-acting analogue)
Radiation- induced	Usually within days/weeks of radiotherapy directly affecting bowel (e.g. treatment to spine or pelvis)	D/w an oncologist as local or systemic steroids may be appropriate

2.5.2 Non drug/ General Measures
Assess fluid and electrolyte balance in all cases.

2.5.3 Drug therapies
Where possible treat underlying cause. Review all drugs, including laxatives and non-prescription drugs. Symptomatic relief can be achieved using:

Loperamide
- 2-4mg p.r.n. PO initially (has less systemic effects and more potent than codeine)
- Titrate regimen thereafter, with dose based on prn requirement.
- Usually 4mg stat and then 2mg after every loose motion.
- Usual maximum 16mg/24hrs (up to 32mg/24hrs occasionally used under specialist direction, requires ECG monitoring as prolongs QT at higher doses).
- Available in capsules or oro-dispersible form.
- Maximum effect may take 16-24 hrs, so initial dosing may need to be more frequent.
- If used regularly can be given b.d.
- Always confirm that diarrhoea is not secondary to colitis or faecal impaction prior to starting Loperamide.

Caution: severe hepatic failure and some drugs e.g. macrolides and –azoles can cause increased plasma concentration which may cause drowsiness ~~(1)~~
Use with caution in patients at risk of *torsade de pointes* or other cardiac arrythmias.

2.5.4 Refractory symptoms/ Specialist referral
Hyoscine butylbromide 60mg/24hrs via subcutaneous syringe pump
Octreotide†: This is an off-licence, infrequently used, drug which can initiated after discussion with, or review by, a Specialist Palliative Care Team; doses of 250 - 500micrograms/day via Continuous subcutaneous infusion.

Consider a colostomy if symptoms intractable and unresponsive to symptom measures.

3.1 Lymphoedema

LYMPHOEDEMA

Key points

Patient/carer education is the mainstay of management:

Scrupulous skin care (emollients, avoiding skin trauma)
Exercise and movement advice
Compression hosiery
Seeking prompt treatment for infection (cellulitis, fungal infection)
Lymphatic drainage massage techniques (including by patients and carers themselves if they have been taught by lymphoedema specialist)

Further considerations for healthcare professionals

Minimise trauma to affected limbs (e.g. venepuncture, cannulae, blood pressure checks)
Avoid drugs that worsen fluid retention where possible (e.g. corticosteroids, NSAIDs, calcium antagonists, pioglitazone)

Main options

Active management of complications:

Worsening oedema: consider:

- Poor adherence (e.g. ill-fitting hosiery)- seek advice from lymphoedema team
- DVT
- Infection (acute or recurrent)
- Recently commenced medicines; e.g. gabapentin/pregabalin, NSAIDs, calcium channel blockers, corticosteroids
- Worsening underlying disease (e.g. if malignancy-related, see 'corticosteroids' below)

Cellulitis: prompt antibiotics *for at least 2 weeks* (choice as for conventional cellulitis) are essential because:

- The immune response in lymphoedematous areas is impaired
- Infection causes further permanent damage to lymphatic drainage
- Systemic flu-like symptoms can be severe (may precede visible skin changes)

Pain: consider:

- Oedema itself (distension and myoligamentous strain): simple analgesics and general management of underlying lymphedema
- Lymphoedema complication (e.g. DVT, infection): treat appropriately
- Underlying disease (e.g. consider axillary recurrence with new pain in a mastectomy-related lymphoedematous arm): urgent referral

Lymphorrhoea (leaking): Gentle bandaging - seek advice from the lymphoedema team

Drug treatment

Diuretics for mixed lympho-venous oedema (lymphoedema alone does not respond): measure limb circumference before and after a 1 week trial of furosemide 40mg o.m. PO, continuing if effective

Corticosteroids for severe malignancy-related lymphoedema: not usually for long-term maintenance. Helpful for lymphoedema in difficult (i.e. non-limb) areas or if lymphoedema is worsening despite the optimal use of non-drug measures (e.g. hosiery, massage)

3.1.1 Treatable Causes

Lymphoedema is not generally a curable condition unless there are treatment options for the underlying process. It can be successfully managed in the majority of cases.

True lymphoedema is oedema due to reduced lymphatic drainage. It is subdivided as:

- **Primary**: no external cause identified. Generally, due to an inherited lymphatic abnormality, though may take years, or a traumatic/infective trigger, to become clinically apparent. A family history is not always present. It is usually clinically apparent by the 4th decade of life.
- **Secondary:** identifiable external cause e.g. surgery, radiotherapy, lymphatic metastases, infection, inflammatory conditions (e.g. rheumatoid arthritis, eczema), obesity, immobility

Chronic oedema can have other causes. It can occur in post-thrombotic syndrome, congestive heart failure, venous stasis, dependency oedema.

Early intervention: when venous oedema is present, it may have a reversible element if treated early. When not actively managed (drugs and /or compression management), venous oedema will progress resulting in extra load on the lymphatic drainage. This will cause progressive lymphatic damage and lymphoedema. This can be known as lympho-venous oedema.

The **clinical features of lymphoedema** change with time:

Underlying process	Appearance
Initial fluid formation	Pitting oedema that reduces on elevation
Subsequent secondary fibrosis	Non-pitting oedema with no reduction on elevation
Finally, secondary overlying skin changes occur	Hyperkeratosis (horny scale, with or without 'furry' appearance) Papillomatosis (cobblestone, 'warty' appearance) Lymphangiomas ('blisters' of dilated lymphatics)

The key aims of lymphoedema management are to minimize oedema through:

- **Activity and regular (gentle) exercise** (especially while wearing hosiery).
  Care should be taken with vigorous, heavy or very repetitive activities that can sometimes exacerbate swelling.
- **Hosiery**: firm garments (with higher compression than used for venous conditions), against which muscles contract improving movement-induced drainage. It is essential that they are well fitting: *ill-fitting hosiery is at best ineffective and at worst causes ischaemic limb injury.* There are different indications for various types of lymphoedema garments, and they should be fitted by a specialist physiotherapist or nurse with lymphoedema experience. Some can be prescribed on an FP10 form.
- **Lymphatic drainage massage** (broadly along lines of patent lymphatic drainage): patients and carers can be taught simple lymphatic drainage, and specialists use a more comprehensive '**manual lymphatic drainage'**
- **Multi-layer bandaging** can be used to rapidly reduce volume before maintaining this reduction with hosiery. Multi- layer bandaging can be arduous and time consuming, requiring daily visits and the use of bulky bandaging (a particular concern if patients are fatigued or unsteady)
- Reducing the risk of cellulitis by scrupulous skin care

3.1.2 Non drug/ general measures

Patient and carer education

- **Promotion of skin integrity**
  Good skin care improves comfort and reduces the risk of cellulitis:
  Protect skin from cuts, burns, bites, sunburn
  Avoid medical procedures to affected limbs (blood pressure readings, venepuncture and injections)
  Regular emollients (e.g. Epimax, Cetraben or Oilatum cream) applied once or twice daily
  On very dry skin, switch to a greasier emollient (e.g. liquid and white soft paraffin ointment 50:50)
  If there is a build-up of scales, wash the affected area with a light cream (e.g. Aquamax Cream, Dermol) using a circular motion in order to soften and lift off the scales, then apply a greasy emollient as above
  Consider Aquamax as a soap substitute. Most cost effective product may vary – check up to date formulary for guidance

- **Prompt treatment for fungal or bacterial infections.**
  Ensure patients are aware of the signs of cellulitis and the need to seek treatment promptly: Warmth and redness; increased pain or tenderness; systemic symptoms such as fever or flu like symptoms.

- **Advice on exercise, positioning and diet**
  Normal activity and regular gentle exercise will increase the effect of the 'muscle pump' on lymphatic drainage. Gradually increase activity levels as sudden, strenuous and repetitive movement can exacerbate swelling. If they have a compression garment, wear this whilst exercising.
  Body Mass Index influences lymphatic drainage
  Elevation of a swollen arm to shoulder height, or swollen leg to hip height, can reduce oedema formation
  Discourage patients with leg oedema from sleeping in a chair.

- **Advice on hosiery**
  It is important that compression garments are well fitting; patients should ask for advice when garments are not comfortable or are slipping. They should be renewed at least every 6 months to maintain the appropriate compression.
  Advice should be sought if patients are experiencing problems applying the hosiery

- **Supportive care:**
  Provide written information about lymphoedema and the patient support organisations (see links at the end). Analgesia and related symptom control may be required and psychological support about adapting to altered body-image or limb function.

3.1.3 Drug therapies

Managing complications

3.1.3.1 Worsening oedema

Check for problems with regular maintenance treatment? (e.g. exercise, use of hosiery, massage techniques) and discuss with lymphoedema team.

Look for evidence of:

- Infection (see 'cellulitis' below)
- DVT (if present, refer for Doppler imaging and appropriate treatment)
- Worsening underlying disease: if malignancy-related, look for lymphadenopathy as may be an indication of recurrence and consider oncology referral.

If no active treatment options, consider a trial of corticosteroids dexamethasone 8mg o.m. PO for two weeks and then reduce by 2mg o.d. per week until minimum effective dose. Not recommended for long term maintenance.

Co- existent venous oedema/congestive cardiac failure: treat with diuretics as needed. Measure limb circumference before/after 1 week trial of diuretic initiation/titration to measure if effective.

3.1.3.2 Cellulitis in lymphoedema (management, prophylaxis)

The immune response in a lymphoedematous area is impaired. Management differs from that of standard cellulitis described in local antibiotic policies because:

- Onset may be faster (hours) or subacute (weeks)
- Systemic upset (fever, flu-like symptoms) is more frequent. It may precede skin changes
- Infection can further damage lymphatic drainage

Prompt treatment, for a minimum of 14 days <u>after clinical response</u> to treatment, is imperative. Continue until the acute inflammation has completely resolved; this may take 1-2 months.

Acute attack

If afebrile, no systemic upset and otherwise healthy: commence oral antibiotics as per local policy, for example:

First-line antibiotics:

- Amoxicillin 500mg t.d.s. PO or Flucloxacillin 500mg q.d.s. PO (if folliculitis, pus crusted dermatitis suggestive of Staphylococcus aureus) for 14 days (minimum) unless penicillin allergic.
- Penicillin allergic: Doxycycline 100mg bd or Clarithromycin 500mg b.d PO
- If no response after 48h, switch to second line antibiotic or admit to hospital if deteriorating systemic signs (pyrexia>38.3°C, delirium, tachycardia, hypotension rigors or vomiting)

Second line antibiotics:

- Clindamycin 300mg q.d.s. PO) for 14 days. If fails to resolve, convert to IV regime

IV regime for acute cellulitis and septicaemia (inpatient admission):

- Flucloxacillin 2g IV every 6h

Penicillin allergic: Clindamycin 600mg IV every 6h

- Review 48 hrs after starting antibiotics. If deterioration, discuss same day with microbiologist: IV antibiotics may be needed.
- Monitor rash and systemic upset (use additional monitoring with CRP / ESR / white cell count, and microbiology if appropriate)
- For monitoring purposes, consider use of digital photography
- Antibiotics should be continued for **not less than 14 days** after clinical response to treatment (1).
- Advise bed rest and elevation
- Decrease level of compression (garments or bandaging) during the acute attack.
- **Prescribe regular and p.r.n. analgesia**. Because of a possible relationship between skin infections, NSAIDS and necrotizing fasciitis, paracetamol and opioids are the preferred analgesics.

If febrile/systemic upset and/or unstable co-morbidities*:*

- If in the community, admit to hospital (likely to need IV antibiotics)
- Inpatients: follow acute hospital cellulitis guidelines

Holiday supply of "if needed" antibiotics

The risk of further cellulitis in lymphoedema is high. It is recommended that patients who have had an attack of cellulitis should:

- Carry a 2 week supply of the above antibiotics if away from home for any length of time
- Start antibiotics immediately familiar symptoms occur (but still seek medical review as soon as possible)

Prophylaxis to prevent recurrent cellulitis (refer to local guidelines where possible)

If ≥2 attacks per year:		
Treat risk factors		Fungal infections, dermatitis (and skin care), open wounds
Start prophylaxis	First line	Phenoxymethylpenicillin (penicillin V) 250mg b.d. PO (500mg b.d. if BMI ≥33)
	Penicillin allergic	Clarithromycin 250mg o.d. °known risk of prolonged QT interval and torsade de pointes and important drug iinteractions (eg on Statins) - can use Doxycycline.50mg o.d.
Second line antibacterials		Clindamycin 150mg o.d. or Doxycycline 50mg o.d. (risk of predisposing to Clostridium Difficile infection)
If prophylaxis successful		Stop after 2 years If relapse occurs, lifelong prophylaxis may be needed

i. ***Pain***

Management depends on the cause:

- **Oedema itself (distension and myoligamentous strain):** analgesics and general management of underlying lymphoedema. Good emollient care may ease distension pain.
- **Lymphoedema complication (e.g. cellulitis, DVT):** analgesics while arranging appropriate treatment
- **Underlying disease:** in malignancy-associated lymphoedema, **pain can be a feature of cancer in recurrence**, requiring urgent referral

In addition to broad-spectrum analgesia (e.g. paracetamol, opioids: see pain guidelines), look for:

- **Neuropathic pain** (e.g. due to lymphadenopathy). Neuropathic-like skin hypersensitivity also occurs in oedema: consider discussion with a specialist or trial of a neuropathic agent
- **Secondary muscle imbalance and articular problems:** seek advice from a physiotherapist

- **Analgesic-induced fluid retention** (e.g. NSAIDs, antiepileptic drugs)

ii. Lymphorrhoea (leaking)

This is difficult to manage: seek advice from the Lymphoedema Team. In the interim:

- Be vigilant for infection; continue scrupulous skin care, moisturising, gentle exercise and elevation if comfort allows
- Cover leaking areas with absorbent dressing; skin fragility often precludes adhesive dressings
- Consider gentle bandaging
- In end of life care, if there is a single point source of leakage, cover with a stoma bag (not generally used in the longer term because of detrimental impact on skin integrity)

3.1.4. Refractory symptoms/ Specialist referral

Specialist services, referral criteria and links to professional and patient organisations

Early diagnosis and prompt referral for treatment is vital

West **Berkshire GP**		
Age	**Condition**	**Referral**
Adults	**Malignant lymphoedema** (secondary to cancer or its treatments)	Sue Ryder Berkshire West Lymphedema Team a
	Primary lymphoedema (very clear history of congenital / hereditary lymphatic abnormalities)	
	Oedema secondary to non-cancer conditions (e.g. post thrombotic syndrome, venous stasis, cardiac, renal or hepatic disease, infection, burns)	Refer to the specialty appropriate to the underlying cause. They may then opt to mak an out of area referral (below)
Children	All lymphoedema	St George's Lymphoedema Team

a. Sue Ryder Berkshire West Lymphoedema Team *(for adults with malignant lymphoedema or a very clear history of primary lymphoedema)* Direct dial: 0118 955 0413 Email: sryc.srlymph@nhs.net

East **Berkshire GP**		
Age	**Condition**	**Referral**
Adults	**Malignant lymphoedema** (secondary to cancer or its treatments)	**Thames Hospice**[a] (any cancer site). *r*
	Primary lymphoedema (caused by congenital / hereditary lymphatic abnormalities)	Out of area referral (below)
	Oedema secondary to non-cancer conditions (e.g. post thrombotic syndrome, venous stasis, cardiac, renal or hepatic disease, infection, burns)	Refer to the specialty appropriate to the underlying cause. They may then opt to make an out of area referral (below)
Children	All lymphoedema	St George's Lymphoedema Team

a. Thames Hospice *(for adults with malignant lymphoedema)*
Windsor Road Maidenhead SL6 2DN Tel 01753 848937
Referral form on Thames Hospice Website: Thameshospice.org.uk/services/lymphoedema-services/

Buckinghamshire, Thame & South Bedfordshire: service via Florence Nightingale Hospice Lymphoedema Clinic 01296 332 600 email: buc-tr.fnh@nhs.net

South Buckinghamshire: service via South Bucks Hospice 01494 552756 mailto: lymph@sbhospice.org.uk

Surrey/Hampshire GP:
serving Guildford and Waverley CCG, Farnham and North East Hampshire CCG, Surrey Heath CCG, North West Surrey CCG. Clinic based at the Beacon Centre, Guildford & Satellite clinics from Farnham Hospital for adults with lymphoedema:

Beacon Centre RSFT Lymphoedema Service
Tel: 01483 956643 Email: rsch.gw.lymphoedema@nhs.net

Out of Area Lymphoedema Referral

St George's (adults or children)	**Oxford** (adults only)	**Basingstoke** (adults only)
Lymphoedema Service St George's Hospital, Clinic B, Lanesborough Wing, Blackshaw Road, London SW17 0QT Tel: 020 8725 1857	Transplant Ward Churchill Hospital Old Road, Headington Oxford, OX3 7LJ Tel 01865 225864 Fax 01865 225473	North Hampshire Hospital Aldermaston Road Basingstoke Hampshire RG24 9NA Tel 01256 313564

Links

The British Lymphology Society (for interested professionals):
British Lymphology Society Tel: 01452 790178
www.thebls.com

The Lymphoedema Support Network (patient support organisation):
Hold a comprehensive list of specialist lymphoedema services in the UK
Tel: 020 7351 4480
www.lymphoedema.org
Email: admin@lsn.org.uk

3.2 Itching

ITCHING

Key points

Where possible address underlying cause:

Cholestasis – biliary stent, corticosteroids
Uraemia – iron deficiency and phosphate level
Neuropathic itch (i.e. a symptom of nerve injury) – options similar to neuropathic pain
Drug-induced pruritus – consider an alternative (e.g. opioid switching; see pain guidelines) and short term use of an antihistamine
Endocrine – carcinoid syndrome, diabetes mellitus (genital candidiasis), hyperparathyroidism (resolves with correction of hypercalcaemia), thyroid dysfunction

Main options

Review medication – any drug can cause an allergic reaction causing pruritis +/-rash.

Emollients are essential

Lifestyle changes

- Keep skin cool (avoiding hot baths pre-bed, light clothes etc)
- Minimise excoriation by keeping fingernails short; rub in emollient rather than scratching with fingernails

Sedative antihistamine-antipruritics (less sedating alternatives may be unhelpful

- **Chlorphenamine** 4mg q.d.s. PO for drug induced pruritis +/- rash

- **Refractory itch**

SSRI (unlicensed) eg Sertraline 50mg daily appears beneficial for itch due to a variety systemic illnesses.

Consider Specialist referral

1.2.1 Treatable causes

Pruritus is often due to an underlying cause, see table: cause specific measures. Wherever possible and if appropriate, treatment should be aimed to address the cause, in addition to providing symptoms relief measures.

1.2.2 Non-drug/ General measure

Adequate skin hydration with emollients is essential as dry skin will exacerbate itch.

Regular emollients

- Use a non-perfumed emollient (e.g. Diprobase, Cetraben or Oilatum cream) on intact skin up to three times a day. Some patients report greater benefit if cream kept in the fridge.
  On very dry skin, switch to a greasier emollient (e.g. liquid and white soft paraffin ointment 50:50)
- Use a soap substitute such as aqueous cream, emulsifying ointment, Cetraben cream or Dermol cream/lotion

- Emollients containing levomenthol 0.5-2% (menthol) or camphor 0.5-3% may relieve pruritus by acting on heat sensitive receptors on sensory nerve endings. Levomenthol in a bland emollient base can be obtained as a special order or OTC products that contain Levomenthol such as Dermacool®, Aquasoothe®, Arjun®, Methoderm® are available. Calamine lotion is not generally recommended due to its drying effect.
- For atopic dermatitis or an active inflammatory skin condition causing redness and eroded or scaly skin, use a topical corticosteroid for 3-7 days e.g. hydrocortisone 1% and apply 30-60 minutes before applying an emollient
- Topical antihistamines and local anaesthetic creams are only marginally effective and occasionally cause hypersensitivity.
- For uraemic pruritis, topical capsaicin cream (usually used for neuropathic pain) applied od to qds may be helpful although some patients find the burning sensation unacceptable. Examples are Axsain® (0.025%) or Zacin® (0.075%) cream.

3.2.3 Drug therapies

Review medication: common allergic drugs reactions include:

Rashes	Urticaria
Cephalosporins (e.g. Cephalexin, Cefradine) Penicillins Phenytoin Sulfonamides (e.g. Co-trimoxazole)	Cephalosporins Penicillins Radio-opaque dyes Sulfonamides

Sedative antihistamine-antipruritics (e.g. chlorphenamine,)

- The antihistamine action is of most relevance for dermatological causes of itch (e.g. urticaria, drug rashes, insect bites, etc). Usual dose of Chlorphenamine is 4mg PO tds up to max 12mg qds.
- Less sedating alternatives (e.g. Cetirizine 10mg o.d. PO) may be as effective, and better tolerated
- Itch due to systemic metabolic disturbance (uraemia, cholestasis) is not mediated by histamine, and antihistamine benefit lies mainly in the non-specific sedative action (especially for sleep disturbance). Less sedating alternatives are probably unhelpful.

Alternatives to antihistamines

- A trial of a phenothiazine with antihistaminic properties at bedtime can be used if pruritis is worse at night such as Levomepromazine 6.25-25mg PO at bedtime.
- A benzodiazepine can be as effective as a sedative antihistamine for some patients

SSRIs† for itch

Serotonin is thought to be an important central nervous system mediator of itch, especially where caused by systemic illness. 2 small RCTs suggest benefit from sertraline (Cholestatic Itch) and paroxetine (Itch of Mixed Causes in Cancer Patients). A case series also describes benefit in polycythaemia vera. Onset of action is quicker than for depression (days rather than weeks).

Consider a trial of **sertraline†** (50mg o.m. PO. increasing to 100mg after 2 weeks if needed) if:

- General measures (emollients *and* lifestyle advice *and* antihistamines) are unhelpful *and*
- Treatment of the underlying cause is already optimal *and*
- Cautions/contra-indications of SSRIs allow

Cause specific measures

The drugs listed in table are "accepted uses" and may be initiated by non-specialists for the indications described:

Cause	**Measures for underlying cause**	**Symptomatic options** if general measures (emollients, antihistamines, etc) unhelpful
Cholestasis*	Is a **biliary stent** possible (discuss with gastroenterologists) Otherwise, consider a trial of **dexamethasone** 8mg o.m. PO for 2 weeks. If helpful, reduce by 2mg per week down to minimum effective dose	**Sertraline**† 50mg o.m. PO. increasing to 100mg after 2 weeks if needed
Uraemia	**Discuss with the renal team**: Optimise **phosphate** balance Treat **iron deficiency** Consider **gabapentin**† (dose as for neuropathic pain, dose reduction needed in renal impairment)	
Haematological	**Discuss with the haematologists**: itch often responds to treatment of the underlying disease	
Neuropathic (i.e. a symptom of nerve injury)	Treatment directed at the underlying cause of the lesion	Treat with antiepileptic drugs or tricyclic antidepressants as with neuropathic pain (e.g. gabapentin†: see pain guidelines)

*__Cholestyramine__ is now rarely used in the palliation of cholestatic itch. The alternatives described here and below are more effective, better tolerated and have fewer drug interactions

3.2.4 Refractory symptoms and Specialist referral

Where itch fails to respond to the above measures, or where there is uncertainty about their use, consider referral to the Specialist Palliative Care Team

Other off-licence, infrequently used agents are amber for this indication (i.e. initiated after discussion with, or review by, Specialist Palliative Care Team), include:

Opioid antagonists and partial agonists (†for this indication): the endogenous opioid system is also an important mediator of itch due to systemic illness, but severe reactions are sometimes seen when opioids antagonists are used for this purpose.

Ondansetron†: Appears helpful in case series, but controlled trial results are conflicting
Rifampicin†
Mirtazapine†
Androgens†
UVB therapy (discuss appropriateness with the dermatologists)

Managing cancer-specific problems in the community

N.B. Refer to acute oncology guidelines in the acute inpatient setting

4.1 Hypercalcaemia of malignancy

Recognition	• Drowsiness • Confusion, agitation, hallucinations • Nausea and vomiting • Constipation
Confirmation	Raised albumin-corrected serum calcium (corrected serum calcium >2.6mmol/L)
Community Management	**If the patient is imminently dying, treat symptomatically only.** However, patients with hypercalcaemia can appear to be extremely unwell and improve markedly with treatment: if in doubt, discuss with a palliative care physician **Symptomatic management for nausea, agitation and/or hallucinations:** • **Haloperidol** 0.5-1.5mg nocte and prn t.d.s. PO/SC (usual maximum 5mg/24hrs) **Active management IV bisphosphonates (if corrected calcium >2.9 mmol/L or patient symptomatic)** •Rehydration with NaCl 0.9% 3-4L over 24 hours (slower rates of infusion if other comorbidities). If the patient is unwell and dehydrated, they will require IV rehydration with sodium chloride 0.9% before and after the IV bisphosphonate therapy. Rehydration is key as all hypercalcaemic pts are dehydrated to some extent and renal tubules need fluid in order to excrete calcium in urine. Mild hypercalcaemia just above upper limit of normal can be treated with rehydration alone. If in doubt, discuss with the Palliative Care Team. •Following rehydration, IV **pamidronate or zoledronate** • Additional guidance is available for community clinicians involved in the prescribing or monitoring of IV bisphosphonates from the Palliative Care Team. **Key points** • Hypercalcaemia can be a feature of worsening disease. Consider the appropriateness of further investigation and/or anticancer treatment (discuss with the oncologists), and arrange for the patient to be given appropriate information by a senior clinician • If prognosis is anticipated to be ≥6 months (unusual with malignant hypercalcaemia outside of the context of breast cancer), and ongoing IV bisphosphonate treatment is anticipated, recommend dental review within the first month (there is a risk of osteonecrosis of the jaw with long term bisphosphonate treatment). • Renal function should be routinely checked prior to treatment with all bisphosphonates. The recommended dose for zoledronate in patients with normal renal function is 4 mg. • Zoledronate in patients with severe renal impairment, i.e. creatinine clearance <30 mL/min, should only be used if benefit clearly outweighs risk • For patients with mild-to-moderate renal impairment receiving zoledronate for **bone prophylaxis**, the dose would be modified as per the summary product characteristics data sheet.

Denosumab 120mg sc can be considered in the community for the management of malignant hypercalcaemia where admission to acute hospital is not wanted or appropriate. It can be considered in patients with severe renal impairment (creatinine clearance <30ml/min), and with hypercalcaemia refractory to bisphosphonates. **This is only under the care of Specialist Palliative Care, Denosumab is a RED drug for this indication/dose.**

4.2 Spinal Cord Compression and Cauda Equina Syndrome

Recognition	The aim is to make the diagnosis *before significant neurological signs are obvious* • Known, or high risk of, bone metastases (e.g. prostate, breast or lung cancer) • Pain: back pain, neuropathic leg pain and/or radicular pain, new spinal nerve root pain (burning, numbness, shooting) • Motor changes: unsteadiness or leg weakness, especially if rapidly evolving (over days) or incongruent with general condition. Commonly described as 'feeling of heaviness of legs'. • Sensory alteration: sensory level • Sphincter disturbance: urinary retention, urinary or faecal incontinence, or altered anal tone (these are late features: do not be reassured by normal sphincter function)
Community Management	Give **dexamethasone** 16mg PO (or other available high dose corticosteroid) as soon as possible, with **omeprazole** 20mg o.d. PO. Thereafter, high dose dexamethasone (with PPI cover) should be continued at a dose of 8mg BD pending further clinical review If active treatment is appropriate: • arrange same day admission to an acute hospital for consideration of whole spine MRI • do not admit to a Palliative Care Unit or hospice – these do not have MRI or radiotherapy facilities If in doubt, discuss with the Palliative Care Team or the patient's oncology team.

4.3 Superior Vena Cava Obstruction (SVCO)

Cause	In patients with known malignancy: • Extrinsic venous compression (mediastinal malignancy, most commonly from lung cancer, lymphoma or breast cancer) • SVC thrombosis (e.g. secondary to indwelling lines)
Recognition	• Respiratory distress (breathlessness, cough, cyanosis) • Upper body venous congestion (distended neck veins, facial plethora) • Oedema of head, neck and upper limbs • Cerebral dysfunction (confusion, seizures, coma) • Other mediastinal symptoms (stridor, dysphagia, vocal cord paresis)
Community Management	Start **dexamethasone** 8mg BD PO (or other available high dose corticosteroid) with **omeprazole** 20mg o.d. PO. If the SVCO is a first presentation of a suspected malignancy, consider holding off steroids, as interpretation of subsequent biopsies may be compromised If active treatment is appropriate: • Sit the patient up, provide oxygen • arrange same day admission to an acute hospital • do not admit to a Palliative Care Unit or hospice – these do not have imaging, interventional radiology or radiotherapy facilities If in doubt, discuss with the Palliative Care Team

4.4 Bronchial Obstruction

Recognition	Stridor in the context of mediastinal malignancy (e.g. from lung cancer, lymphoma, or breast cancer) There may be other mediastinal symptoms (e.g. dysphagia, vocal cord paresis)
Community Management	**If the patient is imminently dying give emergency symptomatic relief**: • **Morphine sulfate** 10mg SC (or slow IV bolus over 2 minutes) or a dose based on 1/6 of a regularly taken 24-hour opioid dose *and* • **Midazolam**: Subcutaneous: 10mg SC and repeat after 5 minutes if not unconscious and imminently dying. Buccal: The buccal route can be used if not immediate access to injectable medication. Intravenous: This can be used in inpatient settings. Give 2mg increments every 1-2 minutes until unconscious using ampoules of 10mg in 5ml strength. Higher doses may be required if receiving regular benzodiazepines or patient is alcoholic. **If not imminently dying, consider:** • If appropriate to consider stenting or anti-cancer treatment, arrange urgent admission to an acute hospital • If the patient wishes to remain at home for end of life care, and understands the implications of not exploring active treatment, seek urgent advice from the Palliative Care Team • Oxygen • **Dexamethasone** 16mg one-off PO, SC or IV (followed by 8mg morning and lunchtime PO) and **omeprazole** 20mg o.d. PO. Monitor blood glucose (in view of high dose corticosteroids) • Symptomatic relief: O **morphine sulfate** liquid 2.5-5mg 4 hourly PO (or an additional dose based on 1/6 of a regularly taken 24-hour opioid dose) o **lorazepam** 0.5mg t.d.s. p.r.n. sublingual †if anxious or panicky • See section 1.1 for more advice on the symptomatic management of breathlessness

4.5 Malignant Ascites

Main options

- Anti-cancer treatment (e.g. endocrine therapy, systemic or intra-peritoneal chemotherapy)
- Drainage (paracentesis)
- Diuretics (**spironolactone** is the diuretic of choice)
- Symptomatic treatment (of nausea, breathlessness, and distension pain)

General approach

- Tense ascites: paracentesis. Subsequently, reduce rate of re-accumulation with diuretics
- Symptomatic, but not tense, ascites: consider diuretics (especially for ascites due to liver metastases: see text)
- Rapidly re-accumulating ascites: if diuretics and/or anti-cancer treatment are ineffective or not possible; consider insertion of tunnelled drain to enable drainage at home; optimise symptomatic treatment and discuss with the Palliative Care Team.

Paracentesis

Prior to the procedure, perform a Full Blood Count and Coagulation Screen looking for potentially increased bleeding/complications risk (e.g. INR>1.4, Platelets<50, neutrophils<1.5, hypotension, renal impairment). Review medication; stop warfarin and low molecular weight heparin 24 hours before the procedure. If on DOAC or antiplatelet medication, seek advice.

When taking informed consent:

- The aim of fluid removal is symptom control. The majority of patients experience improvement in breathlessness, nausea, vomiting and distension-pain
- The fluid will gradually re-accumulate. The rate varies and a tunnelled drain can be a helpful for symptom relief. Drainage can be repeated when this is not possible.
- The commonest adverse effect is short-lived discomfort afterwards, occurring in around a quarter of people. Patients should also be informed of unusual complications: bleeding; infection; visceral perforation; low blood pressure; ongoing leak post procedure (and cutaneous seeding, if ascites is due to abdominal mesothelioma)

The procedure is done by an appropriately trained clinician. Ultrasound evaluation is used if there is diagnostic uncertainty or the procedure is likely to be difficult (e.g. loculated ascites, previously complicated paracentesis, bowel distension).

After the procedure:

- Leave the drain unclamped for the first 5 litres. At this point, if the patient is well and systolic blood pressure >100mmHg, the drain can continue to be left unclamped for a further 5 litres and reviewed again. No more than 10L should be drained at a time. There is no evidence to support the clamping of drains but experience suggests that in frail patients with advanced cachexia or liver failure controlled drainage is sometimes required. Patients do therefore need to be observed.
- If the patient appears more unwell at any stage, check their blood pressure. If hypotensive, clamp the drain and consider administering fluids then review
- If day case, aim to remove the drain within 6 hours if possible, but otherwise after a maximum of 24-48 hours to reduce the risk of infection. It is not always appropriate to drain to dryness. Symptomatic benefit is usually seen after the first few litres are removed: further drainage brings little extra benefit (except, possibly, with breathlessness). Drainage must therefore be tailored to the clinical situation
- Aseptically flushing the drain is only indicated if significant amounts of fluid appear to remain on clinical examination
- If there is diagnostic uncertainty, send fluid for appropriate laboratory investigation (e.g. cytology to establish the presence of peritoneal carcinomatosis)

Diuretics for ascites

Who benefits from diuretics?

Malignant ascites is caused by peritoneal carcinomatosis and/or portal hypertension (due to massive hepatic metastases). Patients with massive hepatic metastases are the most likely to benefit from diuretics, though ascites from other causes does occasionally respond. Where anti-cancer treatment is ineffective or not possible, and ascites is recurring rapidly after paracentesis, a trial of diuretics is sometimes reasonable whatever the suspected mechanism.

Initiating treatment

If baseline U+E and blood pressure are acceptable, commence **spironolactone** 50mg - 100mg o.m. PO. Check that amiloride [or co-amilofruse] is not being received concurrently.

If serum potassium is towards the upper limit of normal:

- Commence **furosemide** 40mg o.m. PO concurrently (furosemide alone is ineffective for ascites). The combination reduces the risk of hyperkalaemia but increases the risk of dehydration
- Stop or reduce other potassium-sparing medication if possible (e.g. ACE inhibitors, ATII antagonists)
- Monitor U+E more frequently (e.g. every 2-4 days)

Monitoring

- Re-check U+E after 5-7 days (or sooner if original results were abnormal)
- After 7 days, if the response is inadequate, increase spironolactone to 100 mg b.d. PO and consider adding in furosemide 40-80mg o.m. PO (partly depending on the serum potassium level).
- Consider further increases after 5-7 days. Monitor U+E after each increment: if abnormal, decrease the dose. Doses up to furosemide 80 mg b.d. and spironolactone 200 mg b.d. are occasionally used, but require frequent biochemical and clinical monitoring
- If the patient's symptoms worsen, consider paracentesis and/or specialist referral

Maintenance

When diuretics are successful, patients should be maintained on the lowest doses possible, with urea and electrotypes (U&E) monitored regularly (weekly initially; progressively less frequently once dose and U+E results are stable). Ensure that it is clear who is taking responsibility for this monitoring and review.

Rapidly re-accumulating ascites refractory to diuretics

Discuss with oncology the option to **consider anti-cancer treatments**

Optimise symptomatic treatment:

- Metoclopramide for vomiting (see section 2.1)
- Opioids and other measures for breathlessness (see section 1.1)
- Analgesia and topical emollients (e.g. aqueous cream) for distension pain

Refer for Specialist-only interventions which may include:

Tunnelled peritoneal drainage catheter: this is placed by interventional radiologists as a 'day case' procedure. This allows regular drainage in the community setting without the need to wait for substantial volumes to accumulate.

Rarely considered:

Peritoneo-Venous Shunts

Intra-peritoneal corticosteroids†

Octreotide†: (limited evidence base): Doses between 150 and 500 micrograms/24 hours are reported to reduce ascitic accumulation in malignancy. Benefit is also reported for chylous ascites (in combination with fat-reduced diet).

4.6 Haemorrhage

URGENT management of major haemorrhage in the imminently dying

(If aim is to resuscitate - follow advanced life support guidelines)

Health professionals with experience of major haemorrhage at the end of life emphasise:

- Staying with the patient to support them and their family
- Using dark-coloured towels/sheets to camouflage blood
- That sedative medication often has little role because death frequently occurs before it can be administered.

If circumstances allow sedation to be used, give **midazolam,** route of administration will be determined by place of care.

Consider prescribing midazolam prn both by injection and for buccal use, in the event of major haemorrhage.

In the community: give midazolam 10mg subcutaneously or buccally and repeat after 5-10 mins if required.

When IV route is appropriate, give midazolam in 2mg increments every 1-2 minutes until unconscious. Higher doses may be required if receiving regular benzodiazepine usage or patient is alcoholic.

Death from major haemorrhage is distressing for all involved:

- Arrange appropriate support and follow up for relatives (via the Palliative Care Team or chaplaincy)
- Consider the need for debriefing of the health care team. As with any other distressing event, also allow time to reflect yourself. Consider discussing with a colleague

Management of non-major haemorrhage

Treat any underlying bleeding diathesis:

- Correction of coagulopathies or platelet disorders (e.g**. vitamin K** [**phytomenadione**], fresh frozen plasma, platelet transfusion) - discuss with a haematologist
- Reversal/discontinuation of anticoagulation or antiplatelet agents (e.g. **vitamin K [phytomenadione]** - discuss with a haematologist or clinical pharmacist)

Local measures depend on site and cause (if in doubt, discuss with the Palliative Care Team):

- Specific treatment (radiotherapy; chemotherapy; laser therapy; cryotherapy; embolisation)
- Local pressure and dressings [e.g. **Kaltostat**]. If insufficient, soak dressings in **adrenaline†** 1:1000 solution or tranexamic acid 500mg injection solution†.
- Nose bleeds: use ribbon gauze soaked in **adrenaline†** 1:10 000). If persistent, consider **lidocaine 5% with phenylephrine 0.5% topical solution†** (seek advice from an ENT surgeon)
- Oral cavity: **tranexamic acid (5%) mouthwash#** 10ml q.d.s. or 500mg of injection solution†.

Systemic haemostatic agents

- **Tranexamic acid** 500mg-1g b.d.-q.d.s. PO. Generally avoided with urological bleeding: risk of ureteric obstruction in upper renal tract bleeding and of clot retention in any renal tract bleeding.

4.7 Seizures

Recognition	Seizures (generalised or partial) occur in 10 to 15% of palliative care patients most often due to primary or secondary brain tumours, cerebrovascular disease, epilepsy or biochemical abnormalities (e.g. hyponatraemia, hypercalcaemia, uraemia). Seizures are frightening to patients and their families. Educate and address any concerns, such as desired management of further seizures, management of risk of seizure recurrence if stopping anti-epileptic drugs (AEDs), for example due to swallowing difficulties. All patients should have a personalised - Seizure Advance care plan., with a prescription for midazolam or diazepam, and training in how to administer them
Community Management	***New –*** Although first seizures are not usually treated, for those with intracranial tumours AEDs (anti-epileptic drugs) are normally commenced following first seizure. There is no evidence of benefit of prophylactic AEDs (before any seizure occurs). Always consider*:* • commencing, or reviewing dose corticosteroid in those with intracranial tumour and seizures • Check bloods (hyponatraemia, hypoglycaemia, hypomagnesaemia, hypocalcaemia, markers of infection) and obtain blood cultures if appropriate • Levetiracetam and lamotrigine do not significantly induce enzymes and will have minimal interactions with other medications such as chemotherapy. • Monitor effect of medication which can lower seizure threshold, such as haloperidol or levomepromazine; review need and dose ***Chronic-*** **Partial or secondary generalised seizures**: sodium valproate, carbamazepine, lamotrigine or Levetiracetam. **Primary generalised seizures** (unlikely in palliative setting): sodium valproate or lamotrigine. In palliative setting for those patients not on antiepileptic medication: **First line - Levetiracetam (Keppra)** • Loading dose of 500mg – 1gram PO • Starting Oral Dose: 250-500mg BD PO. Usual effective dose 500mg bd. • Dose Titration: Increased in 250mg BD-500mg bd steps every 14 days if required to a maximum dose of 1.5g BD. • PO and IV doses are identical. • If fits observed repeat loading dose 500mg-1gram and increase regular dose by 250mg bd. • Requires dose adjustment in renal impairment (e.g. in ESRF, start with 250mg BD, maximum dose 500mg BD) • Do not stop suddenly as may cause rebound seizures, dose reduce (see PCF7) • Common side effects: fatigue, drowsiness, ataxia (see PCF 67). Behavioural disturbance may occur in 3-4%. Antiepileptics have been associated with suicidal ideation: advise patient to report mood or thought disturbance. **Dexamethasone can be added:** If cerebral metastases are likely consider adding/increasing dexamethasone, with blood glucose monitoring (once daily) and PPI cover • Give Dexamethasone 8mg/6.6mg b.d. PO/Subcutaneous • Or consider increase of baseline dexamethasone

	NB increases in steroids can affect and reduce levels of some antiepileptics, leading to an exacerbation of seizure activity as a result. ***Status Epilepticus –a sample advance care plan includes prescription for:*** **Either** **Buccal midazolam prn** (Buccolam™; off-label for adults, but may be easier to administer for some patients than rectal diazepam) • Action prolonged by CYP 3A4 inhibitors (e.g. cimetidine, erythromycin) and renal impairment • Cautions and contra-indications: as for parenteral midazolam • Give 2ml (10mg) from the pre-loaded oral syringe in the box between the lower gum and the cheek. If feasible, divide the volume, giving half to each side of the mouth Or **Rectal diazepam prn** (Usual dose 10mg; 0.5mg/Kg up to a maximum dose of 30mg p.r.n. PR) ***End of life- Loss of oral route prophylactic medication*** **Midazolam** is generally the drug of choice because it's beneficial for concurrent agitation, and is compatible with other drugs given via syringe pump. • If prn midazolam has controlled seizures, commence CSCI (continuous subcutaneous infusion) midazolam 20-30mg/ 24 hrs • Where escalation to phenobarbital required to control seizures, commence regular CSCI phenobarbital 200 to 400mg/24hrs (lower doses than those used for terminal agitation may be sufficient but adjust dose according to prior midazolam and phenobarbital requirements) **Levetiracetam (Keppra)** SC at end of life should only be used when there is a high risk of seizures with discontinuation of oral Keppra, and when it is felt midazolam alone is unlikely to prevent fits, e.g. patients on 2-3 different antiepileptics, patients with recent seizures or when oral route is lost earlier in palliative illness and it is appropriate to avoid sedative effects of midazolam. Starting Subcutaneous dose: • 1g s/c via syringe driver over 24 hours diluted in water for injection. Maximum Levetiracetam 2g per CSCI over 24 hours due to syringe capacity. Doses of up to 3g would require 50ml syringe to be used (fill volume 34ml) • Switching from Oral or IV to Subcutaneous administration: 1 to 1 ratio • Requires dose adjustment in Renal Impairment

5 Drug Handling in Renal Insufficiency

Renal failure either alone or a comorbidity is common in patients in the last year of life. Drugs may be nephrotoxic or may be renally excreted and liable to accumulate either the parent drug or it's metabolites in patients whose renal clearance is impaired.

Classification of renal insufficiency

CKD	eGFR (ml/min/1.73m^2)	Description	Common Symptoms
1	>90	Normal kidney function but urine findings, genetic factors or structural abnormalities point to kidney disease	None – normal renal function
2	60 – 89	Reduced kidney function with some urinary, genetic or structural abnormalities	None
3	30 – 59	Moderately reduced kidney function	May start to see anaemia, fatigue and muscle cramps at lower end of function. This may also impair excretion of drugs.
4	15 – 29	Severely reduced kidney function	In addition: Anorexia, nausea, insomnia, neuropathy, gout
5	<15	End stage renal disease.	In addition: Itch, headache, cognitive impairment, death

Calculation of GFR

MDRD eGFR (Modification of Diet in Renal Disease Study equation). is the standard adopted in England for estimation of renal function. This is more accurate for estimating renal function but is expressed as a function of surface area, assuming all patients have a surface area of 1.73m^2. This makes it unsuitable for calculation of drug clearance where the Cockcroft-Gault equation should be used. Caution is needed where patients are cachexic; where patients are obese or oedematous Ideal Body Weight (IBW) should be used.

Cockcroft-Gault Equation

$$\text{Creatinine Clearance (GFR)} = \frac{F \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum creatinine (mmol/l)}}$$

F = 1.23 for males or 1.04 for females

IBW

Males 50kg + 2.3kg for each inch over 5 feet in height
Females 45.5kg + 2.3kg for each inch over 5 feet

Nephrotoxic Drugs

Drugs causing prerenal damage

- NSAIDs – even short courses can reduce renal perfusion and precipitate AKI
- ACE Inhibitors – especially if renal perfusion already compromised and in renal artery stenosis
- Combining NSAIDs and ACE Inhibitors can precipitate renal damage
- AKI can be provoked by drugs causing excessive GI fluid loss or volume depletion.

Drugs causing intrarenal damage

Intrarenal damage may result in a direct toxic effect on the kidneys or hypersensitivity reactions. Most drugs that cause damage within the kidneys do so as a result of hypersensitivity reactions, which involve either glomerular or interstitial damage.

- Penicillins
- Sulphonamides
- Gold
- Rifampicin
- Captopril
- Phenytoin
- Cephalosporins
- Diuretics

Aminoglycosides, Amphoteracin and Ciclosporine may cause direct renal toxicity to tubules (acute tubular necrosis)

Drugs causing postrenal damage (urinary tract obstruction)

- Anticholinergics (eg, tricyclic antidepressants), and alcohol may cause urinary tract obstruction due to retention of urine in the bladder
- High-dose sulfonamides, acetazolamide or methotrexate may cause crystalluria and could therefore cause urinary tract obstruction.

Other nephrotoxic drugs

- Analgesics:
    - NSAIDs may cause AKI due to hypoperfusion and interstitial nephritis, as well as analgesic nephropathy (chronic interstitial nephritis and papillary necrosis).
    - Analgesic nephropathy has been most commonly seen with combination analgesic products that contain aspirin and/or paracetamol.
    - Discontinuation of the drugs often results in stabilisation or even improvement in renal function but continued use leads to further renal damage.
- Lithium: serum levels of lithium consistently above the therapeutic range have been associated with development of a nephrogenic diabetes insipidus.

Effect of Renal Impairment of Commonly Used Palliative Care Drugs

In all patients it is important to start drugs at the lowest dose and titrate carefully monitoring for adverse effects. For patient in the last days of life symptom control considerations will take precedence over avoidance of nephrotoxicity. Renal impairment categories as per Renal Drugs Handbook.

Analgesics: For strong opioids careful titration to effective dose and monitoring of adverse effects is more useful than blanket dose reductions.

Drug	**Renal impairment**			**Dialysis Clearance**		**Comments**
	Mild GFR 20 – 50ml/min	***Moderate GFR 10 – 20ml/min***	***Severe GFR <10ml/min***	***HD***	***PD***	
Paracetamol (oral)	Normal starting dose	Normal 6 hourly dosing	6 – 8 hourly dosing	Y	N	Generally safe. Reduce dose for low body weight
NSAIDs (Naproxen or Ibuprofen)	Use cautiously	AVOID if possible - titrate from lowest dose if unavoidable	AVOID if possible	N	N	Nephrotoxic and increased bleeding risk. Careful assessment of risks and benefits
Codeine	Normal starting dose - monitor	Reduce dose and titrate slowly	AVOID if possible	N	N	Metabolites accumulate.
Tramadol	Normal starting dose	50 – 100mg 8 hourly titrate as needed	50mg 8 hourly and titrate carefully	Y	not known	50mg 12 hourly for dialysis patients. High risk of delirium
Morphine	75% Normal dose titrate with care	50% normal dose	AVOID if possible	Y	N	. Metabolites can accumulate
Oxycodone	75% - 100% normal starting dose	50 -75% normal dose	Avoid or use low dose	not known	not known	Can accumulate
Fentanyl (TD)	Normal starting dose	75% normal dose	50% normal dose	N	N	May accumulate in long term use – no active or toxic metabolites
Alfentanil (s/c infusion)	Normal dose	Normal dose	Normal dose	N	N	Short acting – given by continuous infusion. SEEK SPECIALIST ADVICE
Methadone	normal	normal	50% - 75% normal	N	N	Seek specialist advice re switch and titration

Antiemetics

Drug	Renal impairment			Dialysis		Comments
	Mild GFR 20 – 50ml/min	***Moderate GFR 10 – 20ml/min***	***Severe GFR <10ml/min***	**HD**	**PD**	
Metoclopramide	Normal dosing	Normal dosing	Normal dosing	Y	N	
Domperidone	Normal dosing	Normal dosing	Start low dose and titrate	N	N	
Cyclizine	Normal dosing	Normal dosing	Normal dosing	not known	not known	
Levomepromazine	Normal dosing	Normal dosing	Start with low dose and titrate	not known	not known	Increased risk of sedation
Haloperidol	Normal dosing	Normal dosing	Start with low dose and titrate	N	N	
Ondansetron	Normal dosing	Normal dosing	Normal dosing	Unlikely	N	

Benzodiazepines

Drug	Renal impairment			Dialysis		Comments
	Mild GFR 20 – 50ml/min	***Moderate GFR 10 – 20ml/min***	***Severe GFR <10ml/min***	**HD**	**PD**	
Clonazepam	Normal dosing	Normal dosing	Small doses titrated to response	N	N	
Lorazepam	Normal dosing	Normal dosing	Small doses titrated to response	N	N	Monitor use and effect carefully
Midazolam	Normal dosing	Normal dosing	Small doses titrated to response	N	N	Use cautiously as infusion if severe renal impairment
Temazepam	Normal dosing	Normal dosing – start low doses	Normal dosing – start low doses	N	N	
Diazepam	Normal dosing	Small doses titrated to response	Small doses titrated to response	N	N	Accumulates with long term use

Adjuvants

Drug	Renal impairment			Dialysis		Comments
	Mild GFR 20 – 50ml/min	***Moderate GFR 10 – 20ml/min***	***Severe GFR <10ml/min***	**HD**	**PD**	
Gabapentin	300mg nocte to max 300mg tds	100mg nocte to 300mg bd	100mg alternate nights to max 300mg nocte	Y	Y	Titrate according to response every 2 – 3 days
Pregabalin	75mg daily titrated to 150mg bd	25mg – 50mg daily – titrated to 150mg daily	25mg daily titrated to 75mg daily	Y	Y	Doses may be divided.
Amitriptyline	Normal dosing	Normal dosing	Normal dosing	N	N	10mg start and titrate slowly
Duloxetine	Use with caution if EGFR <30	Not recommended	Not recommended	N	N	Use with caution if eGFR <30

Antidepressants

Drug	Renal impairment			Dialysis		Comments
	Mild GFR 20 – 50ml/min	***Moderate GFR 10 – 20ml/min***	***Severe GFR <10ml/min***	**HD**	**PD**	
Citalopram	Normal dosing	Normal dosing	Normal dosing - CAUTION	N	UNLIKELY	
Fluoxetine	Normal dosing	Normal dosing	Low dose or alternate days	N	N	
Sertraline	Normal dosing	Normal dosing	Normal dosing	N	N	
Mirtazipine	Normal dosing	Start low and titrate	Start low and titrate	N	N	

Others

Drug	Renal impairment			Dialysis		Comments
	Mild GFR 20 – 50ml/min	*Moderate GFR 10 – 20ml/min*	*Severe GFR <10ml/min*	HD	PD	
Hyoscine Butylbromide	Dose as normal	Dose as normal	Dose as normal	Y	Y	
Glycopyrronium	Dose as normal	Start with 200mcg and titrate	Start with 200mcg and titrate			Titrate against effect
Fluconazole	50 – 100% Normal Dose	50 – 100% Normal Dose	50% Normal Dose	Y	Y	
Baclofen	Start 5mg tds	Start 5mg bd	AVOID	Y	Unknown	Titrate to response avoid in END STAGE RENAL FAILURE

6. Drug Handling in Hepatic Impairment

Caution is recommended when prescribing any drug when there is impaired hepatic function. Many drugs are metabolised in the liver and the half life will be significantly prolonged in liver impairment.

1. Prescribing Principles:

Prescribing principles include:

- use lower starting doses
- increased dose interval (i.e. reduce frequency of administration)
- consider switching to immediate release preparations of opioids in preference to modified release due to prolonged half life.
- regular clinical review
- individualised slow dose titration aiming for the lowest effective dose
- monitor for both early and late onset toxicity
- ensure the patient does not become constipated (may increase encephalopathy)
- sedation may increase encephalopathy
- reduce polypharmacy
- regular blood monitoring of synthetic hepatic function (using Child-Pugh scoring) if clinically appropriate, to guide prescribing.

This is a summary of recommendations, detailed advice in hepatic impairment chapter in PCF6.

Hepatic impairment can be calculated as mild, moderate or severe based on the liver function, severity of encephalopathy and degree of ascites present.

Mild impairment = Child Pugh A = score of 5-6
Moderate impairment = Child Pugh B = score of 7-9
Severe impairment = Child Pugh C = score of 10-15 Child-Pugh Score

	1	**2**	**3**
Bilirubin (micromol/L)	<34	34-51	>51
Albumin (g/l)	>35	30-35	<30
PT (s prolonged) Or INR	<4 <1.7	4-6 1.7-2.3	>6 >2.3
Encephalopathy	None	Grade 1-2 (subtle)	Grade 3-4 (drowsy/ deep coma)
Ascites	None	mild	marked

The severity of **Hepatic Encephalopathy** is graded according to the West Haven Criteria:
Grade 1: Behavioural change, minimal change in level of consciousness
Grade 2: Gross disorientation, drowsiness, possibly asterixis, inappropriate behaviour
Grade 3: Marked confusion, incoherent speech, sleeping most of the day, rousable to vocal stimuli
Grade 4: Comatose, unresponsive to pain

6.1 Opioids in Moderate (Child- Pugh B) and Severe (Child-Pugh C) Hepatic Impairment

- Use IR (immediate release) preparations and stop MR (modified release) opioids due to large increases in half life.
- Opioid doses need reviewing, the dose may need to be decreased and the dosing interval increased as liver failure worsens.

Except for morphine and buprenorphine, the major metabolic pathway for most opioids is oxidation. This is reduced in patients with cirrhosis resulting in increased oral bio-availability. In general, all opioids accumulate in liver failure, increase the risk of hepatic encephalopathy and increase the incidence of side effects

First Line	Use with caution	Avoid
Fentanyl TD patches - Fentanyl not metabolised in liver	Morphine Only use IR (stop MR), Decrease frequency IR to 6 – 8 hourly. Increase in half life in severe impairment by up to 100%.	Codeine- risk profound respiratory depression
	Buprenorphine	Tramadol
	Alfentanil - lower doses may be sufficient	Dihydrocodeine -increased bioavailability due to reduced first pass metabolism
		Oxycodone Only use IR (stop MR) In severe impairment half life can increase by up to 400%. If unavoidable decrease frequency of IR products to 8 hourly
		Methadone – very prolonged half-life, toxicity in hypoalbuminaemia (highly protein bound), risk of fatal QTc prolongation

6.2 Non-Opioid Analgesics in severe (Child-Pugh C) Hepatic Impairment

First line	Use with caution	Avoid
Paracetamol – half life can double start with 500mg 8 hourly to an absolute max of 1g 8 hourly orally	Ibuprofen – avoid in cholestasis	Celecoxib
	Diclofenac – dose unchanged – LFTs 1 – 2 monthly to screen for unpredictable hepatotoxicity	IV paracetamol

7 Benzodiazepines in severe (Child-Pugh C) Hepatic Impairment

Benzodiazepines have been implicated as common precipitants of come in patients with severe hepatic impairment even in usual doses

First line	Use with Caution	Avoid
Lorazepam – no dose adjustment needed	Midazolam	Clonazepam
	Zopiclone	Diazepam

2.4 Anti-emetics in severe (Child-Pugh C) Hepatic Impairment

First Line	Use with caution	Avoid
Cyclizine – reduce dose	Domperidone start 5mg bd – max 10mg tds	
	Metoclopramide start 5mg bd – max 10mg tds	
	Ondansetron max 8mg/24 hours oral/subcutaneous	
	Haloperidol	
	Levomepromazine	
	Prochlorperazine	

2.2 Anti-epileptics in severe (Child-Pugh C) Hepatic Impairment

First Line	Use with Caution	Avoid
Levetiracetam	Sodium Valproate	Clonazepam
	Pregabalin	Phenobarbital
	Gabapentin	Phenytoin – adjust measured levels for low albumin
	Carbamazepine	
	Oxcarbazine	

Phenytoin levels can be corrected for albumin and creatinine using the PCF 7 or the following website: https://www.mdcalc.com/phenytoin-dilantin-correction-albumin-renal-failure

Just-in-Case Medication Summary

The prescription should include the four medications that might be required for end-of-life symptom control, plus diluent.

Levomepromazine OR Haloperidol should be prescribed

Drug and indication	Dose	Concentration	Supply
Morphine Sulfate *Analgesia: Pain, breathlessness*	2mg - 5mg (or 1/6 of total daily subcutaneous dose equivalent if not opioid naïve) up to hourly	10mg/1ml	1 x 10 (ten)
Midazolam *Anxiolytic, sedative: anxiety/distress/myoclonus/fitting*	2mg -5mg up to 2 hourly	10mg/2ml	1 x 10 (ten)
Levomepromazine ** *Anti-emetic/antipsychotic nausea, delirium, agitation*	6.25mg up to 12 hourly	25mg/1ml	1 x 10
Hyoscine Butylbromide *Anti-secretory: respiratory secretions*	20mg up to 4 hourly	20mg/1ml	1 x10
Haloperidol *Anti-psychotic/emetic: delirium, agitation, nausea*	0.5 - 1.5mg up to 4 hourly	5mg/ml	1 x 10
Water for injection	as diluent	10ml	1 x 10

Medicines in syringe driver must be individualised to the symptoms exhibited by the patient and assessed daily.

Calculating starting dose for syringe pump 24 hour continuous subcutaneous infusion

Drug	Calculation of dose	Incremental increases
Morphine Sulfate	50% of total daily oral dose of morphine	Guided by use of PRN medication, and clinical assessment. If more than 30% of previous total daily dose reassess carefully.
Midazolam	Usual starting dose 5mg – 10mg in 24 hours; 20 – 30mg if for prevention of fits	Guided by use of PRN medication and clinical assessment. Titrate in increments of no more than 50%
Hyoscine Butylbromide	Usual starting dose 40mg	Guided by use of PRN medication and clinical assessment. Max 120mg/24hours
Levomepromazine	Usual starting dose 6.25mg (nausea)	6.25mg increments to max 50mg for nausea. Higher doses may be required for severe agitation -
Haloperidol	Usual starting dose 1.5mg	0.5mg increments max 5mg for nausea.

- ** Levomepromazine may also be used for agitation up to 2 hourly at 6.25mg – 12.5mg
- Levomepromazine OR Haloperidol should be prescribed
- PRN doses - opioids must state dose interval and it is desirable to state maximum number of doses before reassessment. (eg. If 3 doses in 4 hours seek medical advice)

Managing your pain with Morphine

Guidance written for people with advanced progressive disease

What is oral morphine?

This is a drug from a group called strong opioids. They are prescribed when pain is severe and is not helped by other medicines. Morphine is the most commonly used member of this group. If morphine is not suitable for you, your healthcare professional can advise on alternatives.

Other Names Include:
Oramorph Liquid (immediate release morphine)
Sevredol tablets (immediate release morphine)

Zomorph capsules (long acting morphine 12 hourly)
MST tablets (long acting morphine 12 hourly)
Morphgesic SR tablets (long acting morphine 12 hourly)
MXL capsules (long acting morphine 24 hourly)

What is morphine used for?

- Morphine is used to treat moderate to severe pain, and to help with breathlessness. It may be used for different sorts of severe pain, due to cancer, heart disease or other illnesses. Morphine is used for pain which can happen at different stages in the course of a disease, and it does not necessarily mean you are close to the end of your life.

It is used when pain is severe and will help you to continue to have as comfortable a life as possible. You will be able to take morphine for as long as you need to – the effects do not wear off over time and the dose can be increased if needed.

How should I take morphine?

Immediate release morphine starts to work after about 30 minutes and last for up to four hours. You may be prescribed this in regular doses while we work out how much pain killer is right for you, and then you may change to a long acting tablet or capsule to control background pain.

Immediate acting morphine can also be taken for any breakthrough pain you have, on top of your regular background dose. If you still have pain an hour after taking a dose of your immediate acting opioid, you may take another dose. If you need to take more than 2 or 3 extra doses each day, tell your doctor or nurse.

Long acting preparations are taken every 12 hours to control pain. The capsule or tablet will release a small amount of painkiller into your system all the time. It is important to get into a routine of taking the morning dose at a time that fits with your normal time to wake up and the evening dose 12 hours later.
MXL capsules are designed to be taken every 24 hours These should be taken at the same time each day.

What do I do if I forget to take a dose?

Take the dose as soon as you remember. Do not take a double dose to make up for the missed one. If you are sick and bring up the medicine, repeat the dose as soon as you feel better.

What side effects are there from taking morphine?

- **Sleepiness**

This is common when you first start to take morphine or when the dose is increased. It should improve after a few days. If sleepiness persists beyond a few days let your doctor or nurse know.

- **Constipation**

This is a very common side effect. It is important to drink plenty of fluids and to take a laxative regularly to prevent constipation. The dose of laxative can be adjusted to make sure you can pass a soft motion regularly.

- **Nausea (Sickness)**

This is common when you first start to take morphine. This usually improves in a few days. Your doctor may need to give you an anti-sickness medication for a few days until this improves.

How will I know if morphine is not going to work for all of my pain?

- You may still have pain despite taking bigger doses of morphine, and may feel unwell in one or more of the following ways:
- Sleepier than usual
- Feeling sick more of the time
- Feeling restless or twitchy
- Having bad dreams, or hallucinations
- Don't worry if this happens. Tell your doctor or nurse, who may reduce that amount of strong opioid you are taking and suggest some other treatments to help the pain.

Will I become addicted to morphine and be unable to stop taking it?

NO – if you no longer to need to take these painkillers your doctor will reduce the dose gradually.

Will morphine always relieve my pain completely?

- Although morphine is very good pain killer it is not helpful for all types of pain. You may need other treatments to help types of pain which are not helped so much with opioids.

• What should I do if I have pain in between my regular doses of morphine?

- If the pain is mild paracetamol may help. You should not take any more than 8 paracetamol tablets in 24 hours and should have at least 4 hours between paracetamol doses. If the pain is more severe, you should take a dose of your immediate acting morphine.
- If you need more than 2 or 3 doses of extra morphine each day, tell your doctor or nurse.
- Some people find doing certain things like having a bath or a dressing change bring on the pain. Your doctor or nurse may suggest that you take a dose of your immediate acting pain killer about half an hour before doing anything that brings on the pain.

• Can I Drive?

- You may be able to drive if your dose has stayed the same for a while and you do not feel sleepy, but you must discuss this with your doctor. You should read the patient information leaflet "Strong pain killers and driving".

• Can I drink alcohol?

- Many people enjoy a small glass of wine or spirits, which help them feel better and improve their appetite. It is best to avoid more than this as you may become too drowsy.

Safe storage of Medicines

- Store your medicines in the labelled box from the pharmacy and only remove the dose you need each time. Keep them out of sight and reach of children. Medicines should be stored in a dry, clean place with no big fluctuations in temperature.
- Always return any unused medicines to your pharmacist, who can dispose of them safely. It is useful to do this anytime your medication is changed, so that you only have the medications you are taking currently to avoid getting confused.

Follow up and further prescribing

Your GP and district nurse will usually be the healthcare professionals leading on your care at home. Your GP will continue to provide prescriptions and assess your symptoms. The primary care team can contact the local palliative care team or your hospice/hospital consultant if they have any questions.

You may have a Macmillan Nurse/CNS who will give you and your primary healthcare team support and advice.

You could fill in the names and numbers here for future reference.

GP: Name ……Number……:

District Nurse: Name……Number…….

Macmillan Nurse/Community Palliative Care Nurse:

Name……...Number…….

Who to contact out-of-hours, particularly during initiation of treatment:

GP out of hours Number…….

Community Palliative Care Team weekend number…….

My long acting strong opioid is called…….

If I have pain in between my doses of long acting medication, I can take…….

Long Acting Strong opioid

	Date	Dose
1		
2		
3		
4		
5		

Immediate Acting Opioid

	Date	Dose
1		
2		
3		
4		
5		

Managing your pain with Oxycodone

Guidance written for people with advanced progressive disease

What is oral oxycodone?

This is a drug from a group called strong opioids. They are prescribed when pain is severe and is not helped by other medicines. Oxycodone is one member of this group. If oxycodone is not suitable for you, your healthcare professional can advise on alternatives.

Other Names Include:
Oxynorm Liquid (immediate release oxycodone)
Oxynorm capsules (immediate release oxycodone)

Oxycontin tablets (long acting oxycodone 12 hours)
Longtec tablets (long acting oxycodone 12 hourly)

What is oxycodone used for?

- Oxycodone is used to treat moderate to severe pain, and to help with breathlessness. It may be used for different sorts of severe pain, due to cancer, heart disease or other illnesses. Oxycodone is used for pain which can happen at different stages in the course of a disease, and it does not necessarily mean you are close to the end of your life.

It is used when pain is severe and will help you to continue to have as comfortable a life as possible. You will be able to take oxycodone for as long as you need to – the effects do not wear off over time and the dose can be increased if needed.

How should I take oxycodone?

Immediate release oxycodone starts to work after about 30 minutes and last for up to four hours. You may be prescribed this in regular doses while we work out how much pain killer is right for you, and then you may change to a long acting tablet or capsule to control background pain.

Immediate acting oxycodone can also be taken for any breakthrough pain you have, on top of your regular background dose. If you still have pain an hour after taking a dose of your immediate acting opioid, you may take another dose. If you need to take more than 2 or 3 extra doses each day, tell your doctor or nurse.

Long acting preparations are taken every 12 hours to control pain. The tablet will release a small amount of painkiller into your system all the time. It is important to get into a routine of taking the morning dose at a time that fits with your normal time to wake up and the evening dose 12 hours later.

What do I do if I forget to take a dose?

Take the dose as soon as you remember. Do not take a double dose to make up for the missed one. If you are sick and bring up the medicine, repeat the dose as soon as you feel better.

What side effects are there from taking oxycodone?

- **Sleepiness**

This is common when you first start to take oxycodone or when the dose is increased. It should improve after a few days. If sleepiness persists beyond a few days let your doctor or nurse know.

- **Constipation**

This is a very common side effect. It is important to drink plenty of fluids and to take a laxative regularly to prevent constipation. The dose of laxative can be adjusted to make sure you can pass a soft motion regularly.

- **Nausea (Sickness)**

This is common when you first start to take oxycodone. This usually improves in a few days. Your doctor may need to give you an anti-sickness medication for a few days until this improves.

How will I know if oxycodone is not going to work for all of my pain?

- You may still have pain despite taking bigger doses of oxycodone, and may feel unwell in one or more of the following ways:
- Sleepier than usual
- Feeling sick more of the time
- Feeling restless or twitchy
- Having bad dreams, or hallucinations
- Don't worry if this happens. Tell your doctor or nurse, who may reduce that amount of strong opioid you are taking and suggest some other treatments to help the pain.

Will I become addicted to oxycodone and be unable to stop taking it?

NO – if you no longer to need to take these painkillers your doctor will reduce the dose gradually.

Will oxycodone always relieve my pain completely?

- Although oxycodone is very good pain killer it is not helpful for all types of pain. You may need other treatments to help types of pain which are not helped so much with opioids.

What should I do if I have pain in between my regular doses of oxycodone?

- If the pain is mild paracetamol may help. You should not take any more than 8 paracetamol tablets in 24 hours and should have at least 4 hours between paracetamol doses. If the pain is more severe, you should take a dose of your immediate acting oxycodone.
- If you need more than 2 or 3 doses of extra oxycodone each day, tell your doctor or nurse.
- Some people find doing certain things like having a bath or a dressing change bring on the pain. Your doctor or nurse may suggest that you take a dose of your immediate acting pain killer about half an hour before doing anything that brings on the pain.

Can I Drive?

- You may be able to drive if your dose has stayed the same for a while and you do not feel sleepy, but you must discuss this with your doctor. You should read the patient information leaflet "Strong pain killers and driving".

Can I drink alcohol?

- Many people enjoy a small glass of wine or spirits, which help them feel better and improve their appetite. It is best to avoid more than this as you may become too drowsy.

Safe storage of Medicines

- Store your medicines in the labelled box from the pharmacy and only remove the dose you need each time. Keep them out of sight and reach of children. Medicines should be stored in a dry, clean place with no big fluctuations in temperature.

- Always return any unused medicines to your pharmacist, who can dispose of them safely. It is useful to do this anytime your medication is changed, so that you only have the medications you are taking currently to avoid getting confused.

Follow up and further prescribing

Your GP and district nurse will usually be the healthcare professionals leading on your care at home. Your GP will continue to provide prescriptions and assess your symptoms. The primary care team can contact the local palliative care team or your hospice/hospital consultant if they have any questions.

You may have a Macmillan Nurse/CNS who will give you and your primary healthcare team support and advice.

You could fill in the names and numbers here for future reference.

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District Nurse: Name……Number…….

Macmillan Nurse/Community Palliative Care Nurse:

Name……...Number…….

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GP out of hours Number…….

Community Palliative Care Team weekend number…….

My long acting strong opioid is called…….

If I have pain in between my doses of long acting medication, I can take……

Long Acting Strong opioid

	Date	Dose
1		
2		
3		
4		

Immediate Acting Opioid

	Date	Dose
1		
2		
3		
4		
5		

Managing your pain with Fentanyl Patches

- Guidance written for people with advanced progressive disease

What are Fentanyl Patches?

Fentanyl is a medicine from a group of medicines called strong opioids; others in this group include morphine and oxycodone. Fentanyl is different because it can be given through the skin in the form of a patch. Patches are used to control on-going pain. Patches are not used to control pain which only lasts a short time "breakthrough pain" – you will be given another quick acting painkiller to use for breakthrough pain.

Other Names Include:
Durogesic D trans, Fencino, Matrifen, Tilofyl.

What are Fentanyl Patches used for?

Fentanyl Patches are used to treat moderate to severe pain. They may be used for different sorts of severe pain, due to cancer, heart disease or other illnesses.
Fentanyl Patches are used for pain which can happen at different stages in the course of a disease, and it does not necessarily mean you are close to the end of your life.

They are used when pain is severe and will help you to continue to have as comfortable a life as possible. You will be able to use fentanyl patches for as long as you need to – the effects do not wear off over time and the dose can be increased if needed.

How should I take them?

- Fentanyl patches release the painkiller into your body at a constant rate for 3 days.
- The patch should be changed at around the same time of day. It is helpful to mark on your calendar the day you need to change your patch.
- If you are using more than one patch to give the correct dose all the patches should be changed at the same time.

1. Take the old patch off, fold it in half, sticky sides together and put it back in its original pouch. The used patch can then be put in the bin with your household rubbish.

2. Wash your hands. Choose a place on the upper body or upper arm. The skin should not have any cuts, scars or spots and should not be too hairy. Clean the skin with water only and make sure it is cool, and completely dry and should not have any cream on the area

3. Tear open the pouch of the new patch. Peel the plastic backing off. Stick the patch onto the clean area of skin. Press it on firmly. Wash your hands. Do not stick the patch on the same place twice in a row.

The leaflet in the packaging contains lots of useful information about how to use the patches: you should read this carefully.

The first patch will take a little time to build up to full strength, so you may need to take your breakthrough medicine to help with the pain. The pain relief will be continuous after the first 3 days. You will still have some breakthrough medication to take in case you have any additional pain. This might be in the form of morphine liquid or tablets or oxycodone liquid or capsules.

What do I do if I forget to change my patch?

If you forget, change your patch as soon as you remember and make a note of the day and time. Change the patch again after **3 days (72 hours)** as usual.
Do not take a double dose to make up for the missed one. If the patch falls off, replace it with a new one as soon as you notice. If the patch has been off for some time you may notice that your pain is worse and you need to use your breakthrough medication.

What side effects are there from using fentanyl patches?

- **Sleepiness**

This is common when you first start to use fentanyl patches or when the dose is increased. It should improve after a few days. If sleepiness persists beyond a few days let your doctor or nurse know.

- **Constipation**

This is a very common side effect. It is important to drink plenty of fluids and to take a laxative regularly to prevent constipation. The dose of laxative can be adjusted to make sure you can pass a soft motion regularly.

- **Nausea (Sickness)**

This is common when you first start to use fentanyl patches. This usually improves in a few days. Your doctor may need to give you an anti-sickness medication for a few days until this improves.

- **Heat effects**

Heat speeds up the way fentanyl is released from the patch and may increase the risk of side effects.

  - Avoid direct heat on the patch from hot water bottles, heat lamps, electric blankets or heat pads.
  - Do not soak in a hot bath (a shower or cooler bath is fine) or sunbathe while using fentanyl patches.
  - If you develop a fever, try to keep your temperature down and contact your doctor if your temperature is above 39°

How will I know if fentanyl patches are not going to work for all of my pain?

You may still have pain despite taking bigger doses of fentanyl patches, and may feel unwell in one or more of the following ways:

- Sleepier than usual
- Feeling sick more of the time
- Feeling restless or twitchy
- Having bad dreams, or hallucinations

Don't worry if this happens. Tell your doctor or nurse, who may reduce the amount of strong opioid you are taking and suggest some other treatments to help the pain.

  - .

Will I become addicted to fentanyl patches and be unable to stop taking them?

NO – if you no longer to need to take these painkillers your doctor will reduce the dose gradually.

Will fentanyl patches always relieve my pain completely?

Although fentanyl patches are very good pain killers they are not helpful for all types of pain. You may need other treatments to help types of pain which are not helped so much with opioids.

What should I do if I have pain while using fentanyl patches?

If the pain is mild, paracetamol may help. You should not take any more than 8 paracetamol tablets in 24 hours and should have at least 4 hours between paracetamol doses. If the pain is more severe, you should take a dose of your immediate acting medicine (morphine or oxycodone)

If you need more than 2 or 3 doses of extra immediate acting medication each day, tell your doctor or nurse.

Some people find doing certain things like having a bath or a dressing change bring on the pain. Your doctor or nurse may suggest that you take a dose of your immediate acting pain killer about half an hour before doing anything that brings on the pain.

Can I Drive?

You may be able to drive if your dose has stayed the same for a while and you do not feel sleepy, but you must discuss this with your doctor. You should read the patient information leaflet “Strong pain killers and driving”.

Can I drink alcohol?

Many people enjoy a small glass of wine or spirits, which helps them feel better and improves their appetite. It is best to avoid more than this as you may become too drowsy.

Safe storage of Medicines

Store your medicines in the labelled box from the pharmacy and only remove the dose you need each time. Keep them out of sight and reach of children. Medicines should be stored in a dry, clean place with no big fluctuations in temperature.

Always return any unused medicines to your pharmacist, who can dispose of them safely. It is useful to do this anytime your medication is changed, so that you only have the medications you are taking currently to avoid getting confused.

Follow up and further prescribing

Your GP and district nurse will usually be the healthcare professionals leading on your care at home. Your GP will continue to provide prescriptions and assess your symptoms. The primary care team can contact the local palliative care team or your hospice/hospital consultant if they have any questions.

You may have a Macmillan Nurse/CNS who will give you and your primary healthcare team support and advice.

You could fill in the names and numbers here for future reference.

GP: Name ……Number……:

District Nurse: Name……Number…….

Macmillan Nurse Name……...Number…….

Who to contact out-of-hours, particularly during initiation of treatment

Out of Hours service number……

My Fentanyl dose

	Date	Dose
1		
2		
3		
4		
5		

If there is pain at any time I can take my fast acting medication……

	Date	Dose
1		
2		
3		
4		
5		

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1.2 Breathlessness

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Section 3 End of Life Symptom Management

For staff working in FHFT Acute Hospitals Trust specific guidance is found on the End of Life APP

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1. INTRODUCTION

The purpose of this document is to provide evidence-based guidelines for staff working within Frimley ICS. This guidance is intended to provide a resource to staff caring for patients in the terminal phase of their illness, ensuring that patients who are in the last few days of life have, where possible, their symptoms controlled and their quality of life maximised. The guidance has been developed by experienced Specialist Palliative Care clinicians and represents expert opinion where evidence is lacking.

This guideline is to support care does not replace the clinical judgement of the practitioner caring for the patient. Support is available from the Specialist Palliative Care Teams if there is any concern.

2. PURPOSE

These guidelines are about managing symptoms in the last days of life where the dying process has been identified. It assumes that the therapeutic aims are therefore:

- To allow the patient to die comfortably
- To support the family/carers and to start to prepare them for bereavement
- To discontinue any burdensome or irrelevant clinical procedures.

3. Compassionate Care and Support for the Dying Patient

Guiding Principles, based on 5 National Priorities for End of Life Care are outlined below. These should guide care in whatever setting that care is delivered. Specific paperwork and guidance may apply to different settings.

PRIORITY 1 - Every life reaches its natural end. We aim to identify dying patients in a sensitive and timely manner.

- Recognition of dying should be based on a multi-disciplinary team (MDT) decision.
- We accept that there might sometimes be uncertainty about recognition of dying and prognosis, but focus should be on caring for and supporting the patient, their family and carers during that time.
- End of life care decisions will be made by senior health care professionals, ideally during the working hours of key team members.
- We advise to avoid such decisions being made at night/weekends/Bank Holidays, unless absolutely necessary.
- Out of hours decisions must remain multi-disciplinary and involve the most senior clinicians available.

PRIORITY 2 - Empathetic communication is fundamentally important.

- If a patient is identified as dying, this information should be sensitively communicated to the patient (if conscious and wishes for information), and to their family or carers, using clear and unambiguous language.
- We acknowledge that this is a difficult situation which invokes strong emotions for the patient and family, as well as staff.
- We will develop and agree a plan of care, taking patient, family or carers' wishes into account.
- Discussions should be driven by the patient where possible and should include consideration of hydration, nutrition, medication and ceilings of care.
- We will discuss and agree a DNACPR order.
- All dying patients will have a named Clinician in charge of their care with appropriate support from the Specialist Palliative Care Team.
- The nurse leading the patient's care on each shift will be identified to the patient, family and carers, in all inpatient environments.

PRIORITY 3 - Wherever possible, the wishes of the patient, family and carers will be sought and respected, and management plans effectively communicated.

- Changes in treatment plans will be discussed with the patient.
- If patients lack capacity, best interest decisions will be made in consultation with family and carers. Any person holding Lasting Power of Attorney will be identified.
- Family and carers must be made aware that the burden of decision-making lies with the medical and nursing team, but they will always be asked to contribute as much as they wish or are able.

PRIORITY 4 – The needs of the patients, their family and carers will be continually explored and assessed.

- Following agreement of a plan of care, consider how the family can access up to date information pertaining to care. This might take to form of a shared folder (as in FHFT hospitals), which allows two-way communication. This must not be used in place of face-to-face communication.

- Families and carers should receive adequate, up to date, and regular information about the care and support of their relative who is approaching the end of their life.
- Future therapeutic needs of the patient will be considered, and anticipatory medications prescribed to help manage pain, agitation, respiratory secretions, nausea and vomiting and breathlessness.
- The patient will be nursed in the most appropriate environment, according to their wishes.
- In the hospital setting side room accommodation should be offered (although it may not be available immediately).
- Unnecessary ward changes and bed moves must be avoided.
- In an inpatient setting, nursing staff must ensure the patient has a regular nursing assessment, at a minimum of four-hourly.
- Families and carers should be allowed to visit in line with the current COVID visiting policy and should be encouraged to participate in nursing the patient, if able.
- This is a vulnerable time for them and they must be treated with empathy and consideration.

PRIORITY 5 - Formulating a personalised care plan for a dying patient

The process may vary in home or nursing home settings but the principles of meticulous documentation and communications with other HCP and families should be followed. In FHFT acute hospitals guidance on process and support is available on the Care of the dying patient app.

- Make the diagnosis of dying following an MDT assessment and agreement that all reversible causes for deteriorating condition have been considered.
- The decision should be led or endorsed where possible by the Clinician in charge, with clear documentation of the process in the medical notes.
- The principles of the Mental Capacity Act (2005) must be applied.
- End of Life Care information leaflets (available from the ward end of life care guidelines pack in FHFT or ICS website) should be offered.
- The difficulty in making an accurate prognosis should also be highlighted
- A personalised care plan for the last days of life can be used for all medical and nursing documentation from this point onwards. Each setting may have their own personalised end of life care plan or choose to document care meticulously in the standard care plan.
- Specific forms for use by medical and nursing staff, including a personalised daily care plan to document care, and a verification of death form., may be in use depending on care setting.
- Ensure that the GP is aware that the patient is in the last days of life and is informed as soon as is practicable when a patient dies.
- If not done already, discuss and complete a DNACPR order with ‘no review date’ or ReSPECT form and file in patient case notes.
    - Explore whether the patient has an advance care plan, advance decision to refuse treatment, or opting out of organ donation.
- Enquire if a family member has been appointed as the lasting power of attorney for health and welfare.

    - Explore and document the preferred place of death (PPD).
    - Recognise that diminished oral intake of fluids and nutrition is a common sign of advanced illness.
- All patients who are able to eat and drink should be offered oral intake.
- All patients should have regular mouth care, and family members can be shown how to perform this if desired.
- Discuss benefits and burdens of clinically assisted hydration and nutrition, if appropriate.

    - Consider and review all medical and nursing investigations, interventions and treatments.

- Continue with interventions and medications which provide comfort and best symptom control.
- This may include e.g. diuretics in end stage heart failure, nebulised bronchodilators or antibiotics in end stage respiratory conditions, and corticosteroids in some complications of advanced cancer.
- If the patient has an implantable cardioverter-defibrillator in situ, ensure that this is deactivated to prevent distressing symptoms (contact the patient's Cardiologist or the ECG technician)
- Review the appropriateness of continuing with nursing interventions such as routine BP/pulse/temp monitoring, fluid balance chart and turning positions.
- Discontinue NEWS scoring and calls, as not appropriate during the dying phase.

    - Prescribe end of life care medications in advance of potential symptoms developing (see Symptom Control Algorithms at the end of this document).
- Separate recommendations for prescribing in patients with severe renal impairment are available under the palliative care guidelines on the FHFT intranet, or on advice from specialist palliative care.
- Consider need for a regular subcutaneous infusion of medications, if symptoms not controlled with as required (PRN) doses of drugs.
- Before a syringe driver is commenced, this must be discussed as far as possible with the patient, their family or carers, and the reasoning documented.

    - Provide on-going support for the family.
    - Assess the spiritual needs of the patient and family. Observe cultural and religious rules related to the dying process. Refer to the Chaplaincy team as required.

    - Explore the patient's, family and carers' wishes related to organ donation. Liaise urgently with transplant/organ donation co-ordinators, if appropriate.

    - Seek further specialist advice from the Palliative Care Team (see contact details at the end of this guidance)

- Care after death

    - Allow family to spend time with the patient in private.

    - Verify and certify the death according to organisational policy. Inform relatives what will be stated as the cause of death on death certificate.

    - Complete last offices following organisational policy and procedure. Allow relatives to participate if they wish to.

    - Inform relatives what happens next, give the bereavement leaflet and explain the role of the bereavement team and when to contact them.

    - Inform the patient's GP of the death.

4. SYMPTOM MANAGEMENT IN THE LAST DAYS OF LIFE

Key Prescribing Questions in the last days of life

1. **Ahead of time**
    a. Pre-emptive prescribing
    b. Differences in specific circumstances
2. **Once the oral route is lost**
    a. What can be stopped? – managing co-morbidities at the end of life
    b. How to prescribe a Continuous Subcutaneous Infusion
        i. Opioid conversion
        ii. Combining drugs in a syringe – what can and can't be mixed?
        iii. Dosing other drugs
    c. What can and can't be given subcutaneously
3. **Problems**
    a. Uncontrolled symptoms (pain; restlessness; secretions; breathlessness; nausea; thirst)
    b. Obtaining medicines out of hours
    c. References and contact phone numbers

4.1 Pre-emptive Anticipatory Prescribing of "Just in Case" medicines.

The pre-emptive prescribing of" just in case "or "Anticipatory" Medication to be given prn for anticipated symptoms can avoid great distress. The cost is negligible and it saves time on the part of both families and out-of-hours health professionals.

Typical maximum doses are described on page 12, but the doses needed by individuals vary widely:
***it is more important to assess the effectiveness of each p.r.n. before repeating or increasing* doses – if a p.r.n. is ineffective, try a different approach or seek advice (see flow diagrams)**.
(See 'More Care, Less Pathway')

A typical "pre-emptive p.r.n." regimen for those approaching the end of life includes 10 ampoules of:

- ***Morphine sulfate*** *(10mg/1ml) 2.5-5mg 1 hourly p.r.n. SC (or a dose based on prior regular opioid usage) for pain, cough or breathlessness*
- ***Mid*azolam** (10mg/2ml) 2.5-5mg 2 hourly p.r.n. SC for anxiety or breathlessness
- **An antipsychotic**, for nausea or agitation. Either:
    - *Haloperidol (5mg/1ml) 0.5-1.5mg 4 hourly p.r.n. SC ***or***
    - *Levomepromazine (25mg/1ml)
        - For nausea/vomiting: 6.25-12.5mg SC BD
        - For agitation/delirium: 6.25-25mg SC 4hrly.
        - Max dose 200mg/24hrs (seek palliative care support for high doses)
- **Hyoscine Butylbromide** (20mg/1ml) 20mg 2 – 4 hourly p.r.n. SC for respiratory secretions
- **Water for injections** 10ml (diluent for Continuous Subcutaneous Infusion)

NOTE *Haloperidol is used if minimising sedation is desirable. Levomepromazine is more sedating but is:

- a broader spectrum anti-emetic.
- preferred if severe terminal agitation is anticipated (i.e. where sedative properties are an advantage)
- Levomepromazine and Haloperidol may reduce seizure threshold

Differences in specific circumstances:

- **History of seizures**: also prescribe Midazolam (10mg/2ml) 10mg SC p.r.n. up to t.d.s. for seizures
- **Parkinson's disease:** use Cyclizine (50mg/ml) 25mg SC p.r.n. t.d.s. in place of Haloperidol for nausea and Midazolam (dose as above) in place of Haloperidol for agitation. If an antipsychotic cannot be avoided, use Levomepromazine in place of Haloperidol

- **End stage renal failure:** consider Oxycodone as alternative to Morphine (Oxycodone 5mg ≡ Morphine sulphate 10mg) and halving Midazolam doses. Seek specialist advice for starting doses if Creatinine clearance < 30ml/min. Alfentanil may be required.

- **Terminal haemorrhage is thought likely**: seek advice from the palliative care team

- **Intestinal obstruction**: seek advice from the palliative care team. In the dying phase, attempts to 're-start' the bowel are usually ineffective. Thus, vomiting and colic are reduced with Hyoscine Butylbromide (anti-secretory and antispasmodic actions, respectively) and nausea with Levomepromazine. For typical doses - see page 12.

5. WHAT CAN BE STOPPED? MANAGING CO-MORBIDITIES AT THE END OF LIFE

Diabetes and insulin Diabetes UK EOLC guidelines 2021	
Type 1 diabetes	• Give a once daily bolus of long-acting insulin (e.g. Glargine) SC at reduced dose (50 – 75% of previous) • Check finger prick blood sugar once a day, and adjust insulin to keep blood sugar between 5 and 19 mmol/l. Check blood glucose once a day at teatime: • If below 8 mmols/l reduce insulin by 10-20% • If above 20 mmols/l increase insulin by 10-20% to reduce risk of symptoms or ketosis
Type 2 diabetes	• Oral tablets usually discontinued without substituting an alternative once the patient is unable to take orally (the lack of oral food intake is sufficient to control the diabetes). • No need to monitor blood sugar if on metformin • If tablets/ GLP -1 RAs (eg dulaglutide) stop these • Insulin - consider stopping if low dose and check capillary blood glucose daily for 2 days and give one off 6 units of rapid acting insulin if this is more than 20mmol, repeat blood glucose in 2 hours. • If insulin continued switch to long acting (eg glargine) at 25% reduction of total daily intake, check blood glucose once a day at teatime: • If below 8 mmols/l reduce insulin by 10-20% • If above 20 mmols/l increase insulin by 10-20% to reduce risk of symptoms or ketosis
Epilepsy and anti-seizure medication	
Epilepsy	At the end of life, once the patient can no longer take medication required to prevent seizures orally, their seizures are prevented with subcutaneous Midazolam: • prescribe **Midazolam** 15-30mg over 24 hours via subcutaneous Continuous Subcutaneous Infusion (the diluent is water for injection) *and* **Midazolam** 5-10mg p.r.n. SC • if the SC route is not readily available for p.r.n. use (e.g. the patient is in their own home), alternatives include o **buccal Midazolam†** (Buccolam™) 10mg p.r.n (buccally) o **Diazepam rectal solution** (0.5mg/kg up to a maximum dose of 30mg p.r.n. PR) • increase the Continuous Subcutaneous Infusion dose if p.r.n. doses are needed and effective • If seizures persist despite Midazolam 60mg/24hrs, seek advice from the Palliative Care Team • Levetiracetam† may be given subcutaneously over 24 hrs either as a replacement (1:1) for oral Levetiracetam, or as an adjunct if Midazolam is not controlling symptoms. Sodium Valproate† may also be used subcutaneously over 24 hrs. Seek advice for the palliative care team

Corticosteroids	
Steroids *contributing to symptom relief* (i.e. symptoms likely to recur if stopped)	Convert to a subcutaneous bolus of Dexamethasone each morning: • Oral Dexamethasone: Dexamethasone 4mg o.m. PO ≡ Dexamethasone 3.3mg (1ml) o.m. SC • Oral Prednisolone: *divide the dose by 6* (e.g. Prednisolone 20mg o.m. PO ≡ Dexamethasone 2.5mg (0.75ml) o.m. SC (see Palliative Care Symptom Control Guidelines for more details)
Steroids *not contributing to symptom relief*	Stopped at the end of life when the oral route is no longer available. If the dying process is already established, Addisonian withdrawal effects are not usually relevant
Cardiovascular conditions	
Heart failure	*Diuretics are usually continued until the oral route is lost*. They retain an important role in preventing pulmonary and peripheral oedema. ACE inhibitors and beta blockers act over longer periods and can thus usually be stopped in the last weeks of life without worsening symptoms. ***Mild-moderate***: diuretics usually discontinued without substituting an alternative once the patient is unable to take orally because of the minimal fluid intake at this stage. ***Severe*** (e.g. the patient is dying from end-stage heart failure). Fluid overload is not inevitable and parenteral diuretics are *not* usually required. However, if fluid overload *does* occur, consider: • Subcutaneous Furosemide† (half the previous PO dose). Usually given as a SC bolus o.d. or b.d. • Opioids (See 'terminal breathlessness')
Implantable cardioverter defibrillators	**East Berks**: Monday – Friday 09.00-17.00 call Pacing Administrator 0300 6153095. Out of hours: Radiopager via Heatherwood & Wexham Park Hospital switchboard on 0300 615000 and ask to page Cardiac Physiologists Pacing and ICD Radiopager **West Berks**: Monday – Friday 09.00-17.00, call pacing clinic (0118 322 6636) Out of hours, contact the Coronary Care Unit (0118 322 6684 or 322 6743)
Angina	Medication usually discontinued without substituting an alternative once the patient is unable to take orally. The minimal exertion at the end of life minimises the risk of angina occurring. If angina symptoms are suspected, or there is particular concern, consider: • Transdermal Glyceryl Trinitrate (e.g. Glyceryl Trinitrate 5mg patch applied for 12hrs each day). *This is very rarely required at the end of life* • Symptomatic management with opioids (see pain flow diagram age 14)
Hypertension	Medication discontinued without substituting alternatives once the patient is unable to take orally

Neurodegenerative Diseases	
Antiparkinsonian medication (e.g. L-Dopa or Dopamine agonists)	Look for an advanced symptom management plan. If no specific plan in place: Continue until oral route is lost: rigidity can make care (e.g. turning) more difficult. • If consciousness is already limited and the patient is dying, control rigidity with Midazolam 10-15mg/24hrs via Continuous Subcutaneous Infusion and 2.5-5mg SC PRN. Titrate if required and effective. • If avoiding drowsiness is desirable (e.g. the anticipated prognosis is longer or uncertain) consider a transdermal antiparkinsonian drug (e.g. Rotigotine 2-4mg/24hrs; prescribers unfamiliar with these products can seek advice from a Parkinson's Disease Nurse Specialist). In an acute hospital, a nasogastric tube offers an alternative route of administration. • Avoid antidopaminergics (Haloperidol; Levomepromazine; Metoclopramide): • Treat restlessness with Midazolam • Treat nausea with Cyclizine or Ondansetron • If distressing hallucinations occur, seek advice. Options include: o where the patient is imminently dying; sedation (e.g. Midazolam) o if the anticipated prognosis is longer; look for other causes (e.g. UTI); consider transdermal Rivastigmine (specialist use only) o in either case, consider reducing the dose of antiparkinsonian drugs if hallucinations are a greater problem than rigidity.
Antispasticity medication (e.g. Baclofen)	Spasticity can be painful and make care (e.g. turning) more difficult. Continue until oral route is lost; then replace with Midazolam 10-15mg/24hrs via Continuous Subcutaneous Infusion. If further 2.5-5mg PRN doses are required and are effective, titrate. If ineffective, or drowsiness is problematic, contact Palliative Care Team

6. HOW TO PRESCRIBE A CONTINUOUS SUBCUTANEOUS INFUSION

A Continuous Subcutaneous Infusion (via a syringe pump (S/P) is used to administer symptom relief to patients who are no longer able to swallow

It not only replaces existing symptomatic relief (e.g. regular Zomorph), but is titrated where necessary to take account of additional (p.r.n.) requirements

Step 1. Are the existing symptom control medications effective?

Look at dose requirements over the previous 24 hr period, including both:
- Regular symptom control medication (e.g. regular MR Opioid)
- P.r.n. usage

If symptoms are controlled by the above, they (or equivalents) are put in the S/P → go to step 2

If symptoms are *not* controlled by the above, consider:
- Dose increases (especially where the above are partially effective or benefit of prn medication is short lived)
- Alternatives (common examples are given in the symptom control flow diagrams below)

Step 2. Converting *effective* symptom control medications into a S/P

Where symptoms have been controlled by SC p.r.n.s alone, the previous 24 hr requirements can be put into the S/P

Calculate the total 24 hr dose requirements of existing oral symptom control medications, then:
- For the following medications, the 24hr S/P dose *is half* the prior 24hr oral dose
  - Morphine MR (e.g. Zomorph), Oxycodone MR (e.g. Oxycontin), Haloperidol, Cyclizine
- For the following medications, the 24hr S/P dose *is the same as* prior 24hr oral dose
  - , Metoclopramide, Hyoscine Butylbromide (Buscopan™),Levomepromazine

Medicines without subcutaneous equivalents
- **Medicines for co-morbidities (e.g. diabetes, steroids, epilepsy)** – see page7
- **Non-opioid analgesia** (e.g. Paracetamol, NSAIDs, antidepressant, antiepileptic drugs). Usually stopped when the oral route is lost: *continuing opioids alone is usually sufficient*. However, if pain is known to be opioid poorly-responsive, options include a non-oral NSAID:
  - Diclofenac 100mg o.d. PR *or*
  - Diclofenac 75-150mg/24hr via SC† syringe pump (use a separate pump: diclofenac is not compatible with other medicines) *or*
  - 'Specialist only' options (e.g. ketorolac) - seek advice from the Palliative Care Team

Step 3. Prescribing the Continuous Subcutaneous Infusion

Write each drug, the dose required, the diluent (usually water for injections), followed by "over 24hrs via subcutaneous syringe pump"

Combining medications in a continuous subcutaneous infusion Not all medicines can be combined in the same syringe. Commonly used combinations are described on page 132

Example. *Over the last 24 hrs, a patient's symptoms have been well controlled on:*
- *Morphine MR 20mg b.d. PO → halved →* Morphine Sulphate 20mg
- *Metoclopramide 10mg t.d.s. PO → same dose →* Metoclopramide 30mg
- *Midazolam, 2 x 2.5mg p.r.n. SCut doses → 5mg total →* Midazolam 5mg

} Over 24hrs via subcut syringe pump

7. CONVERTING PRIOR OPIOID REGIMENS TO A CONTINUOUS SUBCUTANEOUS INFUSION: OPIOID EQUIVALENCE TABLE *[Twycross 2011, Mercadante 2011]* Opioid Equivalence Table

Opioid Equivalence Table

These dose equivalences are **approximations** intended for use by experienced clinicians. Always seek specialist advice before prescribing unfamiliar opioids. Use particular care when converting between higher doses or where doses have recently required rapid titration. In such patients, consider a dose 25-33% lower than predicted by the ratios and ensure P.R.N.s are available

Codeine		Tramadol		Oral Morphine			Subcutaneous Morphine		Oral Oxycodone			Subcutaneous Oxycodone		Subcutaneous Diamorphine*		Fentanyl Patch**
Q.D.S. dose	24 hour total dose (mg)	Q.D.S. dose	24 hour total dose (mg)	4 hour / p.r.n. dose (mg)	12 hour MR b.d. dose (mg)	24 hour total dose (mg)	4 hour / p.r.n. dose (mg)	24 hour total dose (mg)	4 hour / p.r.n. dose (mg)	12 hour MR b.d. dose (mg)	24 hour total dose (mg)	4 hour / p.r.n. dose (mg)	24 hour total dose (mg)	4 hour / p.r.n. dose (mg)	24 hour total dose (mg)	Micrograms per hour
60	240	50	200	2.5-5	10	20	2.5	10	1-2.5	5	10	1	5	1	5	½ x 12***
		100	400	5-10	20	40	2.5-5	20	2.5-5	10	20	2	10	2	10	12
				10	30	60	5	30	5	15	30	2.5	15	2.5	15	12-25
				15	45	90	7.5	45	7.5	20	40	2.5-5	20	5	30	25-37 (25+12)
				20	60	120	10	60	10	30	60	5	30	7.5	40	37 (25+12)-50
Is long term (years rather than months) opioid use anticipated? If so, seek specialist advice before titrating to the higher doses in the section below. Adverse effects (particularly endocrinopathies) are common with longer term higher dose opioids. Higher doses *are* used for opioid-responsive pains in the *palliative prognostic context (weeks to months)* since longer term effects are not relevant. Use particular care when converting between higher doses: consider a dose 25-33% lower than predicted by the ratios and ensure P.R.N.s are available.																
				30	90	180	15	90	15	45	90	7.5	45	10	60	50-75
				40	120	240	20	120	20	60	120	10	60	10-15	80	62 (50+12)-100
				50	150	300	25	150	25	75	150	10	75	15	100	75-125
				60	180	360	30	180	30	90	180	15	90	20	120	100-150
				70	210	420	35	210	35	105	210	15	105	20-25	140	125-175
				80	240	480	40	240	40	120	240	20‡	120	25	160	125-200
				90	270	540	45	270	45	135	270	25‡	135	30	180	150-225

* Where possible, morphine, oxycodone and fentanyl are recommended choices to ensure familiarity with a smaller number of opioids.

** Conversions to and from transdermal patches are especially unpredictable. Prescribers unfamiliar with such products are encouraged to seek specialist advice

*** Matrix fentanyl patches can be cut diagonally in half for smaller dose increments where a smaller patch size is unavailable (unlicensed use)

‡ May require 50mg/ml injection to reduce s/c volume.

These dose equivalences are **approximations** intended for use by experienced clinicians. Always seek specialist advice before prescribing unfamiliar opioids. Use particular care when converting between higher doses or where doses have recently required rapid titration.

8. CONVERSIONS INVOLVING FENTANYL PATCHES

Commencing Continuous Subcutaneous Infusions in patients receiving a stable dose of transdermal Fentanyl

If the patient is pain free, leave the patch in place at the same dose and administer any medicines required for other symptoms via a syringe pump.

If the patient is requiring extra opioid, leave the patch in place and give additional Morphine (or Oxycodone, if Morphine intolerant) alongside via a Continuous Subcutaneous Infusion. This would usually be equivalent to the extra (p.r.n) opioid required in the previous 24 hours.

Why?

The time taken for changes in Fentanyl (whether increasing or stopping to change to a Continuous Subcutaneous Infusion) is too long for patients in the last days of life. The quickest solution is to add further opioid alongside the unchanged patch via a Continuous Subcutaneous Infusion. However, this does add an extra step in p.r.n. calculations.

8.1 P.R.N. calculations for combinations of Fentanyl patches with Morphine Continuous Subcutaneous Infusion

- Use the table to determine the equivalent 24-hour Morphine subcutaneous infusion
- Add this to actual Continuous Subcutaneous Infusion dose to get *overall total 24 hour SC Morphine-equivalent dose*.
- Divide this total by 6 for the p.r.n. SC Morphine dose.
  Example for Fentanyl 50 patch size plus 50mg **Morphine** via Continuous Subcutaneous Infusion:
- The Fentanyl patch is equivalent to 90mg of Morphine over 24hrs via Continuous Subcutaneous Infusion (90mg + 50mg)
- The overall regular opioid dose is therefore 140mg SC Morphine (i.e. 90mg+50mg)
- The p.r.n. SC Morphine dose is therefore 25mg (i.e. 140mg ÷ 6 = 23.33)
- Alternatively take breakthrough dose for 50mcg/hr patch (15mg) and add to breakthrough dose for 50mg/24 hours infusion (8.33mg) to give 23.33 round up to 25mg

10.2 P.R.N. calculations for combinations of Fentanyl patches with Oxycodone Continuous Subcutaneous Infusion

- Use the table to determine the equivalent 24 hours Oxycodone subcutaneous infusion.
- Add this to the actual Continuous Subcutaneous Infusion dose to get the *overall total 24 hour SC Oxycodone-equivalent dose*.
- Divide this total by 6 for the p.r.n. SC Oxycodone dose
  .**Example** for Fentanyl 50 patch size plus 10mg **Oxycodone** via Continuous Subcutaneous Infusion:
- The Fentanyl patch is equivalent to 45mg of Oxycodone over 24hrs via Continuous Subcutaneous Infusion
- The overall regular opioid dose is therefore 55mg SC Oxycodone (i.e. 45mg+10mg)
- The p.r.n. SC Oxycodone dose is therefore 10mg (i.e. 55mg ÷ 6)
- Alternatively take breakthrough dose for 50mcg/hr patch (7.5mg) and add to breakthrough dose for 10mg/24 hours infusion (1.66mg) to give 9.16 round up to 10mg.

9. COMBINING DRUGS IN A CONTINUOUS SUBCUTANEOUS INFUSION

Not all medicines can be combined in the same syringe. Commonly used combinations are described below. If using other medicines concurrently, consider separate Continuous Subcutaneous Infusions, seeking specialist advice about other combinations, or giving longer acting medicines separately as once daily SC boluses (i.e. Haloperidol, Levomepromazine) Further compatibility advice available at www.palliativedrugs.com. This is also accessible via Medusa subscription (https://medusa.wales.nhs.uk})

	Compatible 2, 3 and 4 drug combinations	**Diluent**
Morphine *or* Oxycodone *plus*:	Cyclizine	Water
	Haloperidol	Water
	Hyoscine Butylbromide	Water
	Levomepromazine	Water
	Metoclopramide	Water
	Midazolam	Water
	Octreotide	Sodium chloride 0.9%
Morphine *or* Oxycodone *plus*:	Cyclizine and Haloperidol	Water
	Cyclizine and Midazolam	Water
	Haloperidol and Hyoscine Butylbromide	Water
	Haloperidol and Midazolam	Water
	Haloperidol and Octreotide	Sodium chloride 0.9%
	Midazolam and Hyoscine Butylbromide	Water
	Midazolam and Levomepromazine	Water
	Midazolam and Metoclopramide	Water
	Midazolam and Octreotide	Sodium chloride 0.9%
	Levomepromazine and Hyoscine Butylbromide	Water
Morphine *or* Oxycodone *plus*:	Haloperidol, Midazolam and Hyoscine Butylbromide	Water
	Levomepromazine, Midazolam and Hyoscine Butylbromide	Water

10. PRESCRIBING OTHER DRUGS VIA CONTINUOUS SUBCUTANEOUS INFUSION

Drug	Uses	Usual starting dose	Typical maximum[4]	Diluents
Cyclizine	Nausea and vomiting	75mg/24hrs	150mg/24hrs	Water for injection
Haloperidol	Nausea and vomiting	0.5-1.5mg/24hrs	5mg/24hrs	
	Agitation Hallucinations	2.5-5mg/24hrs	10mg/24hrs	
Hyoscine butylbromide ('Buscopan')	Colicky pain Respiratory secretions GI obstruction	40-60mg/24hrs	120mg/24hrs	
Metoclopramide	Nausea and vomiting	30mg/24hrs	80mg/24hrs	
Midazolam	Anxiety / agitation Breathlessness Sedation	5-15mg/24hrs	Seek advice if needing to exceed 60mg/24hrs	
	Seizures[1]	15-30mg/24hrs		
Levomepromazine	Nausea and vomiting	6.25 -12.5mg BD	25mg/24hrs	
	Agitation / sedation (1st line use)	6.25-25mg 4 hourly	Seek advice if needing to exceed 150mg/24hrs[2]	
	Severe agitation not responding to haloperidol and midazolam. if underlying delirium consider antipsychotic.	25-75mg[2]		
Octreotide	GI obstruction (hyoscine butylbromide often as effective[3])	300microgram/24hrs	600microgram/24hrs	Sodium chloride 0.9%

[1] **Midazolam** is used to replace most oral anti-epileptics *in the last days of life*. Levetiracetam can be used subcutaneously converted 1;1 from the oral maintenance dose. Seek specialist advice in patients losing the oral route *who are not thought to be dying*: alternatives should be considered (e.g. IV anti-epileptic drugs or subcutaneous Levetiracetam).

[2] **Higher doses of levomepromazine** are sometimes required for severe *terminal* agitation unresponsive to other medicines. These are only appropriate when the dying process has irreversibly set in, there is no hope of improvement/reversal, and the therapeutic aim is to allow the patient to die comfortably. If in any doubt, seek specialist advice. See 'terminal restlessness' flow diagram page 9 for other important considerations

[3] For more information about the management of GI obstruction, see the Palliative Care Symptom Control Guidelines. Octreotide could be considered after discussion with a Palliative Care Specialist.

[4]This is a guideline. Prescribers should consider seeking specialist advice if exceeding these typical maximums and/or if there is doubt about their effectiveness or appropriateness. Specialists sometimes recommend drugs or doses not described here. If in doubt, there is specialist palliative care team advice available 24 hours a day.

11. SUBCUTANEOUS ADMINISTRATION OF DRUGS

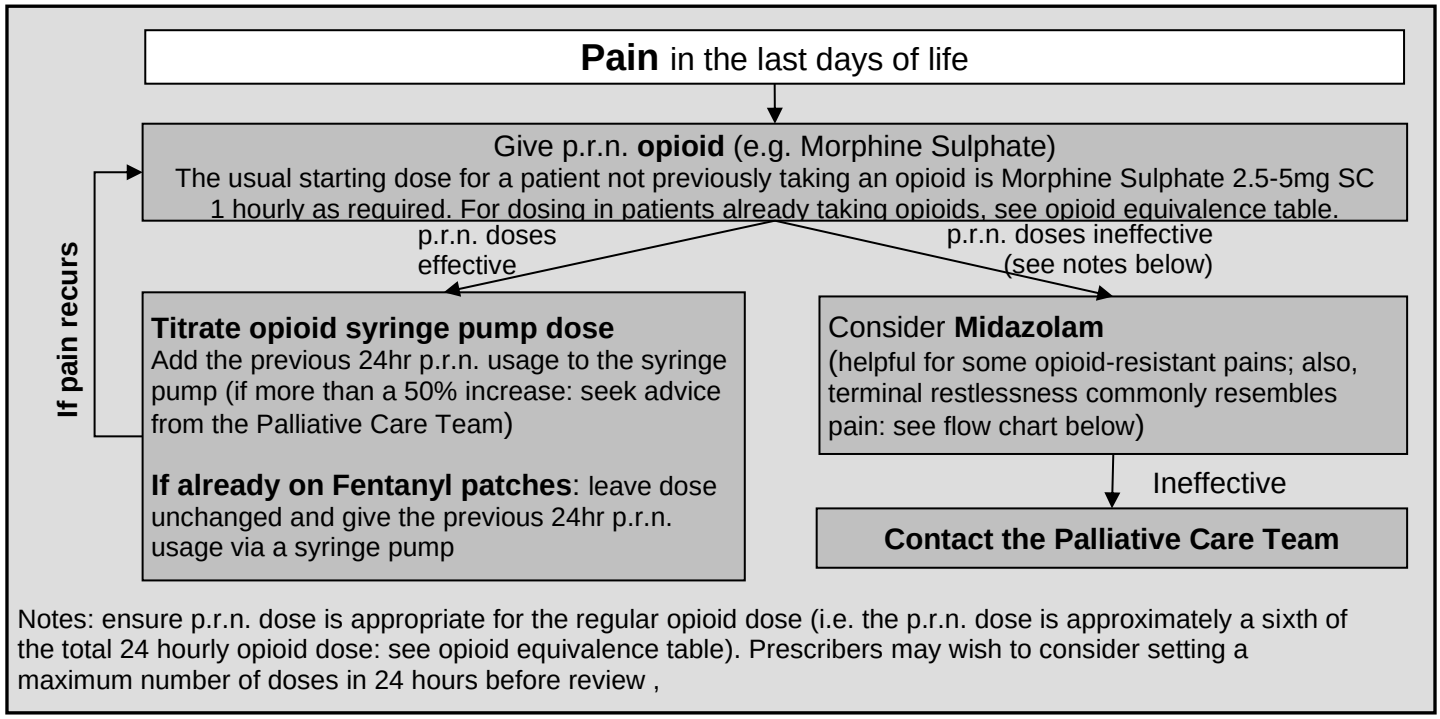
Subcutaneous administration is useful where patients are unable to tolerate or manage medications by mouth. It may avoid the discomfort and access problems of the intramuscular or intravenous routes. However, few agents have a marketing authorisation for use by this route. Those drugs where the subcutaneous route is acceptable common practice are highlighted in each relevant symptom section and summarised in the table below.

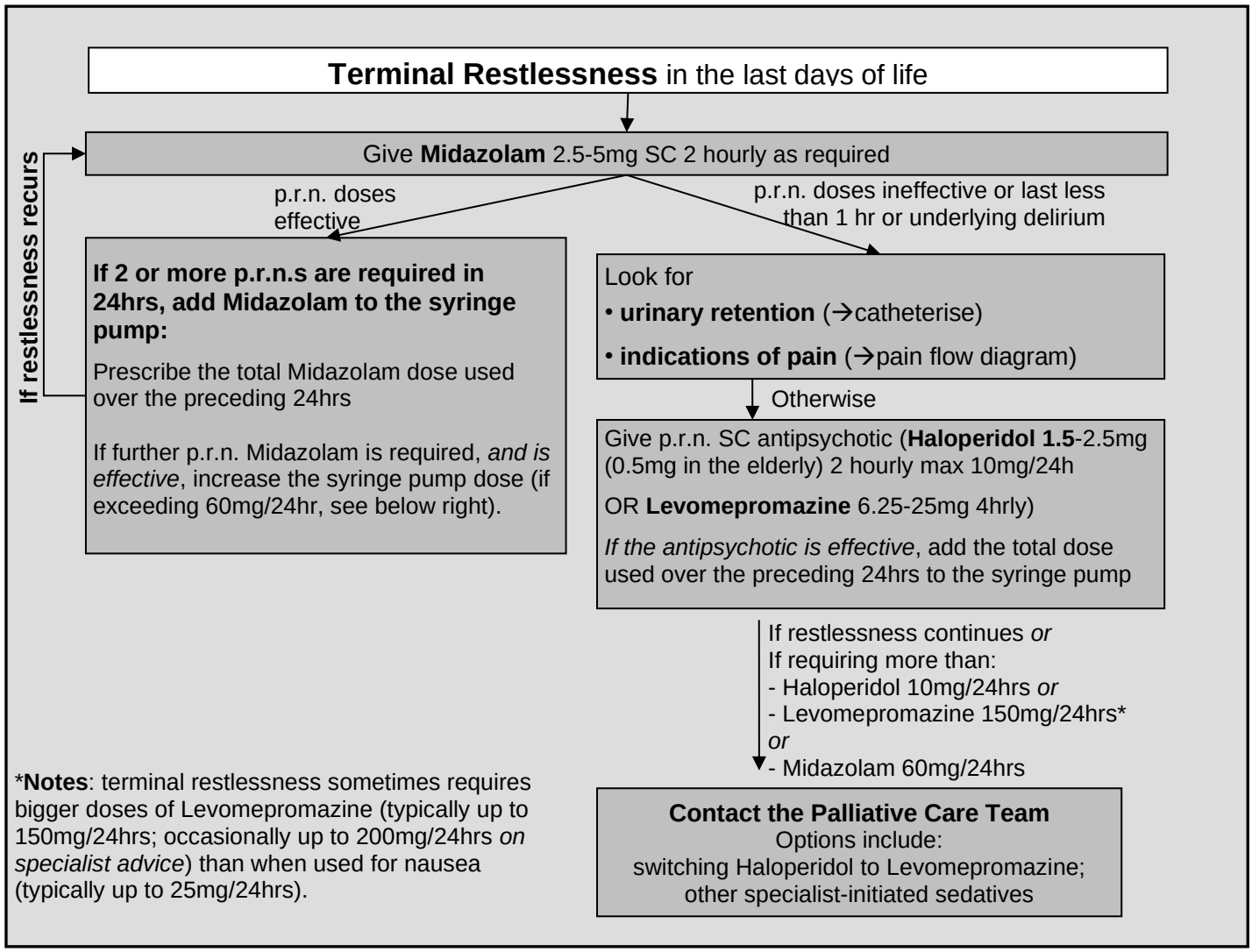
Drug Name	Diluent / flush	Subcutaneous administration	
		Acceptable	Licensed
Chlorphenamine	Sodium chloride 0.9%	Yes	Yes
Dexamethasone	Water / Sodium chloride 0.9%		
Diamorphine[1]	Water / Sodium chloride 0.9%		
Hyoscine hydrobromide	Water / Sodium chloride 0.9%		
Levomepromazine	Water / Sodium chloride 0.9%		
Morphine sulphate	Water / Sodium chloride 0.9%		
Octreotide	Sodium chloride 0.9%		
Oxycodone	Water / Sodium chloride 0.9%		
Alfentanil [2]	Water / Sodium chloride 0.9%	Yes	No
Clonidine [2]	Sodium chloride 0.9%		
Cyclizine	Water		
Diclofenac[3]	Sodium chloride 0.9%		
Fentanyl	Water / Sodium chloride 0.9%		
Furosemide[4]	Water / Sodium chloride 0.9%		
Haloperidol	Water / Sodium chloride 0.9%		
Hyoscine butylbromide	Water / Sodium chloride 0.9%		
Ketamine [2]	Sodium chloride 0.9%		
Ketorolac [2]	Sodium chloride 0.9%		
Levetiracetam[5] [2]	Water/ Sodium chloride 0.9%		
Methadone [2]	Water / Sodium chloride 0.9%		
Metoclopramide	Water / Sodium chloride 0.9%		
Midazolam	Water / Sodium chloride 0.9%		
Phenobarbital[6] [2]	Water		
Valproate[7]	Water		
Diazepam	n/a	**Not appropriate for subcutaneous use**	No
Chlorpromazine	n/a		
Prochlorperazine	n/a		

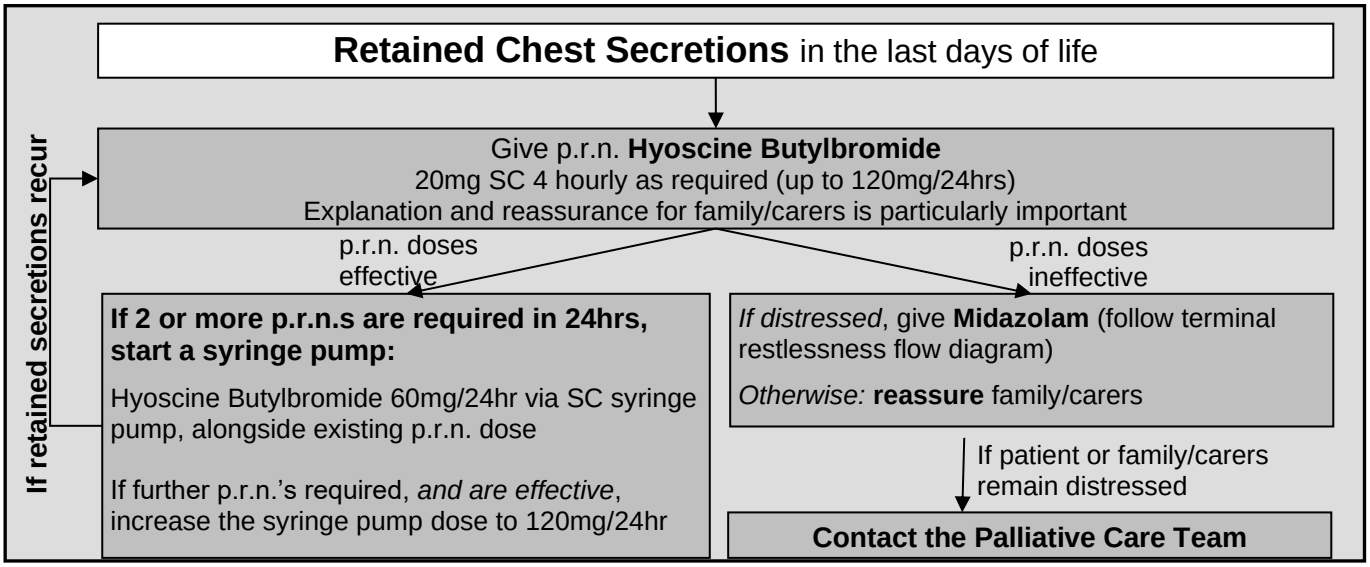
Notes

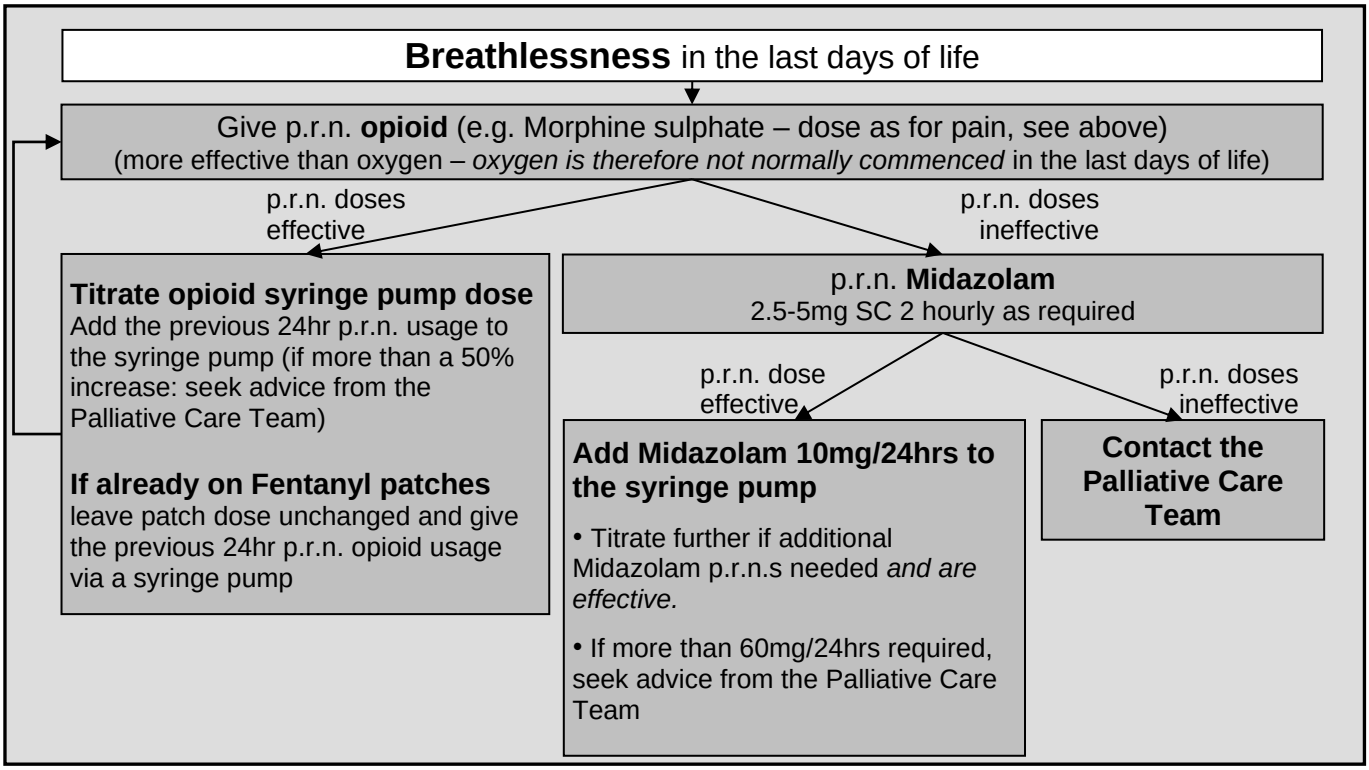
1. Morphine is preferred. **Diamorphine** is rarely used.
2. These drugs are only started on the advice of a specialist but that can subsequently be prescribed by a non-specialist.
3. **Diclofenac** is given by continuous SC infusion only† (i.e. via Continuous Subcutaneous Infusion). Do not administer stat SC injections (tissue necrosis reported).
4. **Furosemide** can be given by SC infusion† or stat SC injection† in those where IV access is problematic. The overnight diuresis from 24 hr SC infusions may be undesirable in those without a urinary catheter/sheath. (Twycross 2011, Zacharias 2011)
5. **Levetiracetam** can be given by subcutaneous infusion on specialist advice only
6. **Phenobarbital** is given by continuous SC infusion† (i.e. via Continuous Subcutaneous Infusion) *on specialist advice only.* Bolus doses are given undiluted IM. Do not administer stat SC injections (tissue necrosis reported). (Twycross 2011).
7. **Valproate** is given via continuous SC infusion† (i.e. via Continuous Subcutaneous Infusion) *on specialist advice only*, using a PO:SC dose ratio of 1:1. The IV sodium valproate preparation is diluted with 30mL of water for injections.

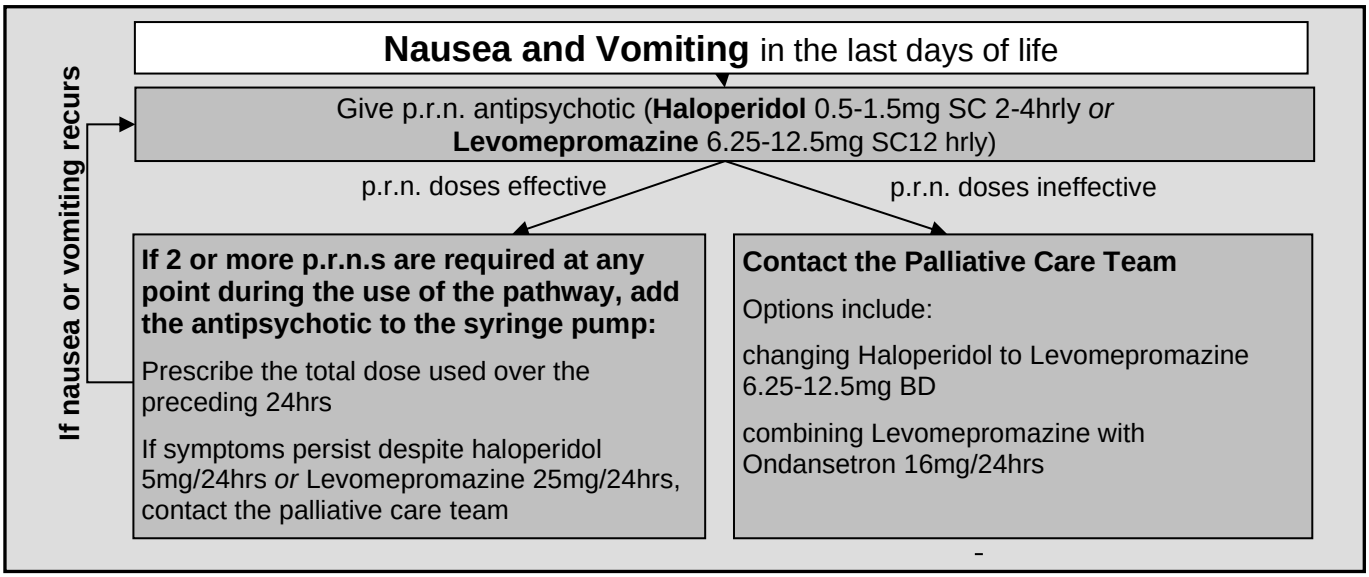
12. UNCONTROLLED SYMPTOMS - MANAGEMENT IN THE LAST DAYS OF LIFE

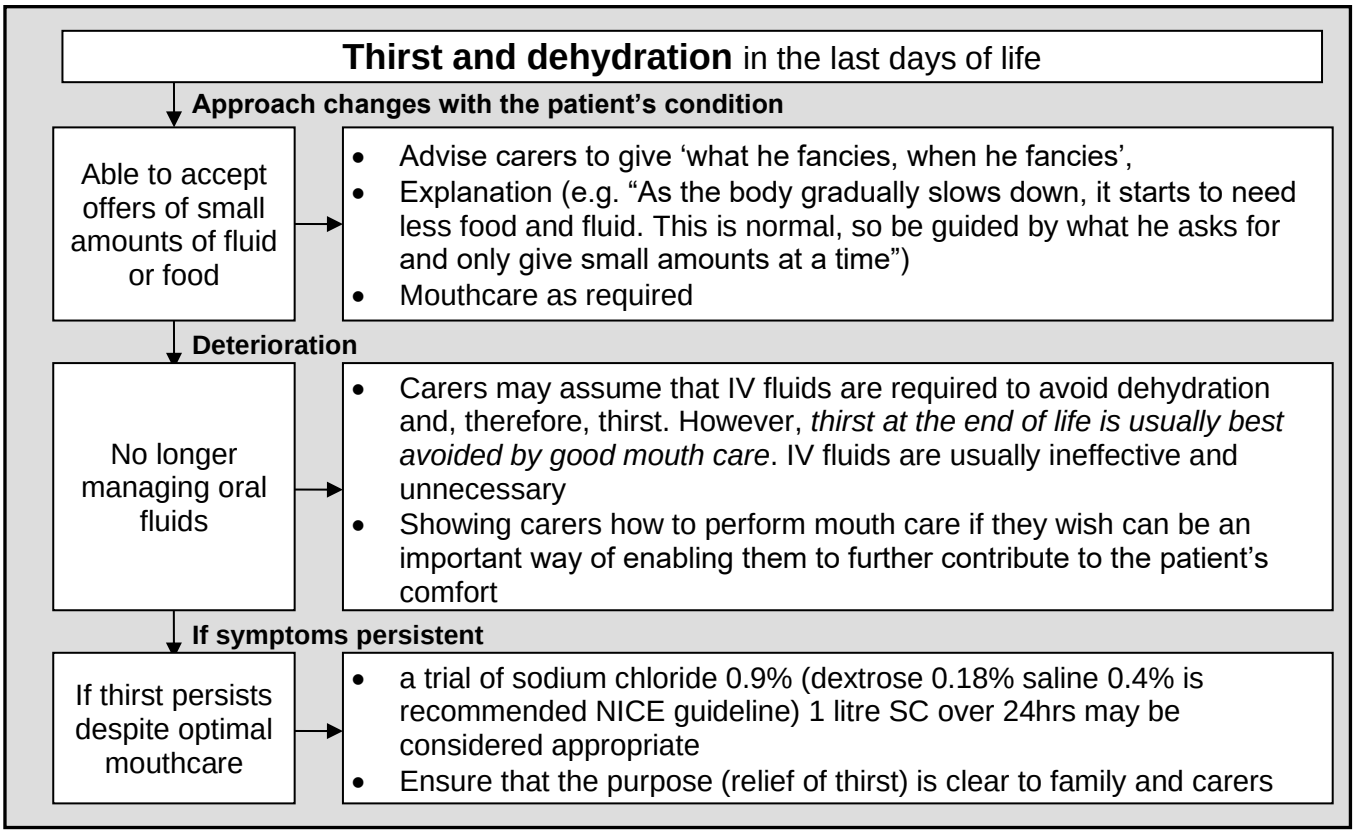





Retained Chest Secretions in the last days of life
Give p.r.n. Hyoscine Butylbromide
20mg SC 4 hourly as required (up to 120mg/24hrs)
Explanation and reassurance for family/carers is particularly important
If retained secretions recur
p.r.n. doses effective
p.r.n. doses ineffective
If 2 or more p.r.n.s are required in 24hrs, start a syringe pump:
Hyoscine Butylbromide 60mg/24hr via SC syringe pump, alongside existing p.r.n. dose
If further p.r.n.'s required, and are effective, increase the syringe pump dose to 120mg/24hr
If distressed, give Midazolam (follow terminal restlessness flow diagram)
Otherwise: reassure family/carers
If patient or family/carers remain distressed
Contact the Palliative Care Team


Breathlessness in the last days of life
Give p.r.n. opioid (e.g. Morphine sulphate – dose as for pain, see above)
(more effective than oxygen – oxygen is therefore not normally commenced in the last days of life)
p.r.n. doses effective
p.r.n. doses ineffective
Titrate opioid syringe pump dose
Add the previous 24hr p.r.n. usage to the syringe pump (if more than a 50% increase: seek advice from the Palliative Care Team)
If already on Fentanyl patches
leave patch dose unchanged and give the previous 24hr p.r.n. opioid usage via a syringe pump
p.r.n. Midazolam
2.5-5mg SC 2 hourly as required
p.r.n. dose effective
p.r.n. doses ineffective
Add Midazolam 10mg/24hrs to the syringe pump
• Titrate further if additional Midazolam p.r.n.s needed and are effective.
• If more than 60mg/24hrs required, seek advice from the Palliative Care Team
Contact the Palliative Care Team





Questions about food and drink are difficult and emotive. Establishing what the concerns are, combined with an awareness of the evidence in this area, can help clinicians to respond appropriately.

- https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/treatment-and-care-towards-the-end-of-life.
  Thirst is closely related to mouth dryness [Viola 1997]. Mouth care and sips of water avoid thirst [McCann 1994]
- IV/SC fluids in the last days of life do not improve:
  - thirst [Viola 1997]
  - consciousness [Waller 1994]
- The clinical impression of many palliative care practitioners is that IV/SC fluids worsen symptoms such as oedema, respiratory secretions, pain, or vomiting. However, this is not clearly demonstrated in the literature [Viola 1997]

Just-in-Case Medication Summary

The prescription should include the four medications that might be required for end-of-life symptom control, plus diluent.

Either Levomepromazine OR Haloperidol should be prescribed depending on local preference

Drug and indication	Dose	Concentration	Supply
Morphine Sulphate *Analgesia: Pain, breathlessness*	2.5 - 5mg (or 1/6 of total daily subcutaneous dose equivalent if not opioid naïve) up to hourly	10mg/1ml	1 x 10 (ten)
Midazolam *Anxiolytic, sedative: anxiety/distress/myoclonus/fitting*	2.5-5mg up to 2 hourly	10mg/2ml	1 x 10 (ten)
Levomepromazine ** *Anti-emetic/antipsychotic nausea, delirium, agitation*	6.25mg up to 12 hourly (nausea) may need up to 4 hourly for agitation.	25mg/1ml	1 x 10
Hyoscine Butylbromide *Anti-secretory: respiratory secretions*	20mg up to 2 hourly	20mg/1ml	1 x10
Haloperidol *Anti-psychotic/emetic: delirium, agitation, nausea*	0.5 - 1.5mg up to 4 hourly	5mg/ml	1 x 10
Water for injection	as diluent	10ml	1 x 10

Medicines in syringe driver must be individualised to the symptoms exhibited by the patient and assessed daily.

Calculating starting dose for syringe pump 24 hour continuous subcutaneous infusion

Drug	Calculation of dose	Incremental increases
Morphine Sulphate	50% of total daily oral dose of morphine	Guided by use of PRN medication, and clinical assessment. If more than 30% of previous total daily dose reassess carefully.
Midazolam	Usual starting dose 5mg – 10mg in 24 hours; 20 – 30mg if for prevention of fits	Guided by use of PRN medication and clinical assessment. Titrate in increments of no more than 50%
Hyoscine Butylbromide	Usual starting dose 40mg	Guided by use of PRN medication and clinical assessment. Max 120mg/24hours
Levomepromazine	Usual starting dose 6.25mg (nausea)	6.25mg increments to max 50mg for nausea. Higher doses may be required for severe agitation -
Haloperidol	Usual starting dose 1.5mg	0.5mg increments max 5mg for nausea.

- ** Levomepromazine may also be used for agitation up to 2 hourly at 6.25mg – 12.5mg
- Levomepromazine OR Haloperidol should be prescribed
- PRN doses - opioids must state dose interval and it is desirable to state maximum number of doses before reassessment. (eg. If 3 doses in 4 hours seek medical advice)

13. OBTAINING DRUGS OUT OF HOURS

Patient location	Sources of medication required for palliative care emergencies
Home or care home	Specific community pharmacies stock the list below of palliative care drugs Out of Hours services stock medicines for use with patients they review
Community Hospitals	Ward stock includes medication required for most palliative care situations. Supplies of such medication are also held by Out of Hours Services
Acute Hospitals	Check ward stock list for availability of the required drug If the drug is not held on the ward, contact Clinical Site Manager, who will locate drug required from another ward or via the on-call pharmacist
Thames Hospice	Contact the On Call Pharmacist via Wexham Park Switchboard.
Phyllis Tuckwell Hospice	Contact the on call Pharmacist via Frimley Park Switchboard.

14.1 Community Pharmacy Emergency Palliative Care Stock Scheme

These pharmacies guarantee to stock the drugs listed below current August 2022 - contracts are reviewed annually. See ICS website for up-to-date list of drugs and pharmacies

FRIMLEY ICS List of community pharmacies that stock Palliative Care EoL/JIC boxes

North East Hants and Farnham

Designated 'Palliative Care' Pharmacies-	**Pharmacy**	**Telephone number**	**Opening hours (as advertised on nhs.co.uk)**	**Delivery service available?**
Aldershot	Wellington Pharmacy 5-7 High Street, Aldershot, GU11 1BH	01252 332551	Mon-Fri 09.00-18.30 Sat 09.00-13.00	Yes
Farnborough	**Boots* Blackwater Retail Park, Farnborough GU14 8BL**	**01252 543629**	**Mon-Sat 08.00-23.59 Sun 10.30-16.30**	**Not always available request to deliver drugs must be signed for and booked in advance.**
Farnborough	Morrison's Pharmacy Links Way, Summit Avenue, Southwood Village Centre, Farnborough, GU14 0NA	01252 377270	Mon-Fri 08.30-20.00 Sat 08.30-13.00 14.00-19.00 Sun 10.00-13.00 13.30-16.00	No
Farnborough	Lloyds Pharmacy in Sainsbury's6 Queensmead, Farnborough, GU14 7GL	01252 542877	Mon-Fri 07.00-23.00 Sat 07.00-22.00 Sun 11.00-17.00	No
Fleet	Morrison's Pharmacy* The Key, Elvetham Heath Way, Elvetham Heath, Fleet, GU51 1HA	**01252 625821**	**Mon-Fri 08.30-20.00 Sat 08.00-19.00 Sun 10.00-16.00**	No
Farnham	**Lloyds in Sainsbury's*** Waterlane, Farnham, GU9 9NJ	**01252 723131**	**Mon-Fri 09.00-21.00 Sat 08.00-20.00 Sun 10.00-16.00**	**No**

East Berkshire

Name	Hours	Address	Phone no	Contact	Email
McParland Bridge Road Pharmacy	M-F 9am-6pm. Sat 9am-5:30pm. Sun closed	119 Bridge Rd Maidenhead SL6 8NA	01628 623125	Aumbreen Masood	bridge@hamcparland.co.uk
Boots The Chemist	M-F 8:45am-5:30pm. Sat 9am-5:30pm. Sun closed	23 High St Ascot SL5 7HG	01344 623236	Hans Dhami	hans.dhami@boots.com
Boots The Chemist	M-Sat 9am - 8pm. Sun 11am-5pm	The Lexicon Shopping Centre, 19- 23 Braccan Walk RG12 1BE	01344 303844	Hazel Corrigan	hazel.corrigan@boots.com
Boots The Chemist	M-F 8:30am-6pm. Sat 9am-5pm; Sun closed	5 The Square Harmans water RG12 9LP	01344 425599	The pharmacist	caroline.shu@nhs.net
Hetpole Pharmacy	M-Sat 9am-6:30pm. Sun closed	398 Dedworth Road Windsor SL4 4JR	01753 868594	Harpreet	hetpole@enimed.co.uk
Tesco Stores	Mon 8am-10:30pm; Tue-Fri 6:30am-10.30pm; Sat 6:30am-10pm; Sun 10am-4pm	The Meadows Sandhurst GU47 0FD	0117 2915649	Preeti Sagoo	preeti.sagoo@tesco.com
Willow Pharmacy	M-F 7-10:30pm. Sat 9:30am-8pm; Sun 10am-10pm	7 Willow Parade Slough SL3 8HN	01753 313000	Subhash Gayam	info@willowpharmacy.co.uk

Surrey Heath

Pharmacy	Address	Phone number	NHS email	website
Lloyds Pharmacy Inside Sainsbury's	Watchmoor Park, Blackwater Valley Road, Camberley GU15 3YN Mon – Thurs 0700 – 2300 Fri Sat 0700 – 2200 Sun 1000 - 1600	01276 62785	nhspharmacy.watchmoorpark.lloydspharmacyfrc28@nhs.net	Pharmacy overview website
BOOTS, Camberley	26-30 Obelisk Way, Camberley GU15 3SD. Mon – Sat 0830 – 1800 Sun 1030 - 1630	01276 691006	maureen.lee2@nhs.net	

Any community Pharmacist can order supplies of a prescribed drug for the same day delivery if ordered before 11.30 am, and for the following morning if ordered before 5.00pm. (Monday to Friday).

16. ACCESS TO SUBCUTANEOUS FLUIDS (COMMUNITY SETTING)

Occasionally it is clinically appropriate to commence subcutaneous fluids for patients within the community setting. This should only be under the advice of a member of the specialist palliative care team. Close liaison with teams providing community-based services is needed as there is no formal policy for accessing this intervention in the community.
The policy in BHFT is under review at time of writing.

17. CONTACT TELEPHONE NUMBERS

Palliative Care Team contact numbers

Frimley Park Hospital 0300 614 5000 7/7 8.30-16.30 Extn 136755 Bleep 5799	**Wexham Park Hospital** 0300 615 3000 7/7 0830 – 1630 0300 615 4879 (ext 154879) Mobile: 07592070321
Phyllis Tuckwell – Frimley South	**East Berkshire – Thames Hospice Palliative Care Response Team.**
main number 01252729400 ART (advice and referral team) 01252 729440 email pth.adviceandreferral@nhs.net	At any time, call • **Single Point of Access** 01753 848925

18. FURTHER INFORMATION

Common queries
- Organ and tissue donation: www.organdonation.nhs.uk
- Donations to medical science: www.hta.gov.uk

19. REFERENCES

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- Royal Marsden Manual online (2012)
- Willcock (2020) Palliative Care Formulary (7th edition). Pages 67 - 71 (furosemide) and 309 - 313 (phenobarbital)
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