

FRIMLEY ICS

ADULT PALLIATIVE CARE SYMPTOM CONTROL GUIDELINES

- 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

Version: 2

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This guideline has been registered with the Frimley Health and Care ICS. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt, contact a senior colleague or expert. Caution is advised when using guidelines after the review date. This guideline is for use across the Frimley Health and Care Collaborative only. Any use outside this location will not be supported by the Frimley Health and Care Collaborative and will be at the risk of the individual using it.

POLICY DEVELOPMENT

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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. Chapter Nine will assist with patients who are imminently dying.

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.

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, nursing homes or the patient's own home). They are designed to aid decision-making by experienced professionals without specialist palliative 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 (concordance) 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 (PCF9 Pharmaceutical Press)

CONTACT DETAILS FOR SPECIALIST PALLIATIVE CARE TEAMS

Patients' location	Daytime weekdays advice	Out of hours advice
Frimley Park Hospital	All referrals to be made on EPIC 08:30 - 16:30, Mon-Sat Ext (03006) 136755 Duty CNS mobile: 07393243073	Out of hours (16:30 - 08:30 Mon-Sat, all day Sun) contact a senior doctor. 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, Mon-Sat Ext (03006) 154879 Or CNS mobile through switchboard.	Out of hours (16:30 to 08:30, Mon to Sat, all day Sun) contact a senior doctor, switchboard then has access to the on call Consultant for telephone advice.
East Berkshire community setting	Single point of Access Thames Hospice 01753 848925	Single point of Access Thames Hospice 01753 848925
Phyllis Tuckwell Hospice	ART (advice and referral team) 01252 729440 Or email pth.adviceandreferral@nhs.net	ART 01252 729440
Royal Berkshire Hospital NHS Foundation Trust	Internal ext. 7826 Urgent queries 0118 322 5111 Voicemail 0118 322 7826 Referrals taken by phone 08.00 to 16.00, 7 days a week	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

CHAPTER ONE - PAIN

1. INTRODUCTION TO PAIN MANAGEMENT

Pain assessment is essential because:

- It is important to identify treatable underlying contributors, such as constipation, infection, pathological fractures, unaddressed fear, depression or sleep disturbance
- Some drugs are effective for some pain types and not others
- 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.

Pain treatment: The WHO ladder versus problem-specific approaches

Pain treatments fall into two groups:

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 stepwise fashion (the World Health Organisation Pain Ladder).

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
- Skeletal muscle spasm
- Smooth muscle spasm (colic)
- Malignant bone pain
- Incident pain and other episodic pains

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, acute (short-term) pain, cancer pain and 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
Cancer	Usually of mixed cause and therefore initially treated with broad-spectrum analgesics (paracetamol, NSAIDs, opioids) Treating the underlying cancer is 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
Chronic	Often amenable to specific approaches, 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. Inexperienced clinicians are advised to seek advice early. https://fpm.ac.uk/opioids-aware	Chronic Pain Team

2. BROAD-SPECTRUM ANALGESICS

2.1 Commencing and titrating broad-spectrum analgesics in palliative care

Paracetamol

Paracetamol 1g PO QDS is the 1st line broad-spectrum analgesic based on tolerability. Reduce dose in low body weight and/or the patient has impaired liver or renal function.

	Weight ≤40kg	Weight 41-49kg	Weight ≥50kg
Oral dosing	500mg QDS	500mg-1g TDS	500mg-1g QDS
Max daily dose	2g	3g	4g
Dry weight should be used If over 50kg (dry weight), 1g QDS PO is safe for short periods (≤ 7 days), If needed regularly long-term (> 7 days), reduce dose. Irrespective of weight where the patients eGFR is less than 30ml/min/1.73m ² , the interval between dosing must be a minimum of 6 hours			

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 painkiller
- You will offer alternatives if ineffective, but that paracetamol is the safest 1st option

If patients struggle with the tablet load, consider caplets, soluble or liquid preparations.

If other analgesics are subsequently added, consider a trial discontinuation of paracetamol to assess contribution to overall analgesia.

Codeine Phosphate

If paracetamol is insufficient, codeine 30-60mg PO QDS may be added, along with a laxative (e.g. senna 7.5 to 15mg BD PO). If a liquid preparation is needed, use codeine (15mg/5ml) 10-20ml PO QDS 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. A substantial proportion of the 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 instead.

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) TDS PRN. 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

First choice strong opioid by all routes.

Morphine is available in two forms:

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

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

Zomorph 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, check formulary for available strengths.

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:

- Morphine solution (10mg/5ml)
- Concentrated morphine solution (100mg/5ml)
- Tablets (e.g. Sevredol). The tablets are scored: i.e. can be halved.
- Orodispersible tablets (Actimorph)

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

Prescribe by brand and 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)
- 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 in appendix 1 to comply with the requirements of the NICE guidance (NICE CG140).

Starting dose of MR morphine

The starting dose for regular modified release morphine is 10mg PO 12 hourly. When regular codeine has been initially effective this starting dose may not be sufficient (codeine 60mg QDS 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 to be calculated. Consider a lower dose (e.g. 5mg PO 12 hourly) for frail debilitated patients.

Remember to also prescribe:

- Regular laxatives (e.g. senna or macrogol): 90% of patients will require a laxative.
- As needed prn antiemetic (e.g. metoclopramide/ haloperidol. 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.

- 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, although 12 hourly preparations are more convenient.

Titration

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

Effective pain control is achieved **or**

Adverse effects appear (see 'opioid adverse effects') **or**

PRN opioid doesn't bring relief and/or two previous dose increases in succession haven't helped.

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

If the severity of the pain warrants more rapid dose titration, discuss with the Palliative Care Team or Pain Team; a parenteral approach may be preferable.

See table below for managing opioid side effects.

Oxycodone

Oxycodone is a strong opioid with similar properties to morphine. Based on morphine equivalent doses, it is twice as potent as morphine. It can be prescribed second line in patients 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.

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.

Fentanyl/buprenorphine

Transdermal fentanyl and buprenorphine differ from titration of oral opioids. Prescribers unfamiliar with the opioid being used are advised to seek advice from the Specialist Palliative Care Team, Pain Team or a Pharmacist.

NSAIDs

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

- Gastroduodenal ulceration: risk factors include:
 - Increasing age
 - Previous ulcer

- Type and dose and duration of NSAID
- Concurrent antiplatelet, anticoagulants, SSRIs or corticosteroids
- Renal: all NSAIDs (including coxibs) can exacerbate renal impairment
- Cardiovascular: there are two cardiovascular safety concerns with NSAIDs:
 - Pro-thrombotic risk (e.g. myocardial infarction).
 - Exacerbation of heart failure.
- Bleeding risk: in thrombocytopenia and anticoagulated patients
- 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 TDS has a good overall (especially gastrointestinal) safety profile. Dose may be titrated up to max 2.4mg/24hrs
Naproxen	250-500mg PO BD (particularly if cardiovascular risk is high and NSAID unavoidable. However, higher gastrointestinal risk than diclofenac and low dose ibuprofen)
Diclofenac	MR 75mg PO BD 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.
Celecoxib†	100mg PO BD or (100mg OD in hepatic impairment) may be required if GI risk is very high, and other NSAIDs have not been tolerated. A PPI is not needed unless the patient has extremely high GI risk. It also does not affect platelet function. Capsules can be opened and sprinkled on food. Celecoxib should be started by specialist palliative care but is the PCF9 NSAID of choice.

Gastroduodenal risk

If NSAIDs can't be avoided in patients with risk factors, prescribe a proton pump inhibitor (PPI) e.g. omeprazole 20mg PO OD. The dose and duration of treatment should still be minimised as far as possible. Famotidine 20mg BD may be used in patients unable to tolerate PPIs.

Parenteral NSAIDs

Patients previously receiving oral NSAIDs do not generally require a parenteral NSAID if oral route is lost (e.g. when approaching the end of life); 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.

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 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
- Skeletal muscle spasm
- Smooth muscle spasm
- Malignant bone pain
- Incident pain and other episodic pain
- Unaddressed fear, depression or other psychosocial distress

Common adverse effects from opioids:

Managed by

1. Opioid dose-reduction (adding non-opioid analgesics if required).
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 '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 <i>not recommended and non-formulary</i> PAMORA (peripherally acting mu opioid receptor antagonists) may be considered in refractory opioid induced constipation, specialist advice should be sought. • Naldemedine 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
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 <u>short-term</u> haloperidol 0.5-1.5mg ON 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 (e.g. 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 antihistamine e.g. chlorphenamine (commonly used despite limited role of histamine in opioid induced itching). Give stat dose, if beneficial prescribe regularly. If severe and persistent, consider opioid switch or ondansetron 8mg TDS PO
Myoclonus	Other drugs may cause this (e.g. gabapentinoids). Consider also metabolic causes. If pain is poorly opioid responsive, reduce dose and add a non-opioid analgesic If pain is fully opioid responsive consider opioid switch If marked myoclonus, give clonazepam† 0.5mg ON 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 and is often transient. Give haloperidol† 0.5-1.5mg PO/SC nocte or metoclopramide 10mg TDS PO/SC for 5 days. 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.

2.2 Switching opioids

Conversion errors can be fatal: The Opioid Equivalence Table below is a quick reference for those familiar with these opioids. 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:

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

Indications for switching opioids:

- **Non-oral route required** (e.g. vomiting, weakness, dysphagia):
 - Subcutaneous (e.g. via 24 hr subcutaneous syringe driver): steady state is achieved more rapidly than with transdermal opioids
 - Transdermal: 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.** (e.g. 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).

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 TD fentanyl.

Dose conversions:

Convert from	Patch instruction	Breakthroughs
Immediate release morphine/oxycodone	Apply patch	Give regular IR doses for 12h (e.g. 3 doses) then use PRNs
Modified release morphine/oxycodone	Apply patch at same time as last dose of MR	Use IR as PRN
CSCI morphine/oxycodone	Apply patch 12h before stopping CSCI	Use PRNs

Patches 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 dispose of them with their normal household waste, 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, long hot baths. Monitor for signs of toxicity in patients with fevers.

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

Transdermal Buprenorphine

The main advantage is in those patients who require transdermal route, but whose opioid requirement is too low for the use of fentanyl.

Occasionally buprenorphine may be used following recommendation of a Specialist Palliative Care Team or Chronic Pain Specialist. 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.

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 Palliative Care input:

- **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
- **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

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

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, upon discussion with palliative care.

See hepatic/renal impairment sections for advice on opioid switches in this cohort.

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**
QDS dose	24 hour total dose (mg)	QDS dose	24 hour total dose (mg)	4 hour / PRN dose (mg)	12 hour MR BD dose (mg)	24 hour total dose (mg)	4 hour / PRN dose (mg)	24 hour total dose (mg)	4 hour / PRN dose (mg)	12 hour MR BD dose (mg)	24 hour total dose (mg)	4 hour / PRN dose (mg)	24 hour total dose (mg)	24 hour total dose (mg)	Micrograms per hour
60	240	50	200	2-5	10	20	2	10	1-3	5	10	1	5	5	½ x 12***
		100	400	5-10	20	40	2-5	20	2-5	10	20	2	10	10	12
				10	30	60	5	30	5	15	30	3	15	15	25
				15	45	90	7.5	45	7.5	20	40	2-5	20	30	37.5

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.

				20	60	120	10	60	10	30	60	5	30	40	50
				30	90	180	15	90	15	45	90	7	45	60	75
				40	120	240	20	120	20	60	120	10	60	80	100
				50	150	300	25	150	25	75	150	10	75	100	Seek specialist advice
				60	180	360	30	180	30	90	180	15	90	120	
				70	210	420	35	210	35	105	210	15	105	140	
				80	240	480	40	240	40	120	240	Max****	120	160	
				90	270	540	45	270	45	135	270	SC Volume	135	180	

* 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 or alternatives

Opioid Induced Hyperalgesia

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

Always SEEK SPECIALIST ADVICE

Management includes:

- Reduce the dose of the causal opioid to about 25%
- Switch to an opioid with less risk of OIH, i.e. fentanyl (highest risk) → morphine → methadone → buprenorphine (lowest risk)
- If occurring at very low doses (less than 10mg/ 24hr) discontinue the opioid completely.
- Use non opioid analgesia

3. PAIN AMENABLE TO SPECIFIC APPROACHES

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

FIRST LINE OPTIONS

Choice of agent	Initial dose	Rate of increase / max
Amitriptyline [†] . Minimal tablet load; syrup available; good 1 st -line choice unless antimuscarinic effects preclude use	10mg - 25mg ON PO	10-25mg every 3-7 days Usual max ¹ : 50-75mg/day
Gabapentin . Few drug interactions; good evidence base and widely used; capsule contents can be dispersed in water if swallowing problems	300mg ON PO (if frail: 100mg ON with slower titration)	300mg every 1-3 days (100mg if frail) Divide doses ³ (BD or TDS) Usual max ¹ : 1800mg/day Absolute max ² : 3600mg/day
Pregabalin can be given twice a day so more convenient than gabapentin. For patients who have swallowing difficulties, capsules may be opened and contents dispersed in water	75mg BD PO (if frail 25- 50mg BD with slower titration)	150mg every 3-4 days (25mg if frail) Absolute max ² : 600mg/day
Duloxetine if both tricyclics and gabapentinoids ineffective, poorly tolerated or contra-indicated	30mg OD PO	Increase to 60mg after 1-2 weeks. Divide doses above 60mg to BD Absolute max ² : 120mg/day

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

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

³Examples 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 ON PO	10-25mg every 5-7 days Usual max ¹ : 50-75mg/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. Apply once daily and remove after 12hrs.	
Carbamazepine . 1 st line for trigeminal neuralgia Otherwise 3 rd line [†] : consider referral.	100-200mg MR BD PO	100-200mg every 1-2 wks. Divide MR doses (BD) Usual max: 800mg/day
Sodium valproate [†] . Single daily regimen helpful where tablet load is problematic; trial results conflicting.	200mg MR ON PO	200mg every 2-5 days Usual max ¹ 800mg/day Absolute max ² : 2500mg/day

NICE guidelines on the treatment of neuropathic pain

NICE clinical guideline 173 (Neuropathic pain in adults: pharmacological management in non-specialist settings) provides guidance on options for the management of neuropathic pain in adults.

1st line systemic treatments:

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.

Amitriptyline†

Minimal tablet load makes it a useful first line agent. It is inexpensive and available as tablets (10mg, 25mg, 50mg) and syrup (10mg/5ml, 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.

Initially 10mg-25mg daily in the evening, increased if tolerated in steps of 10-25mg every 3-7 days in 1-2 divided doses; usual dose 25-75mg in the evening, doses above 100mg should be used with caution. 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 in divided can be used but is rarely tolerated).

Stopping: Avoid abrupt withdrawal after prolonged use.

Gabapentin

A widely used and well tolerated alternative 1st line agent where use of amitriptyline is precluded. Tablets are significantly more expensive than capsules. Capsule contents can be sprinkled† on food or dispersed† in water or fruit juice and taken immediately. The commonest adverse effects are drowsiness and unsteadiness. It has few clinically important drug interactions.

Typical dose titration:

300mg ON PO for first 1 to 3 days, then 300mg BD PO for next 1 to 3 days, then 300mg TDS 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 ON PO for first 1-3 days, then 100mg BD PO for next 1 to 3 days, then 100mg TDS PO thereafter for a stable period (usually at least a week), then subsequent increases of no more than 100mg per day.

If no benefit seen with 1800mg/day, consider stopping gradually 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)

Pregabalin

Acts at the same target as gabapentin. Pregabalin is preferred in fibromyalgic pain (gabapentin lacks evidence in this group). Clinical experience suggests that response is more rapid than with gabapentin and that it is also helpful in patients not responding to, or not tolerating, gabapentin.

Start 75mg BD (in frailer patients: 25-50mg BD 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).

Duloxetine

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.

2nd line systemic treatments: nortriptyline, carbamazepine, 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.

Carbamazepine is rarely used except in trigeminal neuralgia (where it appears to be more effective than other agents).

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 prescribed to patients under 55 years (male and female) unless agreed by two specialists. Females of childbearing potential must be on a pregnancy prevention programme and males should be informed about the risk of having children whilst taking valproate. Always check the latest MHRA guidance before initiating.

Commence 200mg m/r ON (or 100mg syrup BD) 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).

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.

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 can be started by specialist palliative care 2nd line for topical treatment of localised neuropathic pain for patients in whom 1st line treatments are ineffective or poorly tolerated.

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 (TDS to QDS) 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.

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** to palliative care or pain teams.

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#; shared care protocol available)**
- **Methadone**; shared care protocol available.
- **Oral agents related to lidocaine: mexiletine#**
- **Cannabinoid† (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.

3.2 Skeletal muscle spasm

Key points:

- **Physiotherapy referral**
- **Baclofen**
- **Alternatives:**
 - Benzodiazepines (e.g. diazepam 2-5mg ON increased as necessary), where other indications are present (anxiety, sleep disturbance) and use is likely to be short-term
 - Acupuncture
 - Trigger point injections
- **Specialist referral**

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 include 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, and debility (both directly and through pain-avoidance).

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 TDS (OD-BD in elderly, frail or those with moderate renal impairment) and increase as necessary. Typical effective dose for spasticity is generally <20mg QDS (though if further increases are helpful and tolerated, can use up to 100mg/day). Contraindications include peptic ulceration. It can worsen seizure control. Muscle hypotonia may be worsened by concurrent tricyclic antidepressants. If not helpful, wean slowly to prevent withdrawal effects.

Diazepam (2-5mg ON 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 CYP450 inhibitors.

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.

Other agents may be 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**, is licensed for refractory spasticity in multiple sclerosis prescribed by a specialist.
- **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**
- 2nd line: NSAIDs, nitrates[†], nifedipine[†]

Biliary or renal/ureteric colic

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

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 QDS 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 urinary frequency, urinary urgency, urinary incontinence and neurogenic bladder instability • For immediate release oral preparation: start with 5mg PO BD-TDS increased if necessary up to 5mg QDS. In elderly patients start with 2.5-3mg BD, increased if tolerated to 5mg BD)
	Intestine	Mebeverine • Licensed for gastro-intestinal spasm • For immediate release oral preparation: 135mg-150mg TDS, preferably 20-30 minutes before meals
Transdermal patch		Hyoscine hydrobromide (Scopoderm TTS)[†] • Consider where other routes impractical • Monitor for psychotropic effects (e.g. delirium, memory impairment)

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 OM PO)

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 BD PO
- Normal release/short-acting nifedipine (including SL nifedipine) is not recommended for spasmodic pain. It may cause large variations in blood pressure and reflex tachycardia

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

Key points:

Assess fracture risk. Risk factors prompting d/w 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)

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

Drugs:

NSAIDs (+/- paracetamol) are usually extremely helpful - check for risk factors before prescribing

Dexamethasone reduces risk of temporary increase in pain after radiotherapy if given prophylactically.

Opioids may have some benefit – assess response and stop if ineffective.

Orthopaedic surgery especially if bony instability (e.g. movement-induced pain) +/- high fracture risk

Bisphosphonates (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.

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. Mirel's scoring system is a more reliable indicator (see British Orthopaedic Association guidelines).

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 for the prevention of skeletal – related events in adults with solid tumours (TA 265)

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:

The action of conventional prn analgesia 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)

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 immediate release morphine or oxycodone** ~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 oral immediate release morphine or oxycodone 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 background opioid dose.

Identify and treat specific pains (neuropathic, bone, spasm etc)

For painful dressing changes and other procedures. If pre-emptive immediate release opioid is ineffective, discuss with the Palliative Care Team.

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:

- **Morphine (10mg/1ml) for injection applied topically in a carrier suitable for the wound type eg: Intrasite†** for painful ulcers and dressing changes.
- **Morphine mouthwash**
- **Topical local anaesthetic agents (e.g. EMLA†).**
- **Sublingual /Intranasal fentanyl [e.g. Abstral, Effentora].** Although absorbed quickly ($T_{max} \sim 15$ mins.) the duration of action can be up to 4hrs, hence immediate release oral morphine is still the drug of first choice. Transmucosal fentanyl products should only be used in adults on a regular strong opioid for chronic cancer pain for >1 week, with dose of regular strong opioid being equivalent to 60mg of oral morphine in 24 hours.

4. **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) see DVLA “At a Glance” guide.

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. Patients should be advised to carry a copy of their prescription for opioids when driving.

This advice can be supported with the patient information leaflet in appendix 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 is no different to that of people not receiving such medication. Breakthrough 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 and signposting patients:

See <https://www.gov.uk/driving-medical-conditions> for further information on the effect of underlying illness on fitness to drive (and requirement to notify the DVLA).

<https://www.gov.uk/drug-driving-law>

See appendix 1 for patient information leaflets

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] (remains under review at time of writing)

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 [BPS 2007])

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.

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.

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 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 treatment.

Maintenance opioid antagonists (e.g. naltrexone) will render opioid analgesia ineffective.

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.

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.

Are there any differences from using opioids in other patients?

The general principles of use are the same and should include empathic communication with the patient and reassurance that pain will be managed optimally. However:

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 exacerbating factors of severity)

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

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

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.

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 Palliative Care/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

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 cognitively impaired patients:

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**.

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)
- Some pains often respond incompletely to opioids. Specific approaches often help (see above)

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 PHQ-9 or GAD-7
- **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 may achieve 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 ineffective combinations escalating 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)

CHAPTER TWO – RESPIRATORY SYSTEM

1. **BREATHLESSNESS**

Treating the underlying cause offers the best relief

In patients with a 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

Treatable Causes

Comprehensive assessment and examination alongside investigations, if appropriate (e.g. full blood count, chest X ray), may reveal treatable underlying contributors. Consider **pulmonary emboli** in patients with breathlessness disproportionate or unexplained by underlying disease, chest examination and X ray.

In any patient	In patients with malignancy
Anaemia	Pleural effusion (d/w respiratory or oncology if well enough to consider drainage/pleurodesis. Furosemide may help in transudative effusions or pulmonary oedema but often ineffective in malignant exudative effusions)
Bronchoconstriction	Superior vena cava obstruction
Hypoxia	Lymphangitis carcinomatosa
HF	Bronchial obstruction
LRTI	Pericardial effusion
PE	Ascites
Sepsis	
Anxiety/depression	

Non-pharmacological measures

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

- **Breathing exercises**
- **Increased airflow** (opening windows, electric/handheld 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

Drug therapies

Opioids:

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 limited so 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 e.g. 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- e.g. morphine sulfate IR 2mg 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 1mg - 3mg PRN 2hrly 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.

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 BD 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 2-5mg 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** (e.g. citalopram 10mg om for 7 days then increase to 20mg om, 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'

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) in line with BTS oxygen guidance.

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% e.g. 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 CO₂ accumulation secondary to hypoxic drive)- involve respiratory team

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

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 $\geq 4\%$ 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 completing HOOF Form to the oxygen supplier, Dolby Vivisol: Email to hoof.dv@nhs.net

For further advice contact the AIR/RITS team on fhft.respiratorycare@nhs.net or 0300 613 8032

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 QDS is sometimes helpful for breathlessness or to aid expectoration: limited evidence, but minimal risk other than financial cost and medicalisation

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**.

2. COUGH AND RESPIRATORY SECRETIONS

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 QDS.
- SECOND line: **codeine linctus** 15-30mg (5-10ml) QDS PO. Skip this if already on opioids
- THIRD line: **morphine** 2-5mg 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 QDS.
- 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)

Treatable Causes:

Cancer related

Discuss with an oncologist options for radiotherapy or other anti-cancer treatments

The most common cancer cause is large airway irritation from mediastinal or hilar deposits.

Consider a trial of **dexamethasone** 8mg OM PO for 5 days (or SC 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 requiring weaning.

Other cancer causes include:

- Lymphangitis carcinomatosa (discuss with oncology team)
- Radiotherapy/chemotherapy/immunotherapy-induced pneumonitis or fibrosis. Immunotherapy side effects may present several months after treatment
- Pleural effusion (if well enough to consider drainage +/- pleurodesis, discuss with Resp Team)
- Haemoptysis

Other – manage appropriately

- 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 OD). Benefit may take several weeks. If no improvement, consider adding a prokinetic (e.g. **metoclopramide** 10mg TDS) or referral to gastroenterology. If improvement, consider reducing to minimum effective dose after 4-8 weeks. See also NICE guidance.
- Post-nasal drip

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.

Drug therapies

Dry cough:

First line: simple linctus 5-10ml QDS

Second line: codeine linctus 15-30mg QDS (5-10ml) PO or go to third line if already on opioids

Third line: morphine 2-5mg 4 hourly PO if opioid naïve or 5-10mg 4 hourly PO if previously taken opioids/switching from codeine.

Wet cough:

Aid expectoration with 'huffing' and **sodium chloride 0.9% nebulisers** 10ml QDS

Consider a **physiotherapy** referral to teach 'huffing' and other techniques.

Carbocisteine can be used to reduce sputum viscosity. Use 750mg TDS (subsequently reducing to BD). 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 20mg SC 2-4hrly PRN or CSCI 60mg.) Treat associated distress/anxiety with sc midazolam if necessary.

Refractory cough/secretions - 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:

Gabapentin[†] (cough)

Nebulised lidocaine[†] (cough)

Nebulised furosemide[†] (bronchorrhoea)

Octreotide[†] (bronchorrhoea)

3. HICCUP

Key points:

Gastric distension +/- Gastro-oesophageal reflux are the commonest treatable causes.

Other treatable causes include **metabolic disturbance** (e.g. uraemia, uncontrolled diabetes, hypokalaemia, hyponatraemia) or drugs

First line options for persistent hiccup either:

Metoclopramide 10mg TDS (gastric distension is the commonest treatable cause in palliative care patients (**domperidone 10mg TDS** is an alternative if metoclopramide is contraindicated or if EPS is a risk)

PPI or antacid

Causes of Hiccups

Gastrointestinal Causes:

- **Gastric distension** is the most common treatable cause. Clinical features include hiccup, bloating, early satiety, nausea, vomiting. Predispositions include 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** (especially benzodiazepines and corticosteroids, also opioids, dopamine agonists and some chemotherapy agents.)
- Alcohol, infections, psychogenic causes e.g. anxiety

Non-drug / general measures

Identify and treat underlying cause and avoid any triggers

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.

Drug therapies

- **Treat gastrointestinal causes eg;**
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 BD PO, increasing as required to a maximum of 10mg TDS (effective in case reports and a small clinical trial)
Gabapentin[†] 100mg – 400mg TDS

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 considered in discussion with, the Specialist Palliative Care Team include; haloperidol, chlorpromazine, midazolam (usually only at end of life), nifedipine[†]

CHAPTER THREE – GASTROINTESTINAL SYSTEM

1. NAUSEA AND VOMITING

Always attempt to identify cause:

- Check biochemistry to exclude hypercalcaemia or uraemia
- Exclude constipation and bowel obstruction
- 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/metabolic causes - consider haloperidol
- Other causes - consider cyclizine

Second line drug therapies consider:

- Levomepromazine
- Dexamethasone
- Ondansetron

Treatable Causes

Always attempt to identify cause:

- Check biochemistry to exclude hypercalcaemia, hyponatraemia or uraemia
- Exclude constipation and consider bowel obstruction
- 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:

- **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. Consider gastric outlet obstruction and small/large bowel obstruction. Avoid using metoclopramide in COMPLETE bowel obstruction or the presence of colicky abdominal pain.
- **Chemical/metabolic cause**
Address underlying causes where possible (e.g. hypercalcaemia, uraemia, drugs such as opioids).
- **Other situations**
Address underlying cause where possible, e.g. vestibular irritation, raised intracranial pressure, gastritis, reflux, cough.

Non drug/ General measures

Ginger, smaller more frequent meals, avoidance of triggers (smells etc) may help.

Consider role of psychosocial distress - fear and anxiety can exacerbate nausea as well as pain.

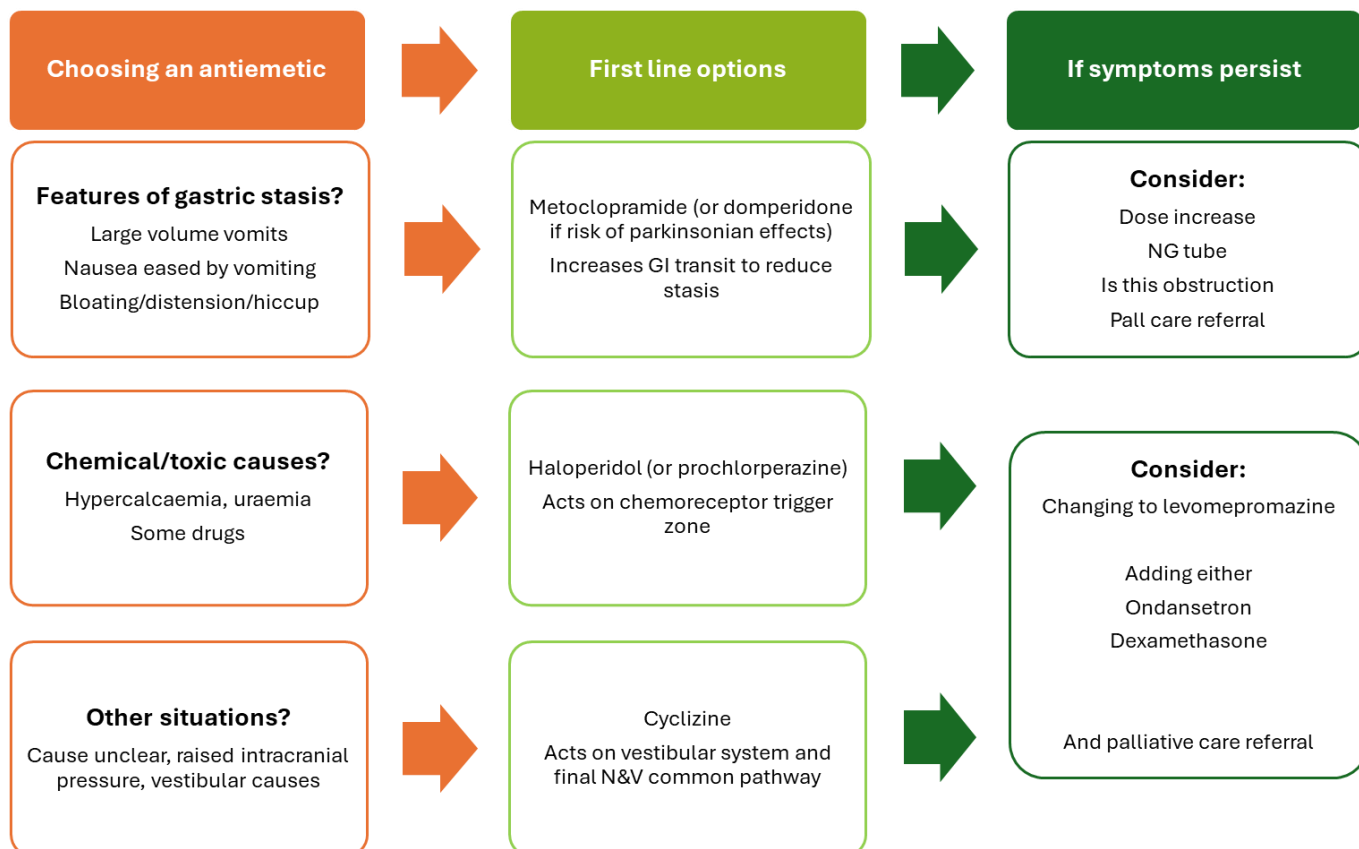
Is there an anticipatory component? Commonly seen with protracted nausea. Consider relaxation therapies or lorazepam.

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. Consider whether oral administration is likely to be effective.



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 OD	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
Olanzapine[†] Broad spectrum second line agent, may be less sedating than levomepromazine. Most evidence in chemotherapy related N&V	2.5mg ON	10mg OD	n/a	n/a
THIRD Line Agents				
Dexamethasone[†] Broad spectrum third line agent Reduce slowly if helpful, quickly if no benefit	8mg	16mg	3.3-6.6mg OM (or morning and lunch)	
Lorazepam[†] For anticipatory nausea or if anxiety a contributor	0.5mg PRN	1mg BD	Replace with midazolam 5-10mg	

Gastric Stasis:

Metoclopramide 10mg TDS PO (or 30-40mg/24hrs via CSCI if marked vomiting or unable to manage orally)
Prescribe additional metoclopramide 10mg PRN PO or SC (usual max 80 -100mg/24h, NB dose reduction in renal impairment)

OR

Domperidone 10mg BD-TDS PO. Dose may be increased cautiously in the absence of additional cardiac risk factors.

Cautions:

- **Metoclopramide:** risk of extra-pyramidal disorders and tardive dyskinesia. Recommendations are for a reduced daily dose and duration of treatment. In the off label palliative population, use can continue longer term, but patients should be monitored.
- **Domperidone:** 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 or inhibit CYP3A4.

Ongoing symptoms:

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

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.

Chemical/ metabolic causes:

Give an anti-dopaminergic antiemetic:

- **Haloperidol**[†] (licensing varies) 0.5-1.5mg nocte and PRN (up to 3 extra in 24 hours) PO/SC. Start with 500microgram – 1.5mg PO stat and nocte, typical maintenance dose 1.5 – 3mg nocte (or 500mcg – 1.5mg BD). 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 and **risk of extra-pyramidal side effects – use lowest dose for shortest duration possible.**
- Alternatives include buccal **prochlorperazine** 3-6mg BD PRN. Contraindicated in bone marrow suppression, epilepsy. Risk of extra pyramidal effects and photosensitivity

Other Causes:

Give an anti-histaminergic antiemetic:

- **Cyclizine** 50mg BD-TDS 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 PRN (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-dopaminergic with the potential to exacerbate parkinsonism:

Likely to be a problem with haloperidol, metoclopramide, prochlorperazine, levomepromazine

Domperidone should be used first line, cyclizine second line (less likely to cause exacerbation of symptoms)

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

Refractory symptoms – if still unresolved refer to specialist palliative care:

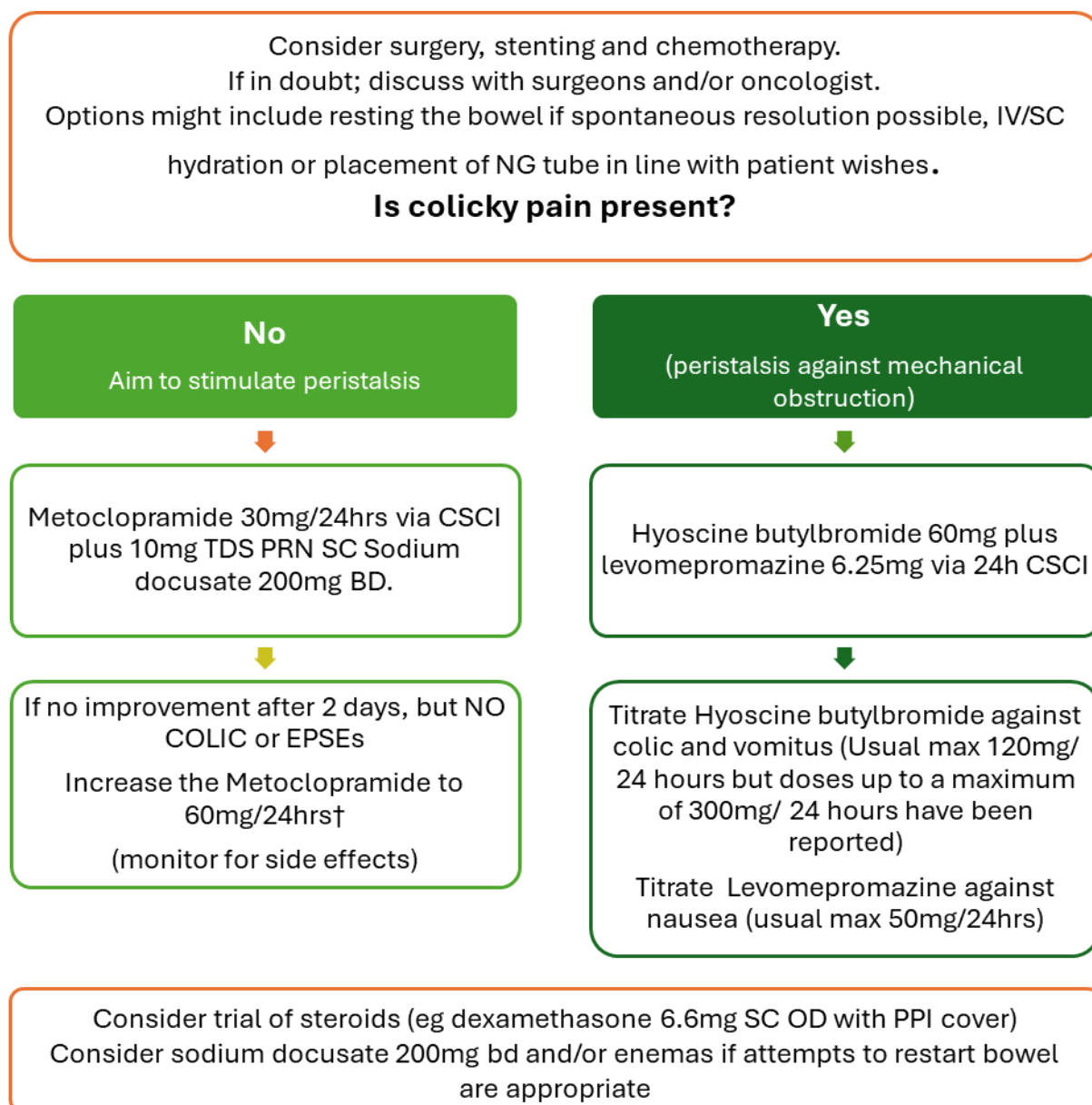
Has gastric stasis or a treatable underlying cause been missed?

If gastritis or reflux are suspected, commence PPI or H2 antagonist, e.g. lansoprazole or famotidine

Consider if oral absorption is effective, is a parenteral antiemetic required? May need conversion of critical meds (e.g. parkinsons/antiepileptics if suspected lack of absorption)

2. 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.



Consider reversible causes and disease modification:

- Options for treating disease related obstruction include surgery, chemotherapy and stenting.
- Constipation should be managed where possible
- Biochemical abnormalities (hypokalaemia or hypomagnesaemia)
- Where disease modification is not possible, proceed to the options described below

Non drug/ General measures:

Provide explanation and support

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 (e.g. frequent or large volume), offer a **nasogastric tube**, to allow aspiration during trial of medication.

Consider requirements for hydration by intravenous or subcutaneous route if appropriate.

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 OD 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.

Steroids:

Consider a trial of steroids with PPI cover. Some evidence of benefit for reducing nausea, but unclear evidence for benefit in resolving the obstruction.

Commence dexamethasone 6.6mg OM SC (if 3.3mg/ml vial). If no benefit after 5-7 days, stop.

Refractory symptoms/ Specialist referral

Octreotide[†] has an anti-secretory effect throughout the alimentary tract. Can be considered if no benefit on vomiting from maximum dose hyoscine butylbromide but may increase the likelihood of colic. A reduction in intestinal contents reduces distension and the likelihood of colic. 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).

3. MOUTH PROBLEMS

Key points

Patients rate mouth problems as one of the most distressing symptoms

Good dental hygiene and regular review of the mouth is of paramount importance

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

Soreness / pain / ulcers:

- **Candidiasis:** (redness +/- white plaques): **nystatin** 5ml QDS or **fluconazole** 50mg OD PO for 7 days
- **Mucositis:** (due to chemo/radiotherapy/haematopoietic stem cell transplantation):
If mild, antiseptic mouthwash can be used (e.g. benzydamine, - can be diluted in water if causes stinging)
Gelclair sachets can provide protection to ulcerated areas and improve oral intake.
Systemic opioids may be required.
Note: steroids are not part of the management of Mucositis
- **Ulcers** (e.g. Recurrent Aphthous ulceration): treat pain
FIRST line with topical anti-inflammatories e.g. **Bonjela** or benzydamine
SECOND line with topical steroids e.g. hydrocortisone oral muco-adhesive buccal tablets 2.5mg QDS. 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 drug causes: antimuscarinics, tricyclic antidepressants and opioids.

Look for and treat oral candidiasis

Support oral hydration

Give advice on oral hygiene and use of 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 with paraffin.

If too weak to self-care, involve carers/relatives in mouth care

If severe, consider specialist referral: parasympathomimetic saliva stimulants (e.g. **pilocarpine**) are used in refractory cases

Drooling:

Refer to dentist if dentures ill-fitting

Consider a barrier (e.g. Proshield, yellow soft paraffin (no paraffin if on oxygen) to maintain surrounding skin integrity

Use antimuscarinic to reduce saliva production - **Amitriptyline** 10-25mg ON, **Transdermal hyoscine hydrobromide** 1mg changed every 72 hrs.

Consider specialist referral:

Glycopyrronium oral solution (unlicensed special) 200mcg TDS up to 1mg TDS

Atropine eye drops 1% (unlicensed route) orally 1 – 2 drop up to QDS

Oral candidiasis

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.

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.

Drug therapies

Nystatin 5ml QDS 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.
Chlorhexidine inactivates nystatin so separate administration by at least 30 minutes

Fluconazole 50-200mg daily for 7 – 14 days.

Use where Nystatin is ineffective or impractical, co-existent oesophageal candidiasis is suspected (e.g. painful swallowing).

Beware of significant drug interactions.

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

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 from oral ulceration/mucositis, especially post radiotherapy, Antacid with oxetacaine (unlicensed special) may be recommended by palliative care or oncology teams

4. CONSTIPATION

Key Points

Patients commencing opioids should routinely be offered laxatives as all opioids will 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

Treatment:

There are 3 broad classes of laxative:

- **Softeners** also increase faecal mass and hence stimulate the bowel e.g. docusate sodium 200mg BD
- Osmotic laxatives
- **Bowel stimulants:** which, by reducing water re-absorption from faeces, also become softeners e.g. senna 7.5-15mg BD

Cost may influence physician’s choice of laxative, but ultimately patient preference & drug tolerability will improve compliance. There is limited evidence to guide the optimal regime for palliative care patients.

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)

Treatable Causes

Patients commencing opioids should 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 care 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 15mg BD. Add a softener if there is colic or hard stool
- **If already constipated:** start with senna 15mg BD. Consider a third day time dose if this is ineffective or increase the laxative the patient is already using if the patient wishes. Maximum dose 30mg TDS.

Key differences from usual care:

- 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

Non-drug/general measures

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

Drug Therapies:

General principles - There are 3 broad classes of laxative:

- **Softeners:** also increase faecal mass and hence stimulate the bowel (e.g. docusate)
- **Bowel stimulants:** which, by reducing water re-absorption from faeces, also become softeners (e.g. senna)
- **Osmotic agents:** act by an osmotic effect on the bowel (e.g. macrogols, magnesium salts)

Cochrane reviews conclude there is insufficient 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 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 BD. If the stool is hard or cramps occur, add a softener e.g. docusate sodium

Macrogols e.g. Laxido, Movicol, Cosmocol (osmotic)

- Not shown to be superior to lactulose in opioid-induced constipation.
- 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.
- Macrogols can interact with starch based thickening agents -causing thin solution which may result in aspiration.

Docusate sodium (softener with some stimulant action)

- Dose: 100mg BD and increase to 200mg BD if needed (sometimes up to 200mg TDS)
- Takes 1-2 days to work

Rectal preparations

- 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.
- Glycerol suppositories 4g are used to soften and lubricate
- Bisacodyl suppositories 10mg act to stimulate the bowel
- If Glycerol and Bisacodyl suppositories are ineffective, an enema may be required.
- Sodium citrate enemas such as micralax work by osmotic effect
- Phosphate enemas are a larger volume enema with osmotic effect, works within 5 minutes.
- Arachis oil enemas can be used to soften hard faeces overnight prior to administration of a phosphate enema. Arachis oil enemas are significantly more expensive than phosphate enemas and contain peanut oil – contraindicated in peanut allergy

Specific problems:

Constipation with colic

- This is caused by peristalsis against stool that won't move
- Unless the patient is obstructed, 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 30mg ON to 15mg BD
- Increase softeners, using rectal softeners initially, if required

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

- Give **hyoscine butylbromide** 20mg PRN QDS 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
- Use rectal intervention and concurrent antiemetics
- If refractory to these, and if opioid induced, consider use of a PAMORA (see below)
- Gastrointestinal obstruction: sodium docusate (200mg BD PO) is the laxative of choice because it softens without substantially increasing stool volume, causing a smaller increase in bowel distension than osmotic laxatives.

Refractory Symptoms/Specialist referral:

If opioid induced constipation is not resolved by use of conventional laxatives consider use of a peripherally acting mu opioid receptor antagonist (PAMORA).

- First line: Naldemidine 200micrograms daily
- Second line Naloxegol 25mg once daily – reduced to 12.5mg once daily in renal impairment or if concomitant use of CYP450 inhibitors
- Methylnaltrexone bromide can only be initiated by palliative care teams.

Combined naloxone-oxycodone (Targinact) is not recommended and is non-formulary.

5. 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)
- In malignancy (e.g. steatorrhoea, carcinoid syndrome, radiation-induced)

For non-specific management of diarrhoea:

FIRST line options:

Loperamide 2-4mg PRN (less systemic effects; more potent than codeine)

Consider BD regimen thereafter, with dose based on PRN requirement.

Usual maximum 16mg/24hrs (up to 32mg/24hrs occasionally used under specialist direction)

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

Treatable causes

Specific causes	Identification	Comments / Treatment
Clostridium difficile-induced	Risk factors • Antibiotic treatment (especially multiple agents/prolonged use) • Increasing age • PPI • Prolonged hospital stay • NG tubes • Severe underlying illness Symptoms: mild diarrhoea to severe bloody diarrhoea Diagnosis: stool sample	Where symptoms are severe, start while awaiting stool results. Treat as per local guidelines (e.g. vancomycin 125mg QDS PO for 10 days)
Drug-induced	Review treatment (including nutritional supplementation) and consider excess laxative use 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 underlying constipation (ensuring patient understands the rationale)
Bacterial overgrowth/ Blind loop	Consider if past history of bowel surgery	Consult local guidelines/specialists for recommended antibiotics
Other	Bile acid malabsorption Inflammatory bowel disease, secondary lactose/ gluten intolerance, autonomic neuropathy (diabetes, paraneoplastic)	Treat underlying cause where possible Seek specialist advice

Malignancy related problems		
Steatorrhoea/pancreatic insufficiency	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 OD 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)
Immunotherapy-related or radiotherapy-related proctitis or colitis	Usually within days/weeks of radiotherapy directly affecting bowel (e.g. treatment to spine or pelvis) Diarrhoea/Colitis may occur as a side effect of immunotherapy (can be early or delayed (months) following treatment)	D/w an oncologist as local or systemic steroids may be appropriate

Non drug/ General Measures

Assess fluid and electrolyte balance in all cases.

Ensure good skin hygiene and consider referral to continence service where appropriate.

Drug therapies

Where possible treat underlying cause. Review all drugs, including laxatives and non-prescription drugs.

Symptomatic relief can be achieved using:

Loperamide

Always confirm that diarrhoea is not secondary to infection, colitis or faecal impaction prior to starting loperamide.

- 4mg stat then 2mg after each loose motion initially
- Usual maximum 16mg/24hrs (higher doses occasionally used under specialist direction, requires ECG monitoring as prolongs QT at higher doses).
- Available in capsules or orodispersible form which may be more appropriate in patients with stomas.
- Maximum effect may take 16-24 hrs, so initial dosing may need to be more frequent.
- If used regularly can be given BD.

Caution: severe hepatic failure, interacts with CYP450 inhibitors - may cause drowsiness

Use with caution in patients at risk of *torsade de pointes* or other cardiac arrhythmias.

Refractory symptoms/ Specialist referral

Hyoscine butylbromide 60mg/24hrs via subcutaneous syringe pump

Octreotide†: This is an off-licence, infrequently used, drug which can be initiated after discussion with, or review by, a Specialist Palliative Care Team; doses of 250-500micrograms/day via CSCI.

Consider a colostomy if symptoms are intractable and unresponsive to symptomatic measures.

1. **LYMPHOEDEMA**

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)

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 myofascial strain): simple analgesics and general management of underlying lymphoedema
- 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 OM 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)

Treatable Causes of lymphoedema

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, 'wart' 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.
- **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

Non drug/ general measures via 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. Diprobase, 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. Aqueous Cream, Dermol) using a circular motion to soften and lift off the scales, then apply a greasy emollient.
Consider aqueous cream only as a soap substitute

- **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, as this will mean their legs are often in a dependent position, meaning they hang down below the level of the heart

- **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.

Drug therapies - managing complications

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
- 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 OM PO for two weeks and then reduce by 2mg OD 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 weight after 1 week trial of diuretic to measure if effective.

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 after clinical response 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.

- 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). Consider use of photography
- Antibiotics should be continued for at least **14 days** after clinical response to treatment
- Advise bed rest and elevation
- Decrease level of compression (garments or bandaging) during the acute attack.
- **Prescribe regular and PRN 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 if appropriate in line with patient's wishes and ReSPECT form. For 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 if familiar symptoms occur (but still seek medical review as soon as possible)

Prophylaxis to prevent recurrent cellulitis should be considered if >2 episodes of cellulitis per year.

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 recurrence**, requiring urgent referral

In addition to broad-spectrum analgesia (e.g. paracetamol, opioids), 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)

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)

Refractory symptoms/ Specialist referral

Early diagnosis and prompt referral for treatment is vital.

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.srymph@nhs.net

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

Out of Area Lymphoedema Referral:

St George's (adults/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	North Hampshire Hospital Aldermaston Road Basingstoke Hampshire RG24 9NA Tel 01256 313564

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

The Lymphoedema Support Network (patient support organisation): www.lymphoedema.org

(Holds a comprehensive list of specialist lymphoedema services in the UK)

2. 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 QDS PO for drug induced pruritis +/- rash

Refractory itch - SSRI (unlicensed) e.g. Sertraline 50mg daily appears beneficial for itch due to a variety systemic illnesses.

Consider Specialist referral

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.

Topical options

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-QDS may be helpful although some patients find the burning sensation unacceptable. Examples are Axsain® (0.025%) or Zacin® (0.075%) cream.

Drug therapies

Review medication: common allergic drugs reactions include:

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

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*	Biliary stent (discuss with gastroenterologists) Otherwise, consider trial of dexamethasone 8mg OM PO for 2 weeks. If helpful, reduce by 2mg per week down to minimum effective dose	Sertraline † 50mg OM 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	
Opioid (including spinal)	Consider a trial of H1 antihistamine or switch opioids	Ondansetron 8mg BD PO †
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†)
* 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		

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 OD PO) may be as effective, and better tolerated
- Itch due to systemic metabolic disturbance (uraemia, cholestasis) is not mediated by histamine, and antihistamines’ benefit lies mainly in their 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
- Gabapentin[†] or pregabalin[†] post-dialysis may be useful in uraemic itch.

SSRIs[†] for itch

Serotonin is thought to be an important central nervous system mediator of itch, especially where caused by systemic illness. Two 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 OM 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

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)

CHAPTER FIVE –ANXIETY AND AGITATION

Anxiety, agitation, and terminal agitation (also referred to as terminal restlessness or agitated delirium) are common but distressing symptoms. They can cause significant suffering for patients and families and pose clinical challenges for healthcare professionals. Effective management requires timely assessment, identification of reversible contributors, proportionate use of non-pharmacological and pharmacological interventions, and careful ethical consideration.

Key points:

Identification and management for delirium often requires palliative care specialist input
Reversible causes should be looked for and treated if appropriate (although not always possible.)
Prioritise non-pharmacological management, utilise pharmacological strategies if this fails (if acutely dying, benzodiazepines and antipsychotics)
Patients and their families should be given psychological support.

1. ANXIETY

Anxiety is a common symptom resulting in excessive fear, worry or apprehension. This can be triggered by symptoms of the background disease or illness progression, uncertainty, social / psychological problems, or existential distress. Exploration of the patient's concerns with history taking and collateral history taking from family and carers may elicit the cause for the anxiety. Listening, and addressing the cause of the anxiety in a calm, empathic and supportive approach will often allay the fears.

Medication Management of Anxiety in Palliative Care

- Oral route available: lorazepam- 0.5-1mg PRN up to 4 hourly- oral or sublingual depending on age, co-morbidities and frailty. Maximum 2-4mg/24h (2mg in elderly patients)
- No oral route: midazolam 2-5mg s/c injection PRN up to 1-2 hourly. Maximum 15mg/24h
- If patients have a longer prognosis, an SSRI may be helpful

2. AGITATION AND TERMINAL AGITATION

Agitation is observable restlessness, emotional distress, or physical overactivity which can be caused by anxiety, delirium, pain, or other physical or psychological causes.

Terminal agitation – agitation/delirium resulting in rapid onset psychomotor restlessness in patient in last few hours/days of life generally with decreased concentration/variable consciousness.

Up to 42% of dying patients experience some features. Caused by combination of physiological causes including end-organ failure, sepsis, metabolic changes, medication toxicity, psychosocial/spiritual factors.

Why is Agitation a problem?

- Distressing / stressful to patients, relatives, medical team.
- Impedes communication at critical stage in disease.
- Can make pain / symptom assessment more difficult.
- Costs- increased need for inpatient care / staffing costs.

All patients with signs of agitation should be assessed for delirium. This is reversible in up to 50% of cases so potentially reversible causes need to be excluded.

Common potentially reversible causes of delirium

Alcohol	Haematological causes	Urinary retention
Anxiety	Infections	Withdrawal from alcohol / nicotine
Biochemical abnormalities e.g. hypercalcaemia, uraemia	Medications e.g. opioids & steroids	Withdrawal from drugs e.g. antipsychotics,
Cardiovascular causes	Nausea	benzodiazepines, opioids
Cerebral pathology	Nutritional deficiencies	
Constipation	Pain	
Dehydration	Positioning	

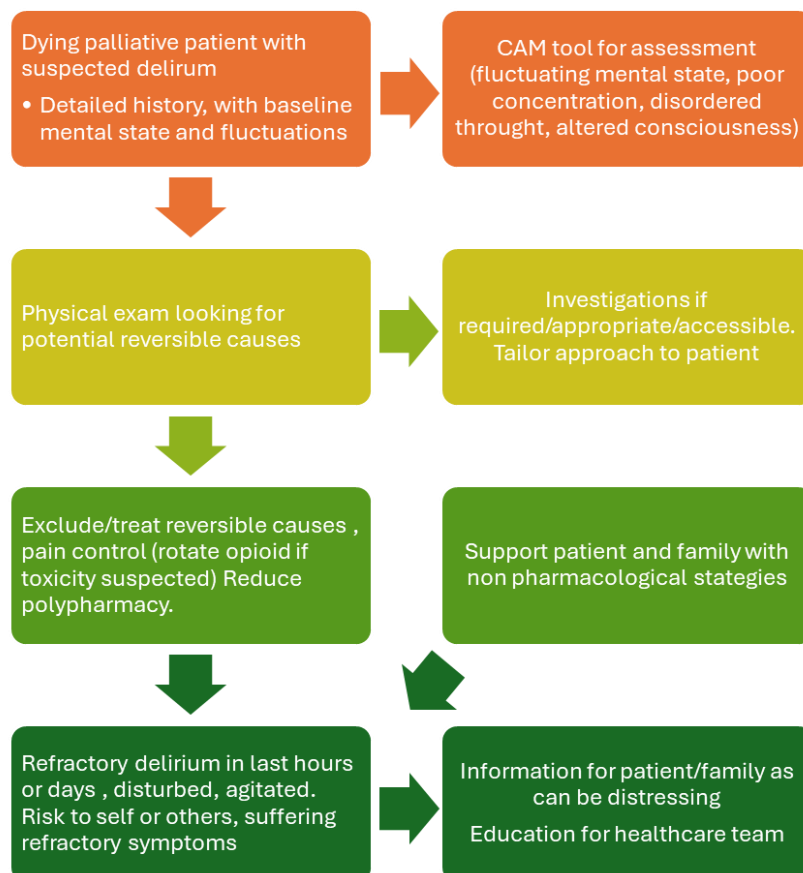
Tools for Assessing Terminal Agitation

Not ideal in severe cases as reduced cooperation or communication problems by patient. Often assessed looking at history, asking relatives and pattern recognition.

- Confusion Assessment Method (CAM) used to assess for delirium. Based on 4 cardinal features of delirium:
 1. Acute onset and fluctuating clinical state
 2. Poor concentration
 3. Disordered thoughts
 4. Altered state of consciousness

A diagnosis of delirium requires features 1 and 2 and either 3 or 4.

- Memorial Delirium Assessment Scale (MDAS)- sensitivity 97%, specificity 95%
- Richmond Agitation-sedation Scale modified for palliative inpatients (RASS-PAL) for assessing balance of sedation with medication



Management of Agitation and Terminal Agitation

Main aims at end of life for management of agitation

1. Preserve patient's comfort and dignity with compassion and reassurance.
2. Reduce agitation, relief of symptoms and distress.
3. Ensure safety of patient, staff, family and other patients.
4. Ease hallucinations, delusions and restlessness

Balanced with preserving lucidity/alertness as much as possible - provide comfort with careful use of sedatives accepting this may affect lucidity. Ideally discuss plans before the patient loses capacity.

Non-pharmacological management:

Inform family of condition and educate about delirium, give reassurance that treating distress is the priority.

Provide emotional, psychosocial and spiritual support and guidance for patient and family.

Agitation can be improved by the presence of family – reassure the family that they are supporting the patient and involve them in the care of the patient.

Warn that may be start of more rapid and irreversible decline.

What can relatives do:

- Report symptoms to healthcare professionals.
- Try to reorientate patient if appropriate to person and place, consider use of photos and pictures
- Get right balance of visitors
- Acknowledge what patients are experiencing and try not to argue with them.
- Listen to what is being said as may have significant meanings.

Other strategies:

- Environment modification- quiet, calm and consistent. Remove high beds, electrical cables, knives, cigarette lighters, Pressure pad alarms on floor or bed.
- Minimise use of catheter, intravenous lines, and physical constraints
- Good lighting
- Re-orientation- clock, orientation board with information such as day and date, familiar objections e.g. family photographs.
- Communication strategies- access to glasses, hearing aids, interpreters, simple supportive language
- Continuity of care from same members of staff; 1:1 nursing may be required.
- Symptom control – manage pain, optimise nutrition and hydration, check bowel and bladder function.
- Try to restore sleep / wake cycle- natural light, reduce noise / stimulation at night.

Pharmacological Management:

Principles

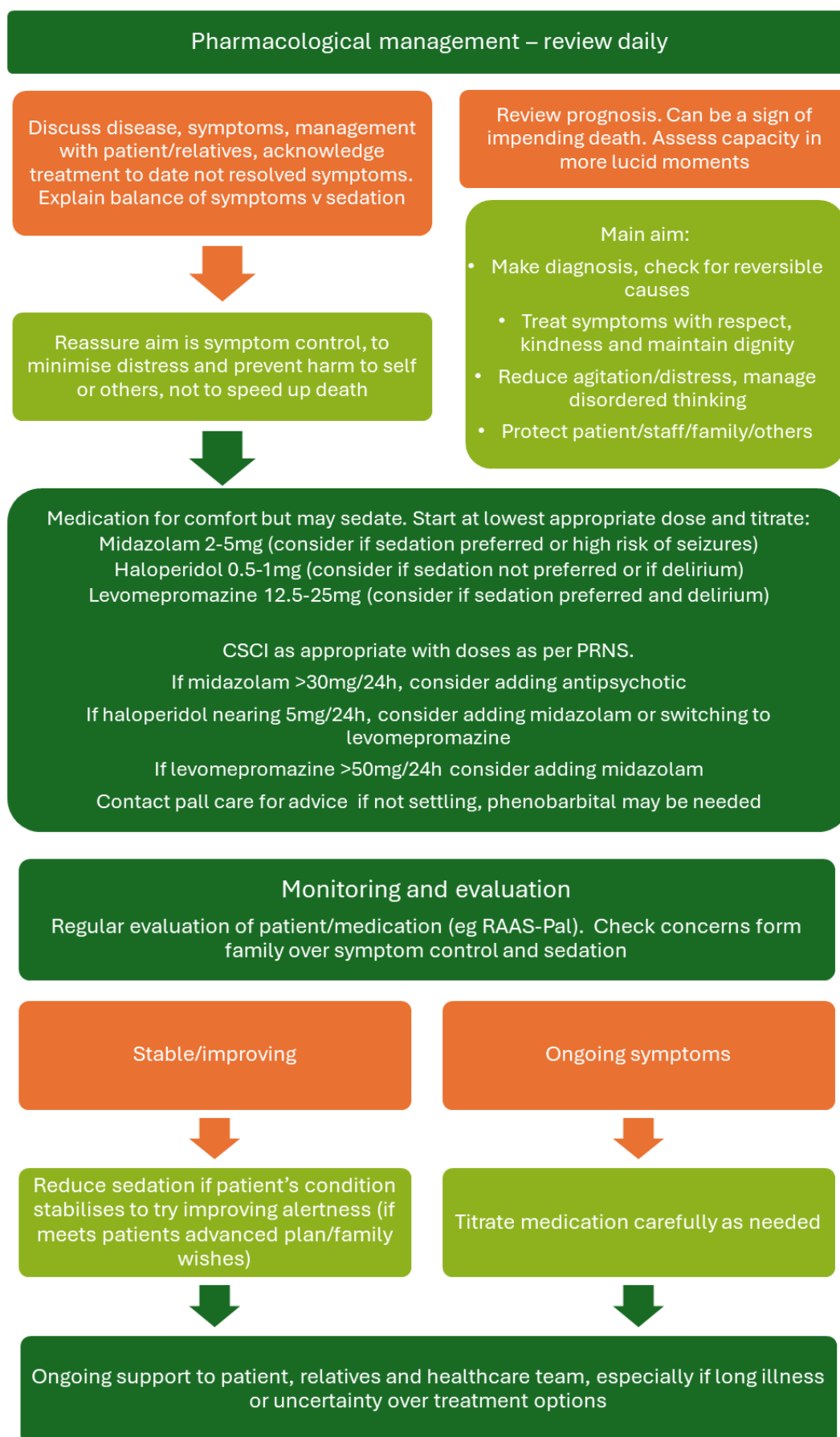
- Review prognosis, acknowledge treatment to date has not resolved symptoms
- Reduce polypharmacy, optimise pain control and consider opioid rotation if toxicity suspected.
- Explore options of balance of symptom control and comfort versus sedation. Balance with potential risks of paradoxical agitation, respiratory depression and aspiration.
- Reassure aim of sedation is symptom control, to minimise distress and prevent harm to the patient or others and not speed up death.
- Sedatives and antipsychotic medication are reserved for when non-pharmacological treatment not helped, and are used when patient is at risk to themselves or others, frightened or overwhelmed.
- Start drugs at lowest appropriate dose and carefully titrate as required.
- Patient specific factors- route of administration / co-morbidities; use lower doses if old / frail.

- Regular evaluation of patient and medication and check concerns from family and symptom control and level of sedation.
- Option to reduce sedation if patient's symptoms stabilise to try and improve alertness (if family's wishes and with consent).
- Palliative sedation may be used if end of life to reduce awareness and relieve suffering from refractory symptoms. They are likely to reduce level of consciousness. Discuss with specialist palliative care.

In a patient who has lost their oral route with terminal agitation, options of benzodiazepines and antipsychotic medication:

Drug Group	Benzodiazepines	Neuroleptic	Neuroleptic	Barbiturate
Drug Name	Midazolam	Levomepromazine	Haloperidol	Phenobarbital SPECIALIST ONLY
Uses	Rapid control of agitation and anxiety	Control of agitation and delirium- particularly if sedation beneficial	Control of agitation and delirium	Control of agitation if benzodiazepines / neuroleptics not helped
Usual PRN dose	2-5mg PRN S/C hourly	12.5-25mg PRN S/C hourly but usually less often	0.5-1mg PRN S/C 2 hourly but usually less often	100-200mg IM PRN or 1-3mg / kg
Usual starting dose in syringe driver	10-30mg over 24 hours	25-100mg over 24 hours	1.5-5mg over 24 hours	300-600mg over 24 hours
Side effects	Paradoxical agitation, respiratory depression, withdrawal if rapidly reduced, tolerance	Lowers seizure threshold, hypotension, paradoxical agitation, extrapyramidal symptoms	Extra-pyramidal side effects more common but less sedating than levomepromazine	paradoxical excitement in elderly, hypotension, nausea and vomiting, Stevens-Johnson syndrome
Caution		Avoid or use with caution in Parkinson's Disease, Lewy Body dementia, high risk of seizures	Avoid or use with caution in Parkinson's Disease, Lewy Body dementia, high risk of seizures	Only for refractory management of terminal agitation under specialist palliative care consultant

Pharmacological Management and Monitoring and Evaluation of Terminal Agitation



3. ETHICAL CONSIDERATIONS

- Respect patient autonomy and preferences.
- Make shared decisions in accordance with patient's wishes and advanced directives.
- Control of symptoms and relief of suffering - a balance is required if sedation required, generally try mild sedation first with the ability to continue to interact before moving to deeper sedation if ongoing agitation.
- Individualised care to suit the needs of each patient.
- Support for relatives and caregivers facing challenging decisions.
- Address any concerns the use of sedation can speed up death due to respiratory depression, hypotension or dehydration.

CHAPTER SIX – PALLIATIVE CARE EMERGENCIES

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

1. <u>HYPERCALCAEMIA OF MALIGNANCY</u>	
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 TDS 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 patients 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 Palliative Care Team. • Following rehydration, IV zoledronic acid or pamidronate as per local guidelines • Additional guidance is available for community clinicians Palliative Care Teams. 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 <30ml/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.

2. SPINAL CORD COMPRESSION AND CAUDA EQUINA SYNDROME	
Recognition	The aim is to make the diagnosis <i>before significant neurological signs are obvious</i>: • 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 PPI. 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. Monitor blood glucose levels whilst on high dose steroids. If in doubt, discuss with the Palliative Care Team or the patient’s oncology team.

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 PPI. 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 If in doubt, discuss with the Palliative Care Team.

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 <i>and</i> Midazolam: Subcutaneous: 10mg repeated after 5 mins if not unconscious but imminently dying. Buccal: The buccal route (dosed as above) can be used if no immediate access to injectable medication. (Intravenous: 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 Palliative Care Team Oxygen Dexamethasone 16mg one-off PO, SC or IV (followed by 8mg morning and lunchtime PO) and PPI Monitor blood glucose (in view of high dose corticosteroids) Symptomatic relief as per respiratory chapter.

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)
Management based on type	• 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.

	Informed consent: The aim of fluid removal is symptom control. Most patients experience improvement in breathlessness, nausea, vomiting and distension-pain. 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 most common 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)
Diuresis	<i>Who benefits from diuretics?</i> 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 OM PO. Check that amiloride is not being received concurrently. If serum potassium is towards the upper limit of normal: • Commence furosemide 40mg OM 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, ARBs) • Monitor U+E more frequently (e.g. every 2-4 days)

	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 BD PO and consider adding in furosemide 40-80mg OM 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 BD and spironolactone 200 mg BD 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 electrolytes (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 • Opioids and other measures for breathlessness • 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): 300mcg BD SC is reported to reduce ascitic accumulation in malignancy. Benefit is also reported for chylous ascites (in combination with fat-reduced diet).

6. HAEMORRHAGE	
Management of major haemorrhage if imminently dying	(If aim is to resuscitate - follow advanced life support guidelines) Ensure HCP/family knows: • Stay with the patient to support them and their family • Use dark-coloured towels/sheets to camouflage blood • That sedative medication often has little role because death frequently occurs before it can be administered. Consider prescribing midazolam for sedation 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.

	If IV route is appropriate, give midazolam in 2mg increments every 1-2 minutes until unconscious. Higher doses may be required if using regular benzodiazepines or excess alcohol. 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.
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 - 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 QDS or 500mg of injection solution†. Systemic haemostatic agents: Tranexamic acid 500mg-1g BD-QDS PO. Generally avoided with urological bleeding: risk of ureteric obstruction in upper renal tract bleeding and of clot retention in any renal tract bleeding.

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 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 seizure	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 of 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 (however monitor closely for skin side effects) • Monitor effect of medication which can lower seizure threshold, such as haloperidol or levomepromazine; review need and dose.
Community management – chronic seizures	Consider if neurology input/imaging is needed. In palliative setting for those pts not on antiepileptic medication: First line - Levetiracetam (Keppra) • Loading dose of 500mg – 1g 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, IV and SC doses are identical. • If fits observed repeat loading dose 500mg-1g 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 PCF9) • Common side effects: fatigue, drowsiness, ataxia (see PCF 9). Behavioural disturbance may occur in 3-4%. Antiepileptics have been associated with suicidal ideation: advise patient to report mood or thought disturbance. If cerebral metastases are likely consider adding/increasing dexamethasone, with blood glucose monitoring (once daily) and PPI cover. Give Dexamethasone 8mg/6.6mg BD PO/SC 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	If not for escalation: 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 Rectal diazepam PRN (Usual dose 10mg; 0.5mg/Kg up to a maximum dose of 30mg PRN PR)

	If refractory to the above, contact the palliative care team urgently who may use the following: • SC midazolam 10mg, repeated after 10-15 mins if needed. • If not responding, loading with 10mg/kg phenobarbital IM. • High doses of the above may be needed via syringe driver.
End of life, loss of oral route	Midazolam is generally the drug of choice because it is beneficial for concurrent agitation, and is compatible with other drugs given via syringe pump. • If PRN midazolam has controlled seizures, commence CSCI midazolam 20-30mg/24 hrs • Where escalation to phenobarbital required to control seizures, use a stat dose of 10-15mg/kg IM (unless IV access available), then as needed additional stat doses of 200mg IM 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/cut 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

CHAPTER SEVEN – DRUG HANDLING IN RENAL INSUFFICIENCY

Renal failure either alone or as 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 its metabolites in patients whose renal clearance is impaired.

1. CLASSIFICATION OF RENAL INSUFFICIENCY:

CKD	eGFR (ml/min/1.73m ²)	Description	Common Symptoms
1	>90	Normal kidney function but abnormal urine findings, genetic factors or structural abnormalities	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, muscle cramps, impairment in 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

Calculation of GFR:

MDRD (Modification of Diet in Renal Disease) eGFR is the standard for estimation of renal function. This is more accurate for estimating renal function but assumes all patients have a body surface area of 1.73m². 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, use IBW. Use up to date resources to help with calculation of CrCl and IBW.

Common 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 because of hypersensitivity reactions, which involve either glomerular or interstitial damage.

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

Aminoglycosides, Amphotericin and Ciclosporin may cause direct renal toxicity to tubules (acute tubular necrosis)

Drugs causing postrenal damage (urinary tract obstruction):

- Anticholinergics (e.g. 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 nephrogenic diabetes insipidus.

2. EFFECT OF RENAL IMPAIRMENT ON 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 and prescribing information as per The Renal Drugs Handbook (5th Edn) unless stated otherwise.

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
	<i>Mild GFR 20 – 50ml/min</i>	<i>Moderate GFR 10 – 20ml/min</i>	<i>Severe GFR <10ml/min</i>	<i>HD*</i>	<i>APD/CA PD**</i>	
Paracetamol	Dose as in normal renal function	Dose as in normal renal function	500mg-1g every 6 – 8 hours	Y	N	Beware of Na concentrations in soluble tablets. Reduce dose for low body weight
Naproxen	Dose as in normal renal function, but avoid if possible	Dose as in normal renal function, but avoid if possible	Dose as in normal renal function but only if on dialysis	N	Slightly dialysed	Nephrotoxic and increased bleeding risk. Careful assessment of risks and benefits
Ibuprofen	Dose as in normal renal function, but avoid if possible	Dose as in normal renal function but avoid if possible	Dose as in normal renal function but avoid if possible	N	N	
Codeine phosphate	Dose as in normal renal function	30mg up to every 4 hours. Increase if tolerated.	30mg up to every 6 hours. Increase if tolerated.	N	Unlikely to be dialysed	Metabolites accumulate. Increased risk of drowsiness

Tramadol hydrochloride	Dose as in normal renal function	50-100mg every 8 hours and titrate as tolerated	100mg every 8 hours and titrate as tolerated	Y	Not known	
Morphine	75% of normal dose	Small doses (50% normal dose) and extended dose intervals. Titrate according to response	Small doses (25% normal dose) and extended dose intervals. Titrate according to response	Y	N	Metabolites can accumulate. Ensure naloxone available. Some units avoid slow release oral preparations
Buprenorphine	Dose as in normal renal function	Dose as in normal renal function but avoid large doses	Reduce dose by 25-50% initially and increase as tolerated. TD: dose as in normal renal function.	Y	Y	
Oxycodone hydrochloride	Dose as in normal renal function, start with 75% of dose	Dose as in normal renal function, start with 75% of dose	start with small doses e.g. 50% of dose	not known	not known	Limited accumulation of metabolites compared to morphine
Fentanyl	Start with 75% of normal dose, titrate to response	75% of normal dose, titrate to response	50% of normal dose, titrate to response	N	N	No active or toxic metabolites
Alfentanil	Dose as in normal renal function	Dose as in normal renal function	Dose as in normal renal function	N	N	SEEK SPECIALIST ADVICE
Methadone	Dose as in normal renal function	Dose as in normal renal function	50% - 75% of normal dose and titrate to response	N	N	SEEK SPECIALIST ADVICE

Antiemetics

Drug	Renal impairment			Dialysis		Comments
	<i>Mild GFR 20 – 50ml/min</i>	<i>Moderate GFR 10 – 20ml/min</i>	<i>Severe GFR <10ml/min</i>	HD*	APD/CAPD**	
Metoclopramide hydrochloride	Dose as in normal renal function	Dose as in normal renal function	Dose as in normal renal function	Y	N	
Domperidone	Dose as in normal renal function	Dose as in normal renal function	Dose as in normal renal function	Unlikely to be dialysed	Unlikely to be dialysed	
Cyclizine	Dose as in normal renal function	Dose as in normal renal function	Dose as in normal renal function	Not known	Not known	
Levomepromazine (methotrimeprazine)	Dose as in normal renal function	Dose as in normal renal function	Start with small dose and titrate if necessary	Not known	Not known	Increased risk of cerebral sensitivity
Haloperidol	Dose as in normal renal function	Dose as in normal renal function	Start with lower dose. For single doses use 100% of normal dose. Accumulation with repeated doses	N	N	
Ondansetron	Dose as in normal renal function	Dose as in normal renal function	Dose as in normal renal function	N	Unlikely to be dialysed	

Benzodiazepines

Drug	Renal impairment			Dialysis		Comments
	<i>Mild GFR 20 – 50ml/min</i>	<i>Moderate GFR 10 – 20ml/min</i>	<i>Severe GFR <10ml/min</i>	HD*	APD/CAPD**	
Clonazepam	Start at low dose and increase according to response.	Start at low dose and increase according to response.	Start at low dose and increase according to response.	N	Unlikely to be dialysed	
Lorazepam	Dose as in normal renal function	Dose as in normal renal function	Dose as in normal renal function, start with low doses	N	Unlikely to be dialysed	Monitor use and effect carefully

Midazolam	Dose as in normal renal function	Dose as in normal renal function	Use sparingly and titrate according to response. Use bolus doses not continuous infusion	N	Unlikely to be dialysed	Use cautiously in continuous infusion if severe renal impairment
Temazepam	Dose as in normal renal function	Dose as in normal renal function Start with small doses	Dose as in normal renal function, start with small doses	N	Unlikely to be dialysed	
Diazepam	Dose as in normal renal function	Use small doses and titrate to response	Use small doses and titrate to response	N	Unlikely to be dialysed	Ensure flumazenil available to reverse effect

Adjuvant analgesia

Drug	Renal impairment			Dialysis		Comments
	<i>Mild</i> <i>GFR 20 – 50ml/min</i>	<i>Moderate</i> <i>GFR 10 – 20ml/min</i>	<i>Severe</i> <i>GFR <10ml/min</i>	HD*	APD/CAPD**	
Gabapentin	GFR 30-60ml/min start at low dose and increase according to response 300mg nocte to max 300mg TDS	GFR 15-30ml/min start at low dose and increase according to response 100mg nocte to 300mg BD	300mg on alternate days or 100mg at night, increased according to tolerability	Y	Probably dialysed	Titrate according to response every 2 – 3 days
Pregabalin	GFR 30-60ml/min initially 25mg TDS and titrate according to tolerability (max 150mg BD)	GFR 15-30ml/min 25mg – 50mg once daily – titrated to tolerability and response (max 150mg twice daily)	GFR <15ml/min 25mg once daily and titrate according to tolerability and response (max 75mg daily)	Y	Y	Doses may be divided.
Amitriptyline hydrochloride	Dose as in normal renal function	Dose as in normal renal function	Dose as in normal renal function	N	N	
Duloxetine	Dose as in normal renal function, start with lower doses	Start at very low dose and increase according to response	Start at very low dose and increase according to response	N	N	Contraindicated by manufacturer if crcl <30ml/min

Antidepressants

Drug	Renal impairment			Dialysis		Comments
	<i>Mild GFR 20 – 50ml/min</i>	<i>Moderate GFR 10 – 20ml/min</i>	<i>Severe GFR <10ml/min</i>	HD*	APD/CAPD**	
Citalopram	Dose as in normal renal function	Dose as in normal renal function	Dose as in normal renal function, use with caution	N	Unlikely to be dialysed	
Fluoxetine	Dose as in normal renal function	Dose as in normal renal function	Use low dose on alternate days and increase according to response	N	N	
Sertraline	Dose as in normal renal function	Dose as in normal renal function	Dose as in normal renal function	N	Unlikely to be dialysed	
Mirtazapine	Dose as in normal renal function	Start at low and monitor closely	Start at low dose and monitor closely	Unlikely to be dialysed	Unlikely to be dialysed	

Other medications

Drug	Renal impairment			Dialysis		Comments
	<i>Mild GFR 20 – 50ml/min</i>	<i>Moderate GFR 10 – 20ml/min</i>	<i>Severe GFR <10ml/min</i>	HD*	APD/CAPD**	
Hyoscine Butylbromide	Dose as in normal renal function	Dose as in normal renal function	Dose as in normal renal function	Y	Y	
Glycopyrronium bromide	Reduce dose by 1/3 (PCF9)	Reduce dose by 1/3 (PCF9)	Reduce dose by 1/3 (PCF9)	No data	No data	Titrate against effect
Fluconazole	50 – 100% of normal dose	50 – 100% of normal dose	50% of normal dose	Y	Y	
Baclofen	5mg every 8 hours and titrate according to response	5mg twice a day and titrate according to response	5mg once a day and titrate to response	Y	Not known	

Dexamethasone, prednisolone	Dose as in normal renal function	Dose as in normal renal function	Dose as in normal renal function	N	N	
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***HD (intermittent haemodialysis).**

For HDF/high flux (intermittent haemodiafiltration) and CAV/VVHD (continuous arteriovenous/venovenous haemofiltration or haemodialysis) - consult the latest renal drug handbook or specialist pharmacy service.

**** APD/CAPD (automated peritoneal dialysis/continuous ambulatory peritoneal dialysis)**

CHAPTER EIGHT – 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.

Prescribing Principles:

- use lower starting doses and increased dose interval (i.e. reduce frequency of administration)
- consider switching to immediate release preparations of opioids in preference to modified release due to their 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 cause, increase, or mask encephalopathy
- reduce polypharmacy
- regular monitoring of synthetic hepatic function -if clinically appropriate, to guide prescribing.

This is a summary of recommendations, detailed advice in hepatic impairment chapter in PCF9.

Hepatic impairment can be calculated as mild, moderate or severe based on the liver function, severity of encephalopathy and degree of ascites present. Use up to date resources to calculate Child-Pugh score.

Mild impairment/well compensated liver function = Child Pugh A = score of 5-6

Moderate functional impairment = Child Pugh B = score of 7-9

Severe impairment/hepatic decompensation = Child Pugh C = score of 10-15

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

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.
- Review opioids, doses 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 bioavailability. In general, all opioids accumulate in liver failure, increase the risk of hepatic encephalopathy and increase the incidence of side effects

Generally safer	Use with caution	Avoid
Fentanyl No increase in half life in severe hepatic impairment	Morphine Only use immediate release (stop modified release), Decrease frequency to every 6 – 8 hours Increase in half life in severe hepatic impairment (by up to 100%.)	Codeine- prodrug (reduced biotransformation with reduced or unpredictable effect)

	Buprenorphine (avoid TD products)	Tramadol
		Alfentanil - if unavoidable start with 50-100 micrograms every 1 hour PRN
		Dihydrocodeine
		Oxycodone Only use IR (stop MR) In severe impairment half life can increase by up to 400%. If unavoidable, decrease frequency of regular IR products to 8 hourly and PRNs to 2-4 hourly
		Methadone – SPECIALIST USE ONLY Very prolonged half-life, toxicity in hypoalbuminaemia, risk of fatal QTc prolongation. Accumulates even without hepatic failure.

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

Use cautiously	Avoid if possible
Paracetamol po – half life can double. Start with 500mg 8 hourly to max 1g every 8 hours.	NSAIDs, if unavoidable use ibuprofen 200mg 8 hourly
	IV paracetamol (contraindicated in severe hepatic impairment by manufacturers)

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.

Use cautiously	Avoid if possible
Lorazepam, start with 500mcg/24h	Clonazepam
Zopiclone	Diazepam
	Midazolam

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

Use cautiously	Avoid if possible
Domperidone, start with 5mg BD, max 10mg TDS	Cyclizine
Metoclopramide, start 5mg every 12 hours, max 10mg every 8-12 hours	Haloperidol
Ondansetron - max 8mg/24 hours (oral/subcutaneous)	Levomepromazine
	Prochlorperazine

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

Generally safer	Use cautiously	Avoid if possible
Levetiracetam	Sodium Valproate	Clonazepam
Gabapentin	Oxcarbazepine	Phenobarbital
Pregabalin		Phenytoin – adjust levels for low albumin
		Carbamazepine

Phenytoin levels can be corrected for albumin against renal function using the PCF 9 or the following website: <https://www.mdcalc.com/phenytoin-dilantin-correction-albumin-renal-failure>

CHAPTER NINE – CARE FOR DYING PATIENTS

1. 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 all settings. 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 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.
- 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 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

Processes may vary between settings but the principles of meticulous documentation and communications with other HCP and families should be followed.

- 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 should be offered.
- The difficulty in making an accurate prognosis should 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 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).
- 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 if appropriate. 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.
 - Complete last offices following hospital 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.

2. SYMPTOM MANAGEMENT IN THE LAST DAYS OF LIFE

Ahead of time

- Pre-emptive prescribing
- Differences in specific circumstances

Once the oral route is lost

- What can be stopped? – managing co-morbidities at the end of life
- How to prescribe a Continuous Subcutaneous Infusion
 - Opioid conversion,
 - Combining drugs in a syringe,
 - Dosing other drugs,
- What can and can't be given subcutaneously

Problems

- Uncontrolled symptoms (pain; restlessness; secretions; breathlessness; nausea; thirst)
- Obtaining medicines out of hours
- See main guideline for contact details for community teams

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 included here, but the doses needed by individuals vary widely:

it is more important to assess the effectiveness of each PRN before repeating or increasing doses – if a PRN is ineffective, try a different approach or seek advice (see flow diagrams below).

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

- a broader spectrum anti-emetic.
- ideal if severe terminal agitation is anticipated (i.e. where sedative properties are advantageous)
- levomepromazine and haloperidol may reduce seizure threshold

Differences in specific circumstances:

- **History of seizures:** also prescribe midazolam (10mg/2ml) 10mg SC PRN for seizures
- **Parkinson's disease:** use cyclizine (50mg/ml) 25mg SC PRN TDS in place of haloperidol for nausea and midazolam 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. For other drugs see chapter seven. 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) and nausea with levomepromazine.

3. 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 glucose daily at teatime, and adjust insulin to keep blood sugar between 6 and 15 mmol/l. 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). - If only on metformin, stop monitoring glucose - If other tablets, GLP-1s, Insulin – stop tablets, consider stopping insulin 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 (e.g. 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	See 'Palliative emergencies' seizure section

Corticosteroids	
Steroids contributing to symptom relief (i.e. symptoms likely to recur if stopped)	Convert to a subcutaneous bolus of Dexamethasone each morning: - Dexamethasone 4mg OM PO $\equiv$ Dexamethasone 3.3mg OM SC - Oral Prednisolone: <i>divide the dose by 6</i> (e.g. Prednisolone 20mg OM PO $\equiv$ Dexamethasone 2.5mg OM SC)
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	<i>Diuretics are usually continued until the oral route is lost.</i> 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 <i>not</i> usually required. However, if fluid overload <i>does</i> occur, consider: - Subcutaneous Furosemide† (half the previous PO dose). Usually given as a SC bolus, if volumes too large, syringe driver may be needed. - Opioids
Implantable cardioverter	East Berks: Monday – Friday 09.00-17.00 call Pacing Administrator 0300 6153095. Out of hours: Radiopager via Heatherwood & Wexham Park Hospital switchboard

defibrillators	on 0300 615000 and ask to page Cardiac Physiologists Pacing and ICD Radiographer West Berks: Monday – Friday 09.00-17.00, call pacing clinic (0118 322 6636) Out of hours, contact the Coronary Care Unit (0118 322 6528) Frimley Park: Complete form on EPIC, ward to contact pacing technicians on bleep 5051, 07747457261, or 0300 613 2167.
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). <i>This is very rarely required at the end of life</i> • Symptomatic management with opioids
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 2-5mg 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: ○ where the patient is imminently dying; sedation (e.g. Midazolam) ○ if the anticipated prognosis is longer; look for other causes (e.g. UTI); consider transdermal Rivastigmine (specialist use only) ○ 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 2-5mg PRN doses are required and are effective, titrate. If ineffective, or drowsiness is problematic, contact Palliative Care Team

4. JUST-IN-CASE MEDICATION SUMMARY AND PRESCRIBING A CSCI

Prescriptions should include medications that might be required for end-of-life symptom control, plus diluent.

Drug and indication	Dose	Concentration	Supply
Morphine Sulfate <i>Analgesia: Pain, breathlessness</i>	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 <i>Anxiolytic, sedative: anxiety/distress/myoclonus/fitting</i>	2mg -5mg up to 2 hourly	10mg/2ml	1 x 10 (ten)
Levomepromazine <i>Antiemetic/antipsychotic: nausea, delirium, agitation</i>	6.25mg up to 12 hourly 6.25-12.5mg up to 2 hourly for agitation	25mg/1ml	1 x 10
Hyoscine Butylbromide <i>Anti-secretory: respiratory secretions</i>	20mg 2- 4 hourly	20mg/1ml	1 x10
Haloperidol <i>Antipsychotic/antiemetic: delirium, agitation, nausea</i>	0.5 - 1.5mg up to 4 hourly	5mg/1ml	1 x 10
Water for injection	As diluent	10ml	1 x 10

Medicines in syringe driver must be individualised to the patient's symptoms and reassessed 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 60mg	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 OR Haloperidol should be prescribed

PRN doses - opioids must state dose interval and it is desirable to state maximum number of doses before reassessment. (e.g. If 3 doses in 4 hours seek medical advice)

4. PRESCRIBING A CONTINUOUS SUBCUTANEOUS INFUSION

A Continuous Subcutaneous Infusion (CSCI), or syringe pump, is used to administer symptom relief to patients with no oral route. It replaces existing symptom control measures and is titrated against PRNs.

Step 1 – are existing symptom control measures effective?

Look at dose requirements over past 24h period, including regular medication (eg MR opioid) and PRN use.

If controlled, add to syringe pump (or equivalent)

If not controlled, consider dose increases (especially if partially effective or benefit wearing off quickly) or alternatives

Step 2 – converting effective symptom control medicines into a syringe pump

1. Where symptoms are controlled by SC PRNs alone, the previous 24 hr requirements can be put into the pump

2. Calculate the total 24 hr dose requirements for oral symptom control medications, then:

- **Halve** the oral 24h dose for Morphine, Oxycodone, Haloperidol, Cyclizine for CSCI admin
- **Keep the oral 24h dose the same** for metoclopramide, hyoscine butylbromide, levomepromazine CSCI admin

3. Non-opioid analgesia is usually stopped when oral route is lost, but if pain is poorly opioid responsive, options include midazolam or NSAIDs such as diclofenac PR 100mg od, or 75-150mg via CSCI (incompatible with other drugs)

4. See section on comorbidities for other medications

5. Seek palliative care advice if required

Step 3 – prescribing the CSCI

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

Check compatibility of medicines in syringe

Example

Over the last 24 hrs, a patient’s symptoms have been well controlled on:

- Morphine MR 20mg BD PO = halved = Morphine Sulphate 20mg
- Metoclopramide 10mg TDS PO = same dose = Metoclopramide 30mg
- Midazolam, 2 x 2.5mg PRN SC doses = 5mg total = Midazolam 5mg

CSCI would contain morphine 20mg, metoclopramide 30mg and midazolam 5mg

Seek advice if unsure

5. CONVERTING OPIOIDS AT END OF LIFE

See opioid conversion table and notes in chapter one section one.

Converting opioids is inherently risky; if any doubt it is safer to dose reduce than increase

Conversions involving patches

Commencing Continuous Subcutaneous Infusions in patients receiving a stable patch

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 PRNs, leave the patch in place and give additional opioid alongside via a CSCI. This would usually be equivalent to the extra PRN opioid required in the previous 24 hours. Start an infusion with the opioid that the patient is already using for breakthroughs.

Why?

The time taken for changes in patches (whether increasing or stopping to change to a CSCI) is too long for patients in the last days of life and dose conversions are complex. The quickest solution is to add further opioid alongside the unchanged patch via CSCI. However, this does add an extra step in PRN calculations.

PRN calculations for combinations of patches with Continuous Subcutaneous Infusion

- Use the table to determine the equivalent 24-hour Morphine subcutaneous infusion
- Add this to actual CSCI dose to get *overall total 24 hour SC opioid-equivalent dose*.
- Divide this total by 6 for the PRN SC dose.

Example for Fentanyl 50 patch size plus 50mg **Morphine** via Continuous Subcutaneous Infusion:

The Fentanyl patch is equivalent to 120mg of oral Morphine over 24 hours, equivalent to CSCI

Morphine 60mg over 24hrs

The overall regular opioid dose is therefore 110mg SC Morphine (i.e. 60mg from the patch conversion +50mg from CSCI)

The PRN SC Morphine dose is therefore 15-20mg ($110\text{mg} \div 6 = 18.3$)

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 via PCF or book.pallcare.info

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

6. 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	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 (1 st 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 patPRNts 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.

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. 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.

7. SUBCUTANEOUS ADMINISTRATION OF DRUGS

Subcutaneous administration is useful where patients are unable to tolerate or manage oral medicines, avoiding the discomfort and access problems of the intramuscular or intravenous routes. However, few agents have 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 sulfate	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}	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 2}	Water		
<i>Diazepam</i>	n/a	Not appropriate for subcutaneous use	No
<i>Chlorpromazine</i>	n/a		
<i>Prochlorperazine</i>	n/a		

Notes

¹Morphine is preferred. **Diamorphine** is rarely used.

²These drugs are only started on specialist advice 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).

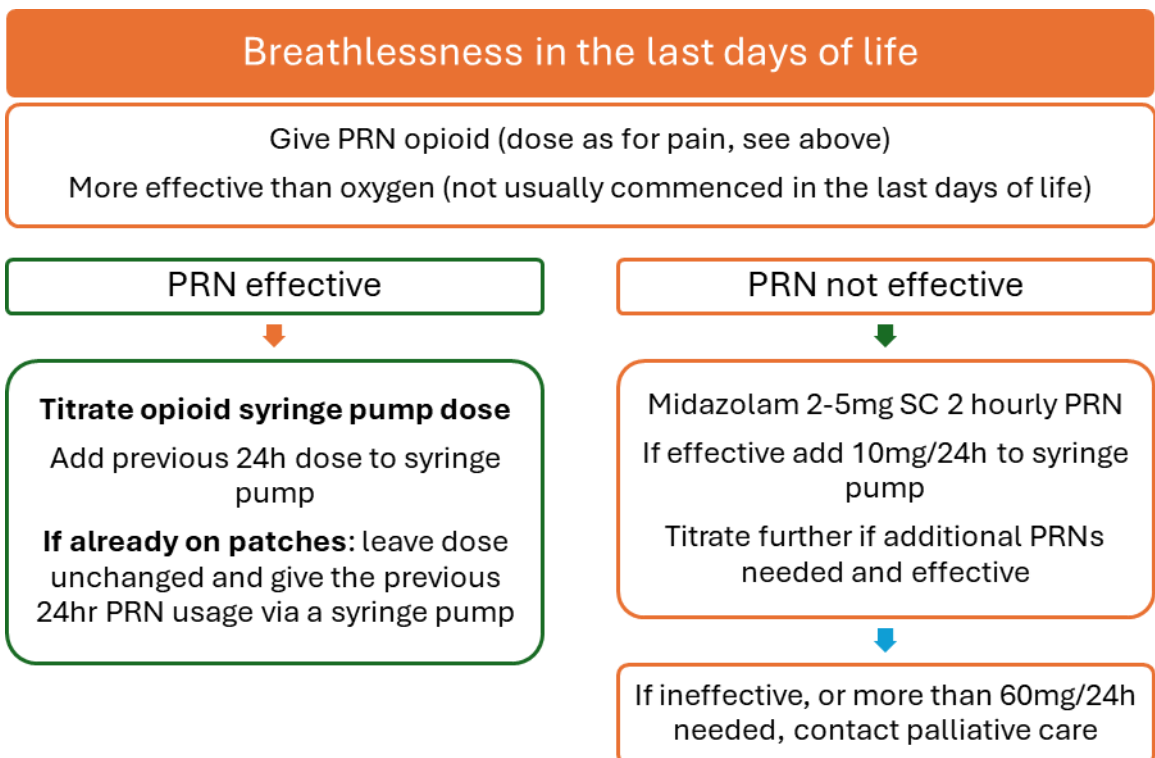
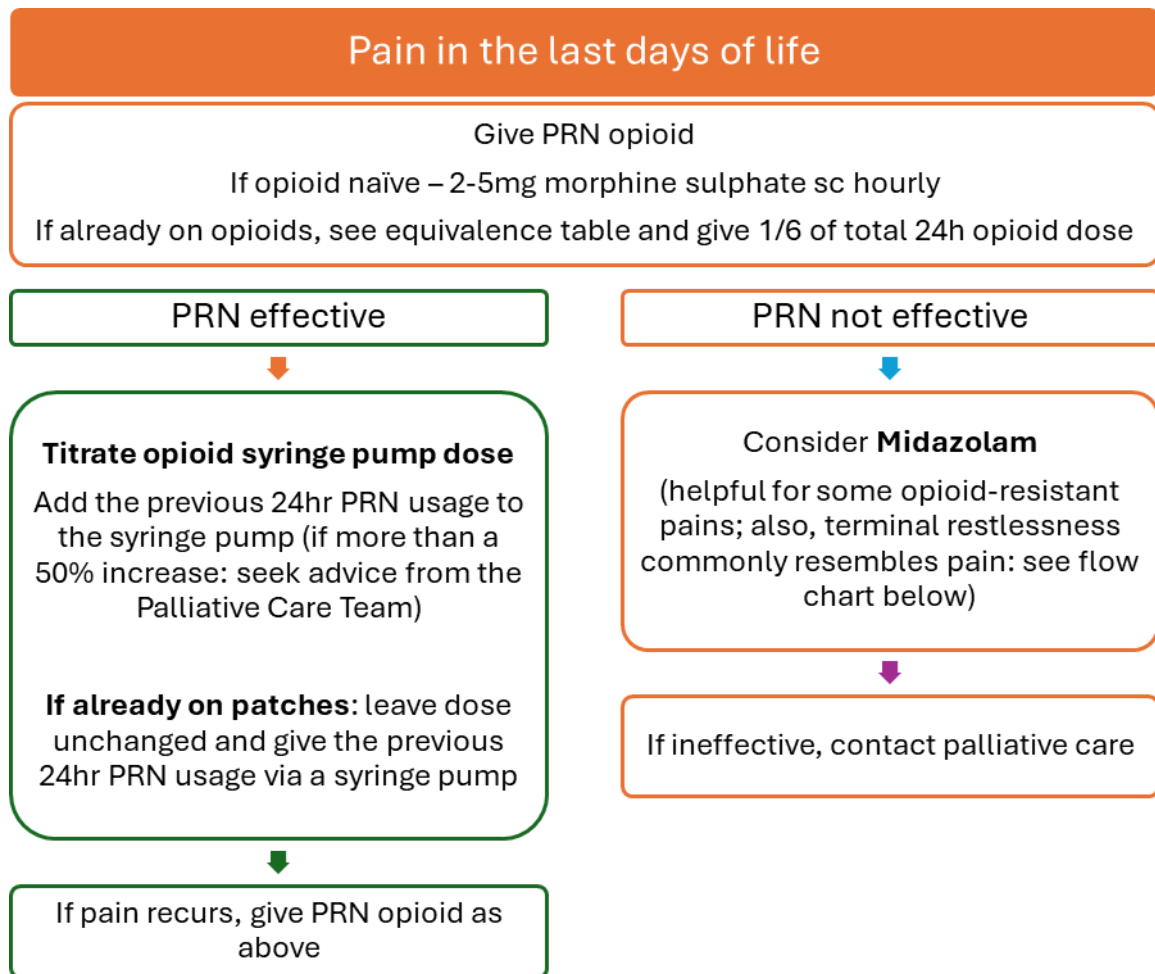
⁴**Furosemide** can be given by SC infusion† or stat SC injection† in those where IV access is problematic. The overnight diuresis from 24 hr SC infusions may be undesirable in those without a urinary catheter/sheath.

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).

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.

8. SYMPTOM MANAGEMENT IN THE LAST DAYS OF LIFE



Terminal restlessness in the last days of life

Give midazolam 2-5mg SC 2 hourly as required

PRN effective



If 2 or more PRNs are required in 24h, add midazolam to syringe driver

Prescribe the total midazolam dose used over the previous 24h

If further PRNs required and effective, increase syringe pump dose (see below if over 60mg/24h)

Notes: terminal restlessness sometimes requires bigger doses of Levomepromazine (typically up to 150mg/24hrs; occasionally up to 200mg/24hrs *on specialist advice*) than when used for nausea (typically up to 25mg/24hrs).

PRN not effective, last less than 1hr, or underlying delirium



Look for urinary retention/indication of pain and treat

Otherwise, give PRN SC antipsychotic

Haloperidol 1.5-2.5mg (0.5mg in the elderly) 2 hourly max 10mg/24h

OR Levomepromazine 6.25-25mg 4hrly)

If antipsychotic is effective, add the total dose used over the preceding 24hrs to the syringe pump



If restlessness continues, or needing more than

Haloperidol 10mg/24h or

Levomepromazine 150mg/24h or

Midazolam 60mg/24h

Contact palliative care

Nausea and vomiting in the last days of life

Give PRN antipsychotic (haloperidol 0.5mg-1.5mg SC 2-4 hourly or levomepromazine 6.25-12.5mg s/c 12 hourly)

PRN effective



If 2 or more PRNs needed, add total 24 hour dose to syringe pump

If recurs, give another PRN as above and add to syringe pump

If symptoms persist despite haloperidol 5mg/24h or levomepromazine 25mg/24h contact the palliative care team

PRN not effective



Contact palliative care team

Options include changing haloperidol to levomepromazine

Combining ondansetron (up to 16mg/24h) with levomepromazine

Retained respiratory secretions in the last days of life

Give PRN hyoscine butylbromide 20mg SC 2-4 hourly as required (up to 120mg/24h).
Explanation and reassurance for family/carers is particularly important

PRN effective



If 2 or more PRNs needed in 24h start a syringe pump

Hyoscine 60mg/24h via syringe driver alongside existing PRNs

If more PRNs needed and effective, increase dose to 120mg/24h in syringe pump

PRN not effective



If distressed give midazolam as per restlessness flow chart

If not distressed, reassure family/carers



If remains distressed contact palliative care team

Nutrition and hydration in the last days of life

Able to accept offers of small amounts of fluid or food

- Advise carers to give ‘what they fancy, when they fancy’,
- Explanation (e.g. “As the body gradually slows down, it starts to need less food and fluid. This is normal, so be guided by what they ask for and only give small amounts at a time”)
- Mouthcare as required

No longer managing oral fluids

- Carers may assume that IV fluids are required to avoid dehydration and, therefore, thirst. However, *thirst at the end of life is usually best avoided by good mouth care*. IV fluids are usually ineffective and unnecessary
- Showing carers how to perform mouth care if they wish can be an important way of enabling them to further contribute to the patient’s comfort

If thirst persists despite optimal mouthcare

- Trial of subcutaneous fluids in appropriate settings
- Ensure purpose (relief of thirst) is clear to family

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. See also <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. Mouth care and sips of water avoid thirst.
- IV/SC fluids in the last days of life do not improve:
 - thirst
 - consciousness
- 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. These guidelines were written before results of the CHELsea II trial have been published.

9. OBTAINING DRUGS OUT OF HOURS

For inpatients, contact the relevant on call pharmacist (or OOH service if community hospital)

If the patient is at home or in a care home, there is a list of community pharmacies commissioned to stock end of life drugs. OOH services also stock medicines for patients under their care.

Community Pharmacy Emergency Palliative Care Stock Scheme

Pharmacies in the scheme guarantee to stock palliative care medication. Check on the Community Pharmacy Thames Valley website for up to date pharmacies and stocklists: <https://cptv.org.uk/commissioned-services/berkshire-locally-commissioned-services/>

Appendix 1 – PATIENT INFORMATION LEAFLETS

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 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 or Morphgesic SR tablets (long acting morphine 12 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 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.

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 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: NameNumber.....:

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		

Immediate Acting Opioid

	Date	Dose
1		
2		
3		

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 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.

GP: NameNumber.....:

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		

Immediate Acting Opioid

	Date	Dose
1		
2		
3		

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:

Fencino, Matrifen, Mezolar.

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 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: NameNumber.....:

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		

Painkillers and Driving information for Patients

The medicines you are taking do not automatically stop you driving in the United Kingdom¹. 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 occur². From March 2015 it 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).*

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