



Mid Trent Cancer Network

# **MID-TRENT CANCER NETWORK SYMPTOM CONTROL GUIDELINES**

May 2006



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## Foreword

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These guidelines have been approved by the Mid-Trent Palliative Care Network Group and include emergencies, specific symptoms and the care of the dying.

Many of the guidelines reflect those found in the Network-adopted Palliative Care Formulary book and website ([www.palliativedrugs.com](http://www.palliativedrugs.com)) or Symptom Management in Advanced Cancer and are reproduced with the permission of Dr Robert Twycross and Dr Andrew Wilcock. To facilitate their use in practice, the guidelines are purposely concise with a self-imposed limit of two pages and an absence of references. Although the guidelines have been collated in this document for convenience, they should *not* be viewed as quick-fix 'recipe book' to be used in isolation. Thus clinicians are recommended to read the appropriate sections in the book(s)/website. Similarly, this is intentionally not an exhaustive list of every symptom.

Some guidelines are intended for use only by or in conjunction with a specialist palliative care service, e.g. methadone. Further, guidelines are no substitute for asking for help and clinicians should make use of local sources of advice detailed in the 'obtaining advice' section.

Thanks are due to Dr Robert Twycross and the members of the Network Palliative Care Group, in particular Dr Costello, Dr El-Khoury, Dr Fallon, Dr Finn, Dr Hallam, Dr Kutarski and Dr Wilcock.

These guidelines will be reviewed in 2009.

Dr Vincent Crosby  
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Mr Bob Neilans  
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Network Palliative Care Group

## Further reading

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Ellershaw J and Wilkinson S (2003) Care of the dying. A pathway to excellence. Oxford University Press, Oxford. See also [www.lcp-mariecurie.org.uk](http://www.lcp-mariecurie.org.uk).

Twycross R, Wilcock A (2001) Symptom Management in Advanced Cancer (3rd Edition) Radcliffe Medical Press Ltd, Oxon

Twycross R, Wilcock A, Charlesworth S and Dickman A (2002) Palliative Care Formulary (2nd Edition), Radcliffe Medical Press Ltd, Oxon. See also [www.palliativedrugs.com](http://www.palliativedrugs.com).

## Other Mid-Trent Cancer Network Palliative Care Group publications

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Guidelines for Communicating Bad News with Patients and their Families, 2006.

Mid Trent Cancer Network Supportive and Palliative Care Strategy (2006-2009).

Palliative Care Cancer Pain Standards, Guidelines and Patient Information for Hospitals (3rd Ed.) July 2005.

Palliative Care Cancer Pain Standards and Guidelines for the Community (3rd Ed.) July 2005.

Palliative Care Pocket Book (2nd Ed) 2006.

Standards for Supportive and Palliative Care Services, Mid Trent Cancer Network Palliative Care Group (2nd Ed) 2006.

Copies can be obtained from the Network Office or website:

Mid-Trent Cancer Network Office  
c/o Department of Clinical Oncology  
Nottingham University Hospitals NHS Trust  
City Campus  
Hucknall Road  
Nottingham  
NG5 1PB

0115 9627988

Fax: 0115 8402652

Email: [midtrencancer@ncht.trent.nhs.uk](mailto:midtrencancer@ncht.trent.nhs.uk)

Website: [www.mtcn.nhs.uk](http://www.mtcn.nhs.uk)

## Obtaining advice

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For full contact details, see the Mid-Trent Palliative Care Network Directory of Dedicated Palliative Care Services.

### LINCOLNSHIRE

#### ST BARNABAS HOSPICE, LINCOLNSHIRE

*Nettleham Road Inpatient Unit*  
01522 511566  
Fax: 01522 520877

*Day Hospice & Education Centre*  
*Hawthorn Road*  
01522 518200  
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#### UNITED LINCOLNSHIRE HOSPITAL NHS TRUST

Lincoln County Hospital  
Hospital Macmillan Service  
01522 512512 Ext 3112  
Bleep 3977

Pilgrim Hospital Boston  
Hospital Macmillan Service  
01205 364801 Ext 3542

Grantham and district hospital  
Hospital Macmillan Service  
01476 565232 Ext 4628

Grantham and Sleaford Community Palliative Care Service  
01476 565232 Ext 4588; 4664; 4627; 4850  
Fax: 01476 575877

#### WEST LINCOLNSHIRE PRIMARY CARE TRUST

Community Palliative Care Services  
Lincoln: 01522 545230  
Gainsborough: 01427 816539

#### EAST LINCOLNSHIRE PRIMARY CARE TRUST

Community Palliative Care Services  
Mablethorpe 01507 479843  
Louth 01673 857740  
Holbeach 01205 364801 Ext 3541  
Skegness 01205 364801 Ext 3543  
Boston 01205 364801 Ext 3542  
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**LINCOLNSHIRE SOUTH WEST TEACHING PRIMARY CARE TRUST**

Community Macmillan Services

01778 394185

01778 425376

**GIFTS HOSPICE SERVICES, GRANTHAM**

01476 591010

Fax: 01476 577884

**NOTTINGHAMSHIRE**

**JOHN EASTWOOD HOSPICE, SUTTON-IN-ASHFIELD**

Mansfield

01623 622626

Fax: 01623 654934

**NEWARK AND DISTRICT MACMILLAN SERVICE**

Newark Hospital

01636 685881/685776

**BEAUMOND HOUSE**

Newark

01636 610556

Fax: 01636 613262

**HAYWARD HOUSE MACMILLAN SPECIALIST PALLIATIVE CARE UNIT**

Nottingham University Hospitals Trust (City Campus)

0115 962 7619 (Direct Line)

0115 969 1169 (Hospital switchboard)

Fax: 0115 962 7779

**NOTTINGHAM UNIVERSITY HOSPITALS TRUST (QUEEN'S CAMPUS)**

Hospital Palliative Care Team

0115 919 4402 (Direct line)

Fax: 0115 849 3309

**NOTTINGHAMSHIRE HOSPICE**

Woodborough Road, Nottingham

0115 910 1008

0115 962 1222 (Hospice@Home)

Fax: 0115 985 8164

**NOTTINGHAM CITY PRIMARY CARE TRUST**

Community Macmillan Nurses

0115 993 4976

Fax: 0115 962 7779

## **SOUTH HUMBER (NORTH & NORTH EAST LINCOLNSHIRE)**

### **NORTH EAST LINCS NHS TRUST**

Macmillan Palliative Care Team  
Diana, Princess of Wales Hospital  
Grimsby  
01472 302430  
Fax: 01472 875561

### **ST ANDREWS HOSPICE**

Grimsby  
01472 250623, 250503  
Fax: 01472 250387

### **SCUNTHORPE AND GOOLE HOSPITALS NHS TRUST**

Macmillan Palliative Care Nursing Team  
Scunthorpe General Hospital  
01724 387709  
Or, bleep via switchboard 01724 282282  
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### **LINDSEY LODGE HOSPICE**

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### **NORTH LINCOLNSHIRE PRIMARY CARE TRUST**

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## Abbreviations

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### General

*	specialist use only
BNF	British National Formulary
SPC	Summary of Product Characteristics
WHO	World Health Organisation

### Medical

CrCl	creatinine clearance
CRP	C-reactive protein
CSF	cerebrospinal fluid
MAOI	mono-amine oxidase inhibitor
NMDA	N-methyl D-aspartate
NSAID	non-steroidal anti-inflammatory drug
SSRI	selective serotonin re-uptake inhibitor
TCA	tricyclic antidepressant
WBC	white blood cell count

### Drug administration

a.c.	ante cibum (before food)
b.d.	bis in die (twice daily), alternative b.i.d.
CIVI	continuous intravenous infusion
CSCI	continuous subcutaneous infusion
ED	epidural
IM	intramuscular
IT	intrathecal
IV	intravenous
IVI	intravenous infusion
m/r	modified release; alternative slow release, controlled release
p.c.	post cibum (after food)
PO	per os, by mouth
PR	per rectum
p.r.n.	pro re nata (as needed, when required)
o.d.	omni die (daily, once a day)
o.m.	omni mane (every morning)
o.n.	omni nocte (at bedtime)
q4h	quarta quaque hora (every 4 hours); or other specified time
q.d.s.	quater die sumendus (four times a day)
SC	subcutaneous
SL	sublingual
stat	immediately
TD	transdermal
t.d.s	ter die sumendus (three times a day); alternative, t.i.d.
WFI	water for injection

### Units

dl	decilitre
g	gram
kg	kilogram
L	litre
mg	milligram
ml	millilitre
mmol	millimol

## Use of medicines outside their licence

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- 1 In palliative care, up to 25% of all prescriptions are for drugs given for unlicensed indications and/or by unlicensed routes.
- 2 *The licensing process for drugs in the UK regulates the activities of pharmaceutical companies and not a doctor's prescribing practice.* The Medicines Act 1968 specifically safeguards a doctor's clinical freedom.
- 3 Drugs prescribed outside their licence can be dispensed by pharmacists and administered by nurses.
- 4 In the UK, a doctor may legally:
  - prescribe unlicensed medicines
  - in a named patient, use unlicensed products specially prepared, imported or supplied
  - use or advise the use of licensed medicines for indications or in doses or by routes of administration outside the licensed recommendations
  - supply another doctor with an unlicensed medicine
  - override the warnings and precautions given in the licence
  - use unlicensed drugs in clinical trials.
- 5 The responsibility for these actions rests with the doctor. In addition to clinical trials, such prescriptions may be justified:
  - when prescribing generic formulations (for which indications are not described)
  - with established drugs for proven but unlicensed indications
  - for conditions where there is no other treatment, even in the absence of strong evidence
  - when using drugs in individuals not covered by licensed indications, e.g. children.
- 6 Doctors have a duty to act with reasonable care and skill in a manner consistent with the practice of professional colleagues of similar standing. Thus, when prescribing outside the terms of a licence, doctors must be fully informed about the actions and uses of the drug.
- 7 It has been recommended that when prescribing a drug outside its licence, a doctor should:
  - record in the patient's notes the reason for this
  - explain the position to the patient (and family) in sufficient detail to allow them to give informed consent; the Patient Information Leaflet obviously does not contain information about unlicensed indications.
  - inform other professional caregivers, e.g. pharmacist, nurses, general practitioner, involved in the care of the patient to avoid misunderstandings.
- 8 *However, in palliative care, the use of drugs for unlicensed uses or by unlicensed routes is so widespread that such an approach is impractical.* In most instances, the harm done by creating anxiety and (possibly) increasing noncompliance is likely to exceed any benefits. This is a grey area and each doctor must decide how explicit to be.



## Acute inflammatory episodes in lymphoedema

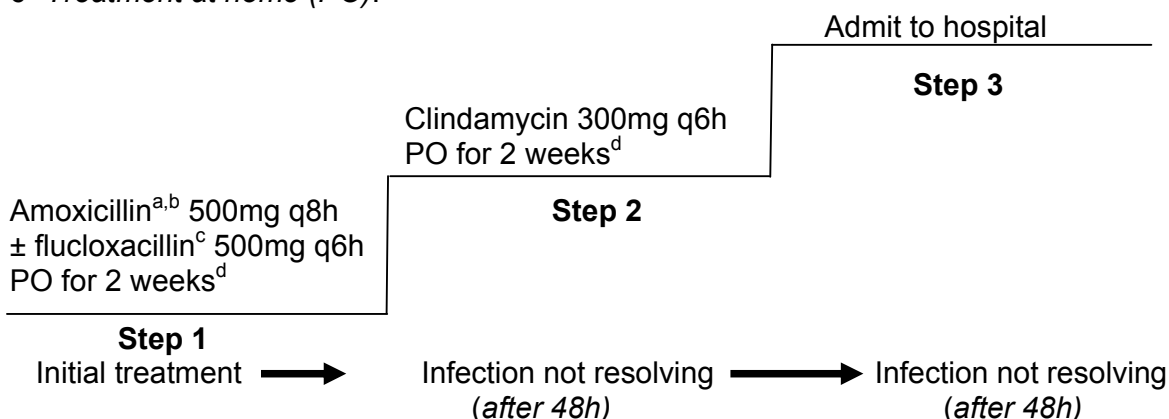
In lymphoedema, Acute Inflammatory Episodes (AIEs), often called cellulitis, are common. AIEs are frequently associated with septicaemia (e.g. fever, flu-like symptoms, hypotension, tachycardia, delirium, nausea and vomiting). It is often difficult to isolate the pathogen responsible for an AIE. However, *Streptococcus* is the mostly likely infective agent.

### Evaluation

- 1 Clinical features
  - mild: pain, increased swelling, erythema (well-defined or blotchy)
  - severe: extensive erythema with well-defined margins, increased swelling, blistering and weeping skin; often accompanied by fever, nausea and vomiting, pain and, when the leg is affected, difficulty in walking.
- 2 Diagnosis is based on pattern recognition and clinical judgement. The following information should be solicited.
  - present history: date of onset, precipitating factor (e.g. insect bite or trauma), treatment received to date
  - past history: details of previous AIE, precipitating factors, antibiotics taken
  - examination: include the sites of lymphatic drainage to and from the inflamed area.
- 3 Establish a baseline
  - extent and severity of rash: if well demarcated outline with pen and date
  - level of systemic upset: temperature, heart rate, blood pressure, CRP, WBC
  - swab cuts or breaks in skin for microbiology before starting antibiotics.
- 4 Arrange admission to hospital for patients with septicaemia or those who deteriorate or fail to improve despite antibiotics.

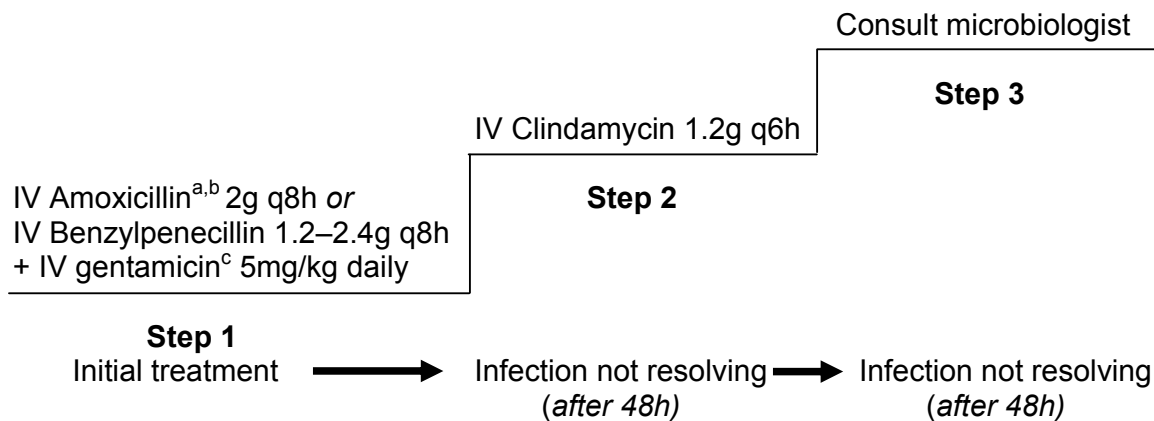
### Antibiotics

- 5 All AIE should be treated promptly with antibiotics to prevent increased morbidity associated with increased swelling and accelerated fibrosis.
- 6 *Treatment at home (PO):*



- a. use clindamycin 300mg q6h in patients with penicillin allergy
- b. if there is a history of animal bite or lick, consider co-amoxiclav 2 tablets q8h (ciprofloxacin if penicillin allergic) to cover *Pasteurella multocida*, *Eikenella corrodens* and *Capnocytophaga canimorsus*
- c. add only if features suggestive of *Staph. aureus* infection, e.g. folliculitis, pus, crusted dermatitis
- d. continue for 2 weeks *after* a clinical response to treatment.

7 *Treatment in hospital (IV)*. Choice of antibiotics may vary with local policy. The following is based on the Lymphoedema Support Network recommendations:



Switch to PO amoxicillin 500mg q8h or clindamycin 300mg q6h when inflammation improving, no fever for 48h and CRP falling.

- a. IV clindamycin 1.2g q6h is an alternative for patients with a history of penicillin allergy
- b. if there is a history of animal bite or lick, consider co-amoxiclav, or ciprofloxacin if penicillin allergic
- c. dose adjusted according to renal function.

8 Antibiotic prophylaxis: For patients with  $\geq 2$  episodes of AIE/year:

- prescribe phenoxymethylpenicillin 500mg (1g in those >75kg) o.d. or if allergic to penicillin erythromycin 250mg o.d. or clarithromycin 250mg o.d. *for two years*
- if AIE develops despite antibiotics, consider a switch to clindamycin 150mg o.d. or clarithromycin 250mg o.d.
- if AIE develops on discontinuation of antibiotics, restart *life-long* prophylaxis.

## General

9 Remember:

- bed rest and elevation of the affected limb in a comfortable position, supported on pillows is essential
- AIE are painful; analgesics should be prescribed regularly and p.r.n.
- compression garments should not be worn until limb is comfortable
- daily skin hygiene should be continued; washing and gentle drying
- emollients should not be used in the affected area if the skin is broken.

10 Patients should be educated about:

- why they are susceptible to AIE, i.e. skin crevices harbour bacteria, stagnant fluid, reduced immunity
- the consequence of AIE, i.e. increased swelling, more fibrosis, reduced response to treatment
- the importance of seeking prompt medical attention and treatment; in situations when accessing medical care may be difficult, e.g. holidays, provide a 2-week course of amoxicillin 500mg q8h (clindamycin 300mg q6h for those allergic to penicillin)
- the importance of daily skin care, i.e. to improve and maintain the integrity of the skin
- reducing risk, e.g. protect hands when gardening, cleanse cuts, treat fungal infections
- prophylaxis with antibiotics.

## Anaphylaxis

- 1 Anaphylactic shock is rare in palliative care and is generally associated with *antibiotics, aspirin, another NSAID or heparin*. A possible case of anaphylactic shock has been recorded in a woman with known peanut allergy who received *an arachis (peanut) oil* enema. Anaphylaxis is:
  - specific to a given drug or chemically-related class of drugs
  - more likely after parenteral administration
  - more frequent in patients with aspirin-induced asthma or systemic lupus erythematosus.
- 2 Clinical manifestations of anaphylactic shock typically develop *within minutes* of taking the causal drug and relate to the release of large amounts of histamine and other mediators (Box 1). Laryngeal oedema and/or bronchoconstriction occurs in only 10% of patients.

### Box 1 Clinical features of anaphylaxis

#### Essential

Hypotension *and/or* respiratory difficulty (laryngeal oedema, bronchoconstriction)

#### Possible

Flushing	Tingling of the extremities
Urticaria	Weakness
Angioedema	Agitation

- 3 Management comprises urgent treatment with adrenaline (epinephrine) followed up with an antihistamine and hydrocortisone (Box 2). However, because their impact is not immediate, corticosteroids are of secondary value.

### Box 2 Management of anaphylaxis in adults

- 1 Oxygen is of primary importance.
- 2 Adrenaline (epinephrine) 1:1000 (1mg/1ml), 500microgram (0.5ml) **IM**; repeat every 5min until blood pressure, pulse and breathing are satisfactory.
- 3 However, if:
  - an adrenaline (epinephrine) auto-injector is used, 300microgram (0.3ml) is generally sufficient
  - the patient is unconscious, double the dose
  - the patient is on a TCA (e.g. amitriptyline, desipramine), MAOI or a  $\beta$ -blocker, halve the dose.
- 4 Chlorphenamine, e.g. Piriton<sup>®</sup>, to counter histamine-induced vasodilation:
  - 50mg IM or IV over 5–10 min
  - 25–50mg PO q4–6h for 72h to prevent relapse.
- 5 Hydrocortisone sodium *phosphate* or *succinate*<sup>a</sup> 100–500mg IM or slowly IV for patients with bronchospasm, and for all severe or recurrent reactions to prevent further deterioration. Note: hydrocortisone may take 4–6h to act.
- 6 If still shocked, give 1–2L of IV fluid (a crystalloid may be safer than a colloid).
- 7 If bronchospasm has not responded to the above, give a nebulised  $\beta_2$ -adrenergic agonist, e.g. salbutamol 5mg.

- a. the acetate is unsuitable because of delayed absorption and the microcrystalline structure precludes IV use.

- 4 If there is doubt about the adequacy of the circulation, the initial injection can be given as a dilute IV solution, i.e. *1 in 10 000 (1mg/10ml), 500microgram (5ml) over 5min*. However, because injecting adrenaline (epinephrine) IV too rapidly can cause ventricular arrhythmias, IV administration is generally discouraged unless intensive care facilities are available.
- 5 Sometimes emergency tracheotomy and assisted respiration may be necessary.

*These guidelines are based on the recommendations in the BNF.*

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## Delirium

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- 1 Delirium (acute confusion) results from disordered levels of arousal and cognition. The onset is typically acute (hours to days) and generally accompanied by evidence of the underlying causal condition. Clinical features include:
  - prodromal symptoms (restlessness, anxiety, sleep disturbance and irritability)
  - fluctuating course
  - disorientation for time, place or person
  - memory impairment (cannot register new material)
  - disorganised thinking and incoherent speech
  - reduced attention (easily distractible)
  - affective symptoms (emotional lability, sadness, anger, euphoria)
  - altered perceptions:
    - misinterpretations
    - hallucinations
    - illusions
    - delusions (poorly formed)
  - motor abnormalities (tremor, asterixis, myoclonus, altered tone and reflexes).
- 2 Delirium can be classified as:
  - hyperactive (agitated) characterised by hallucinations and delusions
  - hypo-active (lethargic), characterised by confusion and sedation
  - mixed, alternating features of both agitation and lethargy.

### Evaluation

- 3 Delirium is precipitated or exacerbated by many factors and, in palliative care, is generally multifactorial. Common causes are infection, drugs (e.g. psychotropics, opioids, corticosteroids) alcohol or drug withdrawal, biochemical disturbances, intracerebral pathology, psychiatric illness, urinary or faecal impaction. The cause of the delirium may not be identified in up to 1/2 of patients with advanced cancer.

### Management

- 4 *Correct the correctable*  
Underlying causes should be sought and appropriately treated.
- 5 *Non-drug treatment*  
Attempt to help the patient to express their distress. Hallucinations, nightmares and misinterpretations often reflect the patient's fears and anxieties. Their content should be explored with the patient. In addition:
  - keep calm and avoid confrontation
  - respond to the patient's comments
  - clarify perceptions, and validate those which are accurate
  - explain what is happening and why
  - state what can be done to help
  - repeat important and helpful information
  - when indicated, recommend some tablets or an injection 'to help settle things down so that you can relax and rest for a few hours'
  - stress to both the patient and the family that delirium is not madness, and that they can expect lucid intervals

- continue to treat the patient with courtesy and respect
- restraints should never be used
- bed rails should be avoided, they can be dangerous
- patient should be allowed to walk about accompanied
- allay fear and suspicion, and reduce misinterpretations by use of:
  - use of night light
  - not changing the position of the patient's bed
  - explaining every procedure and event in detail
  - the presence of a family member or close friend.

## 6 *Drug treatment*

Treat sooner rather than later, before symptoms are marked, persistent and cause distress to the patient and/or family.

Benzodiazepines should not be used *alone* as they may worsen delirium. The exception is delirium associated with alcohol withdrawal for which benzodiazepines are the drug of choice.

Generally, haloperidol is the drug of choice for delirium. It is as effective as phenothiazines, e.g. chlorpromazine, but is safer to use. It can be give PO, PR, SC, IM and IV:

- 1.5–3mg stat & o.n in the elderly
- 5mg stat & o.n. in the younger patients or if poor response in the elderly
- 10–30mg o.n. (or in divided dosage) if poor response *or* consider levomepromazine.

Haloperidol, e.g. 5mg, combined with benzodiazepines, e.g. diazepam or midazolam 10mg, can be useful when a period of sedation is required in an agitated delirious patient. If the patient is already receiving regular psychotropic medication, a higher dose may be indicated.

Rarely, it may be necessary to give an agitated patient who is a danger to themselves an injection against their wishes. Although dependent on the circumstances and previous medication, haloperidol 5–10mg and midazolam 10mg would generally be a good choice, given either SC or IM. Forcing the patient to have an injection is an assault which can be justified only on the grounds of necessity. This should be seen as the last resort and taken only after discussing the situation with other team members.

- 7 Occasionally, a dying patient becomes severely agitated despite the above measures. It is occasionally necessary to heavily sedate a patient as the only way to contain the situation, i.e. give sedation sufficient to diminish the level of consciousness, generally with a combination of levomepromazine and midazolam.

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## Hypercalcaemia of malignancy

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- 1 *Stop and think!* Are you justified in treating a fatal complication in a moribund patient?
- 2 The following together comprise a set of indications for treating hypercalcaemia:
  - *corrected* plasma calcium concentration of >2.8mmol/L
  - symptoms attributable to hypercalcaemia
  - first episode or long interval since previous one
  - previous good quality of life (in the patient's opinion)
  - medical judgement that treatment will achieve a durable effect (based on the results of previous treatment)
  - patient willing to undergo IV therapy and requisite blood tests.
- 3 IV bisphosphonates are the treatment of choice for hypercalcemia of malignancy.
  - initial response is highest with zoledronic acid (~90%), with ibandronic acid equal to pamidronate disodium (~75%)
  - a longer response can be obtained with zoledronic acid and ibandronic acid compared with pamidronate disodium
  - the SPC for pamidronate disodium recommends higher doses for higher initial calcium levels, but some suggest that the higher dose should always be given irrespective of the initial calcium level, to increase the likelihood of a response.
- 4 Patients should be well hydrated with 0.9% saline 1–3L/24h:
  - Zoledronic acid:*
    - give 4mg IV in 100ml 0.9% saline or 5% glucose over 15min
    - if serum calcium does not normalize, repeat after 7 days
    - 8mg has been used in refractory hypercalcaemia [unlicensed dose]
    - measure serum creatinine before each dose; no dose adjustment is required in mild–moderate renal impairment.
  - Ibandronic acid:*
    - if the corrected serum calcium is <3mmol/L give 2mg; if >3mmol/L give 4mg
    - for both doses, give IV in 500ml 0.9% saline or 5% glucose over 2h.See manufacturer's SPC.
  - Pamidronate:*
    - maximum recommended dose/treatment is 90mg IV
    - concentration should not exceed *60mg/250ml*
    - the manufacturers recommend that in patients with normal renal function an infusion rate of  $\leq 1\text{mg}/\text{min}$ , *i.e.* *60mg/h*; in mild-moderate renal impairment (Cr Cl 30–90ml/min) the infusion rate should not exceed *20mg/h*
    - repeat after 1 week if the initial response inadequate
    - repeat every 3–4 weeks according to plasma calcium concentration
    - measure serum creatinine before each dose. No dose adjustment is required in mild–moderate renal impairment.
- 5 In palliative care, treatment with bisphosphonates will probably not be initiated in patients with hypercalcemia and severe renal impairment. If it is considered appropriate, see advice in bisphosphonates for metastatic bone pain (p.29).



## Rapid IV/SC titration of morphine for severe pain

- 1 Initial dose titration in *opioid-naïve* patients with small boluses of IV/SC morphine provides a method of rapidly determining (generally in <40min) morphine-responsiveness and probable maintenance requirements.
- 2 It is not generally necessary, but has been used to manage acute on chronic pain states and chronic pain where it is difficult to follow up a patient (e.g. India).
- 3 Two methods are reproduced here; one with 10min intervals between boluses and one with 1min intervals (Box 1 and Box 2). *About 80% of patients obtain relief with 10mg or less.* IV patient-controlled analgesia (PCA) can be used but is more costly, requires inpatient admission and takes >10h to achieve relief.
- 4 In patients already receiving a strong opioid, higher doses can and should be used. Other strong opioids can also be used for rapid pain relief, e.g. IV fentanyl.

### Box 1 Rapid titration of morphine dose in opioid-naïve patients (Institute of Palliative Medicine, India)

#### Prerequisites

Pain  $\geq 5/10$  on a numerical scale.

Likelihood of a partial or complete response to morphine.<sup>a</sup>

#### Method

Obtain venous access with a butterfly cannula.

Give metoclopramide 10mg IV routinely.

Dilute the contents of 15mg morphine ampoule in a 10ml syringe.<sup>b</sup>

Inject 1.5mg every 10min until the patient is pain-free or complains of undue sedation.

If patients experience nausea, give additional metoclopramide 5mg IV.

#### Results

Dose required (with approximate percentages):

1.5–4.5mg (40%)

6–9mg (40%)

10.5–15mg (15%)

>15mg (5%).

Complete relief in 80%; none in 1%.

Drop outs 2%.

Undesirable effects: sedation 32%; other 3%.

#### Ongoing treatment

- prescribe a dose of oral morphine q4h which is similar to the IV requirement, rounded to the nearest 5mg, i.e. relief with morphine 3–6mg IV → 5mg PO etc.; the minimum dose is 5mg q4h
- instruct patients to take p.r.n. doses and to adjust the dose the next day according to need.

a. most patients will already be taking an NSAID

b. ampoule strength varies from country to country; if local standard ampoule = 10mg/ml, a bolus dose of 2mg in 2ml would be reasonable.

**Box 2** Rapid titration of morphine dose in opioid-naïve patients (based on practice at Cleveland Clinic, Ohio)

<i>Sequence</i>	<i>IV</i>	<i>SC</i>
Dose	1mg/min up to 10mg	2mg q5min up to 10mg
Pause	5min	10min
Dose	1mg/min up to 10mg	2mg q5min up to 10mg
Pause	5min	10min
Dose	1mg/min up to 10mg <sup>a</sup>	2mg q5min up to 10mg <sup>a</sup>

*Maintenance IV/SC dose*

Regard cumulative effective dose as the equivalent of a q4h dose, and prescribe accordingly.

**Example**

Cumulative effective IV dose = 9mg.

If giving intermittent injections, dose = 9mg q4h, rounded to 10mg.

If CIVI, total daily IV dose = 9mg x 6 = 54mg/24h.

Round this up or down to convenient number of ampoules, i.e. 50mg or 60mg.

P.r.n. dose = 5–10mg q1h.

*Maintenance PO dose*

Double the IV dose to obtain the q4h dose, and prescribe accordingly.

**Example**

Cumulative effective IV dose = 9mg.

Double IV dose = 18mg, and round up to convenient 20mg q4h dose.

If q12h = 60mg m/r.

P.r.n. dose = 10–20mg q1h.

a. review cause if relief inadequate after a total of 30mg.

## Spinal cord compression

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- 1 Spinal cord compression occurs in 3–5% of patients with advanced cancer. Cancers of the breast, bronchus and prostate account for 40%. Most occur in the thorax. There is compression at more than one level in 20%. Below the level of L2 vertebra, compression is of the cauda equina (i.e. peripheral nerves) and not the spinal cord.

### Pathogenesis

- 2 Spinal cord compression is caused by:
  - a vertebral metastasis ± vertebral collapse (85%)
  - an extravertebral tumour extending through the intervertebral foramina into the epidural space, e.g. lymphoma (10%)
  - an intramedullary tumour (originates from within the spinal cord), e.g. ependymoma
  - an intradural tumour, i.e. arising from the meninges or nerve roots
  - an epidural blood-borne metastasis.

### Clinical features

- 3 Symptoms/signs include:
  - pain >90%
  - weakness >75%
  - sensory level >50%
  - sphincter dysfunction >40%

However, the aim is to make the diagnosis *before* obvious and significant neurological deficits are present. A high degree of clinical suspicion is required, because early symptoms may be vague and findings non-specific.

The patient may be unaware of sensory loss until examined, particularly if this is confined to the sacrum or perineum. Pain generally predates other symptoms and signs of cord compression by several weeks or months. Pain may be caused by:

- vertebral metastasis
- root compression
- compression of the long tracts of the spinal cord (funicular pain).

Radicular and funicular pains are often exacerbated by neck flexion or straight leg raising, and by coughing, sneezing or straining. Funicular pain is generally less sharp than radicular pain, has a more diffuse distribution (like a cuff or garter around things, knees or calves) and is something described as a cold unpleasant sensation.

### Evaluation

- 4 Includes:
  - history and clinical findings
  - a plain radiograph shows vertebral metastasis and/or collapse at the appropriate level in 80%; a bone scan does not often yield additional information
  - MRI is the investigation of choice
- 5 Rapid onset complete paraplegia (over 24–36h) has a poor prognosis; it is almost always caused by infarction of the spinal cord secondary to tumour compression and thrombosis of a spinal artery.

## Management

- 6 Spinal cord compression must be treated as an emergency. Patients with paraparesis do better than those who are totally paraplegic. Recovery is more likely with lesions of the cauda equina (= peripheral nerves). Loss of sphincter function is a bad prognostic sign.
- 7 The main options are:
- corticosteroids
  - radiotherapy

These act in different ways and can be given concurrently. Corticosteroids may bring about early improvement in physical signs and pain relief by reducing peritumour inflammation. Radiotherapy brings about improvement more slowly by reducing tumour size.

- 8 Dexamethasone is given in high doses initially. Regimens vary, for example:
- 16mg PO stat and o.d.
  - 12mg PO stat and 24mg PO o.d. for 3 days
  - 100mg IV stat and 24mg PO q.d.s. for 3 days.
- Dexamethasone is rapidly reduced to 12–16mg o.d., after which reductions are made according to the rate and completeness of response.
- 9 Surgery is occasionally indicated; it should be considered if:
- neurological symptoms and signs progress despite radiotherapy and dexamethasone
  - there is a solitary vertebral metastasis
  - the diagnosis is in doubt.

Vertebral body resection with anterior spinal stabilisation is the operation of choice. Laminectomy (posterior decompression) may well exacerbate spinal instability and cord injury because cord compression is often anterior.

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## Superior vena caval obstruction

Superior vena caval (SVC) obstruction is generally caused by extrinsic compression by metastases in the upper mediastinal lymph nodes (Box). Lung cancer is responsible for 80% of cases. It occurs in about 15% of patients with lung cancer, particularly small cell. It is also associated with other malignancies such as lymphoma, breast cancer and testicular seminoma. Venous thrombosis can cause an acute onset.

### Box Clinical features of superior vena caval obstruction

#### Symptoms

Dyspnoea (50%)  
Neck and facial swelling (40%)  
Trunk and arm swelling (40%)  
A sensation of choking  
A feeling of fullness in the head  
Headache  
Chest pain  
Cough  
Dysphagia  
Cognitive dysfunction  
Hallucinations  
Seizures

#### Signs

Thoracic vein distension (65%)  
Neck vein distension (55%)  
Facial oedema (55%)  
Tachypnoea (40%)  
Plethora of face (15%)  
Cyanosis (15%)  
Arm oedema (10%)  
Vocal cord paresis (3%)  
Horner's syndrome (3%)

#### If severe

Stridor  
Coma  
Death

### Management

SVC obstruction with severe symptoms is an emergency. Refer immediately to the oncology team for evaluation. Options include:

- *corticosteroids* high-dose, e.g. dexamethasone 16mg o.d./8mg b.d. PO
- *radiotherapy* to the mediastinum
- *chemotherapy* (lymphoma and small cell lung cancer)
- *metal stent* in patients who fail to improve with the above, or if SVC obstruction recurs, introduced into the SVC via the brachiocephalic or femoral vein.

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## Ascites

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- 1 Median survival in patients with cancer-related ascites is 2–3 months (longer in ovarian cancer responsive to chemotherapy).
- 2 Cancer-related ascites is produced by two main mechanisms:
  - peritoneal carcinomatosis
    - increased vascular permeability
    - impaired subphrenic lymphatic drainage
    - *albumin-rich exudate*
    - *chylous (milky) exudate in extensive disease*
    - cancer cells generally found on cytology.
  - portal hypertension
    - massive liver metastases
    - hepatocellular cancer ± cirrhosis
    - hyperaldosteronism and fluid retention
    - *albumin-poor transudate*
    - cytology negative.
- 3 The difference between the plasma and ascites albumin levels helps differentiate a transudate from an exudate. A plasma-ascites albumin gradient of:
  - <11g/L = an exudate
  - >11g/L = a transudate.
- 4 Paracentesis, repeated as necessary, is the treatment of choice for patients with ascites due to peritoneal carcinomatosis; spironolactone ± furosemide may be of benefit in ascites due solely to portal hypertension.

### Paracentesis

- 1 Achieves relief in 90% of patients.
- 2 Patients who have trouble-free paracentesis can generally be managed as day-cases.
- 3 For elective drainage, the preferred method is insertion of a small bore catheter under ultrasound guidance in the Radiology Department. Platelet count and clotting tests (PT & APTT) should be checked beforehand. Send ascitic fluid for albumin and cytology (if diagnosis/mechanism is in doubt) and microbiology.
- 4 In emergencies, e.g. ascites causing distressing pain or breathlessness, or if patient does not want to leave home, drainage can generally be safely undertaken without diagnostic imaging. In this circumstance, infiltrate the skin, subcutaneous tissues and peritoneum with local anaesthetic and under sterile conditions insert an IV cannula (e.g. 18 gauge, grey) into the right or left iliac fossa.
- 5 Note:
  - clamping drainage tubes to control the drainage rate is generally unnecessary, certainly for volumes less than 5L, and possibly for volumes up to 10L
  - hypotension is rare, and IV hydration is unnecessary unless the patient is dehydrated
  - there is no evidence to support the use of IV albumin in malignant ascites
  - ascites accumulates up to several hundred ml/day, so a drain left in is likely to continue to drain until it becomes blocked.

- 6 Remove the cannula when rate of drainage minimises or stops, or in day-cases, after a maximum of 6h, and apply a dressing pad. If there is excessive leakage, apply a stoma bag over the site until it becomes minimal.
- 7 Patients often feel 'washed out' for several hours after the procedure, and may experience abdominal discomfort, necessitating analgesia. If the patient feels unwell at any point, stop the drainage and check the blood pressure. If hypotensive, give IV fluids, e.g. 1L of IV saline 0.9% over 2h. This is rarely necessary.

### **Diuretic treatment**

Spironolactone should be considered for patients with ascites due to portal hypertension. The patient must have a reasonable prognosis, as elimination of the ascites can take up to 4 weeks. Hypotension is rare (compared with >10% of patients when ascites secondary to peritoneal cancer is treated with diuretics).

- 1 Monitor body weight and renal function.
- 2 Start with spironolactone 100–200mg o.m.
- 3 Increase by 100mg every 5–7 days to achieve a weight loss of 0.5–1kg/24h.
- 4 Typical maintenance dose is 300mg o.m.; occasionally a dose of 400–600mg is necessary (2/3 of patients are controlled on 300mg or less).
- 5 Consider adding furosemide 40mg o.m. if not achieving the desired weight loss after 2 weeks; discontinue furosemide when a satisfactory result is reached.

### **Indwelling catheter**

If a patient requires paracentesis more than every 2 weeks, an indwelling drainage device should be considered.

### **Shunts**

An abdomino-venous shunt is another option in patients with rapidly accumulating ascites and a prognosis of >3 months; not often used in cancer-related ascites.

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## Bisphosphonates for metastatic bone pain

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### Background

Bisphosphonates are stable analogues of naturally occurring pyrophosphate compounds that:

- inhibit bone dissolution by interfering with osteoclast function and/or inducing their apoptosis (programmed cell death)
- impair post-translational protein modification important in cell signalling
- reduce macrophage production of pro-inflammatory cytokines
- have an anticancer effect via inhibition of matrix metalloproteinase, altered cell adhesion, anti-angiogenic activity and induction of apoptosis.

### Bisphosphonates as adjuvant analgesics

Bisphosphonates are used for metastatic bone pain generally when more conventional methods have been exhausted:

- an effect is generally seen within 14 days
- evidence stems mainly from disodium pamidronate or sodium clodronate
- benefit is more likely in patients with breast cancer or myeloma, and with an IV bisphosphonate.

### Prophylactic use in patients with myeloma or bone metastases

Disodium pamidronate and zoledronic acid IV or ibandronic acid PO/IV given long-term decrease the incidence of new skeletal events in patients with bone metastases:

- benefit is most evident for patients with breast cancer or myeloma and is less clear for other types of cancers
- only studies >6 months in duration have shown a reduction in vertebral and non-vertebral fractures, hypercalcemia and the need for radiotherapy
- studies >2 years duration have also shown a reduced need for orthopedic surgery
- the incidence and severity of pain is reduced with a number needed to treat (NNT) of 11 at 4 weeks and 7 at 12 weeks
- there is no impact on survival or the occurrence of spinal cord compression.

### Renal toxicity of bisphosphonates

Risk factors for bisphosphonate-induced renal damage include:

- dehydration
- increased baseline serum creatinine concentration
- multiple treatments
- concurrent use of other nephrotoxic drugs.

The risk of renal toxicity is reduced by ensuring adequate hydration and adhering to the recommended dose and infusion rate. Renal function should be monitored and the dose of bisphosphonate adjusted as appropriate.

### Dose and use

#### Metastatic bone pain

Several regimens have been recommended for when more conventional methods have been exhausted:

- patients should be well hydrated, using 0.9% saline if necessary
- zoledronic acid 4mg IV; if helpful repeat every 3–4 weeks for as long as benefit is maintained
- disodium pamidronate 90mg IV (50% of patients respond, usually within 7–14 days); if helpful repeat 60–90mg every 3–4 weeks for as long as benefit is maintained
- disodium pamidronate 120mg IV, repeated p.r.n. every 2–4 months.

**Prophylactic use to reduce the incidence of skeletal-related events in patients with multiple myeloma or breast cancer**

Patients should be well hydrated, using 0.9% saline if necessary.

*Pamidronate*

Reconstitution and dilution instructions vary for different products; see the relevant manufacturer’s SPC. Final dilution is generally to a maximum of 60mg/250ml in 0.9% saline or 5% glucose. Dose recommendations differ slightly for patients with multiple myeloma as they are at greater risk of renal impairment/renal toxicity:

- recommended dose and frequency (*multiple myeloma*); give 90mg IVI at a maximum rate of 20mg/h every 4 weeks
- recommended dose and frequency (*breast cancer*); give 90mg IVI at a maximum rate of 60mg/h (i.e. 1mg/min) every 3–4 weeks
- dose reduction is *not* required in mild–moderate renal impairment (creatinine clearance 30–90ml/min) but the infusion rate should not exceed 20mg/h
- very limited pharmacokinetic data suggest that the AUC of disodium pamidronate is increased 3-fold in severe renal impairment; the manufacturers advise avoiding it in patients with creatinine clearance <30ml/min.

*Zoledronic acid:*

- for dose in patients with renal impairment, see Table
- otherwise, give 4mg IV in 100ml 0.9% saline or 5% glucose over 15min every 3–4 weeks
- daily supplements of calcium 500mg and vitamin D 400 units are recommended, e.g. Calcichew-D<sub>3</sub><sup>®</sup> Forte.

*For both:*

- serum creatinine should be measured before each dose. Treatment should be withheld if creatinine increases by:
  - 44micromol/L in patients with a normal baseline creatinine concentration (i.e. <124micromol/L), *or*
  - 88micromol/L in patients with a raised baseline creatinine concentration (i.e. >124micromol/L)
- treatment may be resumed at the same dose as before when serum creatinine returns to within 10% of the baseline value.

**Table** Dose reduction for zoledronic acid in patients with cancer involving the bones and mild–moderate renal impairment <sup>a,b,c</sup>

<i>Baseline creatinine clearance (ml/min)</i>	<i>Recommended dose</i>	<i>Amount of concentrate</i>
>60	4.0mg (i.e. no reduction)	5.0ml
50–60	3.5mg	4.4ml
40–49	3.3mg	4.1ml
30–39	3.0mg	3.8ml

a. manufacturer’s recommendations for patients with multiple myeloma or bone metastases  
 b. no data exist for severe renal impairment (creatinine clearance <30ml/min) because these patients were excluded from the studies  
 c. reduced doses are diluted in 100ml 0.9% saline or 5% glucose and given IVI over 15min.

## Blood transfusion in palliative care

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- 1 The following criteria should all be met for a non-emergency blood transfusion in palliative care:
  - symptoms attributable to anaemia, e.g. fatigue, weakness and breathlessness on exertion, which:
    - are troublesome to the patient
    - limit routine activity
    - are likely to be corrected by transfusion
  - expectation that a blood transfusion will achieve a durable effect, e.g. at least 2 weeks
  - patient willing to have a transfusion and requisite blood tests.
  
- 2 Contra-indications:
  - no benefit from previous transfusion
  - patient is moribund, i.e. the patient's condition is terminal
  - if the transfusion can best be described as simply prolonging a patient's death
  - if the main reason is a demand by the family that 'something must be done'.

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## Opioids for breathlessness

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- 1 Generally, opioids are more beneficial to patients who are breathless at rest than those breathless only on exertion. Breathlessness on exertion generally recovers within a few minutes, much quicker than the time it takes to administer and obtain benefit from an opioid. Thus non-drug measures should be used in this circumstance.
- 2 Morphine and other opioids reduce the ventilatory response to hypercapnoea, hypoxia and exercise, decreasing respiratory effort and breathlessness. Improvements are seen at doses that do *not* cause respiratory depression.
- 3 A systematic review supports the use of opioids by the oral and parenteral but *not* the nebulised route, and the latter should not be used except in a clinical trial.
- 4 In *opioid-naïve* patients:
  - start with small doses of morphine, e.g. 2.5–5mg PO p.r.n.; larger doses can be poorly tolerated
  - if  $\geq 2$  doses/24h are needed, prescribe morphine regularly and titrate the dose according to response, duration of effect and undesirable effects
  - relatively small doses may suffice, e.g. 20–60mg/24h.
- 5 In patients *already taking morphine for pain* and with:
  - *severe* breathlessness (i.e.  $\geq 7/10$ ), a dose that is 100% or more of the q4h analgesic dose may be needed
  - *moderate* breathlessness (i.e. 4–6/10), a dose equivalent to 50–100% of the q4h analgesic dose may suffice
  - *mild* breathlessness (i.e.  $\leq 3/10$ ), a dose equivalent to 25–50% of the q4h analgesic dose may suffice.
- 6 Sometimes morphine by CSCI is better tolerated and provides greater relief than PO, possibly because there are no peaks and troughs in the plasma concentration.

### Severe breathlessness in the last days of life

- 1 Patients often fear suffocating to death and a positive approach to the patient, their family and colleagues about the relief of terminal breathlessness is important:
  - no patient should die with distressing breathlessness
  - failure to relieve terminal breathlessness is a failure to use drugs optimally
  - give an opioid with a sedative-anxiolytic parenterally, e.g. (dia)morphine and midazolam by CSCI and p.r.n.
  - if the patient becomes agitated or confused (sometimes aggravated by a benzodiazepine), haloperidol or levomepromazine should be added.
- 2 If using an alternative opioid to morphine, adopt the same approach as above.
- 3 Because of the distress, inability to sleep and exhaustion, patients and their carers generally accept that drug-related drowsiness may need to be the price paid for greater comfort. However, in the absence of overwhelming distress, sedation is not the primary aim of treatment and some patients become mentally brighter when their breathlessness is reduced. Even so, because increasing drowsiness also generally reflects the deteriorating clinical condition, it is important to stress the gravity of the situation and the aim of treatment to the relatives.



## Oxygen (from Hayward House)

- 1 The non-emergency use of continuous oxygen therapy will only be used for patients who are *breathless at rest* following a formal evaluation of its effects using the audit proforma. This will identify the flow rate of oxygen that corrects SaO<sub>2</sub> to ≥90%.
- 2 Oxygen must be prescribed by the admitting doctor. A verbal prescription is acceptable if undue delay is anticipated.
- 3 The correct prescription of oxygen will include on the drug card details of:
  - source (oxygen concentrator or cylinder, entered in 'Gas' section)
  - delivery device (nasal cannulae or face mask and mask type i.e. 'medium' concentration')
  - flow rate.

**Example:** A correctly completed oxygen prescription

<i>Date</i>	<i>Time</i>	<i>Gas</i>	<i>Mask type or nasal cannulae</i>	<i>Flow rate</i>	<i>Continuous or intermittent</i>	<i>Doctor's signature</i>
2.12.05	1500	Oxygen concentrator	Nasal cannulae	2L/min	Continuous	A.N.Other
10.12.05	1100	Two oxygen concentrators	Mask, medium concentration	3L/min each	Continuous	A.N.Other

- 4 Any change in prescription will require amendment of the prescription chart.
- 5 Oxygen will be delivered by oxygen concentrators unless humidification is required. At lower flow rates (2–4L/min), one oxygen concentrator and nasal cannulae will be used. For higher flow rates (6–8L/min), two oxygen concentrators will be joined using a Y connector to a Lifecare 2000 medium concentration face mask (Table 1).

**Table 1** Use of oxygen concentrators to deliver a range of oxygen concentrations

<i>Desired oxygen concentration</i>	<i>Oxygen source</i>	<i>Flow rate</i>	<i>Delivery device</i>
28% <sup>a</sup>	Concentrator	2L/min	} Nasal cannulae
36% <sup>a</sup>	Concentrator	4L/min	
50% <sup>b</sup>	2 concentrators joined with a Y connector, each set at 3L/min <sup>c</sup>	6L/min	} Lifecare 2000 medium concentration face mask <sup>d</sup>
70% <sup>b</sup>	2 concentrators joined with a Y connector, each set at 4L/min <sup>c</sup>	8L/min	

- a. manufacturer's data
- b. Hayward House data using two Devilbiss 4L oxygen concentrators. Approximate concentration of oxygen inside the mask determined by Fisher-Packel oxygen analyzer with a healthy volunteer breathing at a resting tidal volume and respiratory rate
- c. If insufficient concentrators are available, oxygen concentrations of 50 and 70% can be obtained by using cylinders with a flow rate of 6 and 8L/min respectively and a Lifecare 2000 medium concentration face mask
- d. higher oxygen concentrations were not seen with a high concentration face mask.

6 Humidification will be considered for patients with problems such as nasal crusting or viscid sputum. It requires the use of an oxygen cylinder and cold nebuliser (Table 2).

**Table 2** Use of oxygen cylinders and a Kendall Respiflo MN cold nebuliser

<i>Oxygen concentration setting on cold nebulizer</i>	<i>Oxygen concentration delivered<sup>a</sup></i>	<i>Oxygen cylinder flow rate</i>	<i>Delivery device</i>
28%	30%	5L/min	A converted Lifecare 2000 medium concentration face mask. <sup>b</sup> <ul style="list-style-type: none"> <li>• remove the swivel connector in order to attach the elephant tubing</li> <li>• remove the plastic discs to enlarge the holes in the side of the mask</li> </ul>
35%	33%	8L/min	
40%	40%	8L/min	
60%	56%	8L/min	
80%	65%	8L/min	
98%	75%	8L/min	

a. Hayward House data using two Devilbiss 4L oxygen concentrators. Approximate concentration of oxygen inside the mask determined by Fisher-Packel oxygen analyzer with a healthy volunteer breathing at a resting tidal volume and respiratory rate

b. higher oxygen concentrations were not seen with a high concentration face mask.

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## Notes

The oxygen concentration received by a patient is dependent on various factors, including their breathing pattern, the oxygen source and delivery device and cannot be accurately predicted. Every patient's oxygen therapy should be individually titrated according to response.

In patients with carbon dioxide (CO<sub>2</sub>) retention who depend upon hypoxia for their respiratory drive, oxygen therapy can result in ventilatory depression. This is associated with increasing drowsiness (CO<sub>2</sub> narcosis) and other symptoms/signs, e.g. headache, peripheral vasodilation (warm extremities, bounding pulse), sweating, muscle twitching and flapping tremor. If suspected clinically, do not exceed an oxygen concentration of 28% and consider blood gas measurements to guide oxygen therapy.

For more information, see also the Oxygen Audit background form (available from [www.palliativedrugs.com](http://www.palliativedrugs.com) RAG panel).

## Opioid-induced constipation

All opioids constipate, although to a varying extent. Morphine is more constipating than methadone and fentanyl. The aim of treatment is to achieve a regular bowel action without straining, generally every 1–3 days.

- 1 Ask about the patient's past (premorbid) and present bowel habit and use of laxatives; record the date of last bowel action.
- 2 Palpate for faecal masses in the line of the colon; examine the rectum digitally if the bowels have not been open for >3 days or if the patient reports rectal discomfort or has diarrhoea suggestive of faecal impaction with overflow.
- 3 For inpatients, keep a daily record of bowel actions.
- 4 Encourage fluids generally, and fruit juice and fruit specifically.
- 5 When an opioid is prescribed, prescribe co-danthramer *strong* or co-danthrusate:

	Co-danthramer <i>strong</i> capsules	Co-danthramer <i>strong</i> suspension	Co-danthrusate capsules	Co-danthrusate suspension
<b>Dantron content</b>	37.5mg/capsule	75mg/5ml	50mg/capsule	50mg/5ml
<b>Start with:</b>				
prophylactic	1 o.n.	2.5ml o.n.	1 o.n.	5ml o.n.
if constipated	2 o.n.	5ml o.n.	2 o.n.	10ml o.n.
<b>If necessary, adjust every 2–3 days up to:</b>				
	3 t.d.s.	10ml b.d. or 20ml o.n.	3 b.d.	15ml b.d.
<b>Total daily dose of dantron</b>	337.5mg/day	300mg/day	300mg/day	300mg/day

- 6 It is sometimes appropriate to optimise a patient's existing laxative regimen, rather than change automatically to co-danthramer.
- 7 During dose titration and subsequently, if >3 days since last bowel action, give suppositories, e.g. bisacodyl 10mg and glycerine 4g or a micro-enema. If these are ineffective, administer a phosphate enema and possibly repeat the next day.
- 8 If co-danthramer/co-danthrusate causes intestinal colic, divide the total daily dose into smaller more frequent doses, e.g. change from co-danthramer *strong* 2 capsules b.d. to 1 capsule q.d.s. Alternatively, change to an osmotic laxative, e.g. macrogol 3350 (Movicol<sup>®</sup>) or macrogol 4000 (Idrolax<sup>®</sup>) 1–2 sachets o.m.
- 9 If the maximum dose of co-danthramer/co-danthrusate is ineffective, halve dose and add an osmotic laxative, e.g. macrogol 3350 (Movicol<sup>®</sup>) or macrogol 4000 (Idrolax<sup>®</sup>) 1 sachet o.m., and titrate as necessary.
- 10 An osmotic laxative, e.g. a macrogol (Movicol<sup>®</sup>, Idrolax<sup>®</sup>) may be preferable in patients with a history of colic with colonic stimulants, e.g. dantron, senna, bisacodyl.



## Bowel management in paraplegia and tetraplegia

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Management is governed by the level of the vertebral lesion:

- above T12–L1 = cauda equina intact → spastic bowel, generally with preserved sacral reflex; often responds to digital stimulation of the rectum; the presence of an anal reflex is indicative of an intact sacral reflex
- below T12–L1 = cauda equina involved → flaccid bowel; generally requires digital evacuation of the rectum.

### **Aim**

To achieve controlled regular evacuation of softish formed faeces:

- every day in long-term paraplegia/tetraplegia (e.g. post-traumatic)
- every 1–3 days in late-stage cancer

and thus prevent either incontinence (faeces too soft; over-treatment with laxatives) or an anal fissure (faeces too hard; under-treatment with laxatives) which can cause autonomic dysreflexia in paraplegia above T7 vertebrae and tetraplegia (see next page).

### **Non-drug treatment**

In patients with a good appetite:

- maintain a high fluid intake
- encourage a high roughage diet, e.g. wholegrain cereals, wholemeal foods, greens, bran or a bulk-forming agent, e.g. Regulan, Fybogel.

In patients with a poor appetite, particularly if taking morphine or other opioid, a bulking agent is generally contra-indicated.

### **Spastic bowel**

- if rectum very full, consider a digital evacuation, otherwise
- insert 2 glycerine suppositories or a micro-enema into the rectum, and wait 30–60min.
- if strong sacral reflex, some faeces will be expelled
- if necessary, proceed to digital stimulation:
  - insert gloved and lubricated finger
  - rotate finger clockwise 3–4 times
  - withdraw and wait 10min
  - if necessary, repeat 3–4 times.

If glycerine suppositories and micro-enemas do not work satisfactorily, substitute:

- bisacodyl suppositories 10-20mg *or*
- a sodium acid phosphate & sodium bicarbonate suppository (Carbalax); causes rectal distension by producing CO<sub>2</sub> and thereby stimulates reflex evacuation. (Note: may cause pain in people with normal rectal sensation.)

Patients who are unable to transfer to the toilet or a commode will need nursing assistance. Sometimes it is preferable for a patient to defaecate into strategically placed pads on the bed.

### **Flaccid Bowel**

Generally requires digital evacuation. A pattern will emerge for each patient, allowing the rectal measures to be adjusted to the individual patient's needs and response.

### **Use of laxatives**

- some people with paraplegia/tetraplegia, particularly if taking opioids or other constipating drugs, require oral laxatives in addition to the rectal measures described above. Which laxative is used depends partly on local availability, fashion, and individual preference
- for someone taking opioids, cautiously prescribe a colonic stimulant laxative, e.g. senna 15mg b.d., bisacodyl 5–10mg b.d. Adjust the dose as necessary to produce soft formed faeces in the rectum.
- Beware:
  - docusate, a faecal softener, may result a soft faecal impaction of the rectum, and faecal leakage through a lax anus
  - oral bisacodyl in someone not on opioids often causes multiple uncontrolled evacuations, at the wrong time and in the wrong place.

### **Autonomic dysreflexia**

This is a potential problem in paraplegia above T7 vertebra and in tetraplegia, and it:

- is caused typically by a distended bladder, constipation/faecal impaction, or anal fissure
- manifests as headache (often pounding), profuse sweating, nasal stuffiness, facial flushing, and bradycardia
- is caused by a stimulus below the level of the lesion causing sympathetic autonomic overactivity → vasoconstriction and hypertension; this stimulates parasympathetic overactivity above the lesion via the carotid and aortic baroreceptors.

As a general rule, headache in someone with paraplegia/tetraplegia should lead to action: check the urinary catheter and, if draining satisfactorily, proceed to rectal examination.

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## Management of death rattle

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Death rattle is a term used to describe noisy rattling breathing which occurs in about 50% of patients near the end of life. It is caused by fluid pooling in the hypopharynx, and arises from one or more sources:

- saliva (most common)
- respiratory tract infection
- pulmonary oedema
- gastric reflux.

Rattling breathing can also occur in patients with a tracheostomy and infection.

Because the patient is generally semiconscious or unconscious, drug treatment for death rattle is mainly for the benefit of relatives, other patients and staff.

### Non-drug treatment

- ease the family's distress by explaining that although the rattle sounds distressing, the semiconscious/unconscious patient is not distressed by it; it may help to use snoring as an analogy
- position the patient semiprone to encourage postural drainage; but upright or semirecumbent if the cause is pulmonary edema or gastric reflux
- oropharyngeal suction but, because it is distressing to many moribund patients, generally reserve for unconscious patients.

### Drug treatment

#### Saliva

Because they do not affect existing secretions, an antimuscarinic antisecretory drug needs to be given promptly as soon as the onset of death rattle is detected. They are generally given SC (Table). Alternatives to injections include:

- atropine 1% ophthalmic solution, 4 drops SL q4h p.r.n. (dose administered may vary with product and drop size, e.g. 200–500microgram/drop)
- scopolamine *hydrobromide* TD 1.5mg/3days post-auricular patch (but *not* optimum for an imminently dying patient).

There is less evidence to support the use of these routes. Even so, SL administration is standard practice at many centres in the USA.

**Table** Antisecretory drugs SC for death rattle

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<i>Drug</i>	<i>Stat SC dose</i>	<i>CSCI dose/24h</i>
Glycopyrronium	200microgram	600–1200microgram
Hyoscine <i>butylbromide</i>	20mg	20–60mg <sup>a</sup>
Hyoscine <i>hydrobromide</i>	400microgram	1200–2400microgram

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a. some centers use up to 120mg.

Note:

- by injection, the efficacy of the different drugs is broadly similar; the rattle is reduced in 1/2–2/3 of patients
- the onset of action of glycopyrronium is slower compared with hyoscine *hydrobromide*
- hyoscine *hydrobromide* crosses the blood-brain barrier and possesses anti-emetic and sedative properties, but there also a risk of developing or exacerbating delirium.

### **Respiratory tract infection**

Occasionally it is appropriate to prescribe an antibiotic in an imminently dying patient if death rattle is caused by profuse purulent sputum associated with an underlying chest infection:

- e.g. ceftriaxone, mix 1g ampoule with 2.1ml lidocaine (lignocaine) 1%, and give 250–1000mg SC/IM o.d.
- some centers use larger volumes of lidocaine (lignocaine) and administer a divided dose at separate SC/IM sites o.d. or give b.d.

### **Pulmonary oedema**

Consider furosemide 20–40mg SC/IM/IV q2h p.r.n.

Note: beware precipitating urinary retention.

### **Gastric reflux**

Consider metoclopramide 20mg SC/IV q3h p.r.n., but do not use concurrently with an antimuscarinic because the latter blocks the prokinetic effect of the former.

### ***Rattling breathing causing distress to a patient***

In a semiconscious patient, if rattling breathing appears to be causing labored breathing and/or distress, supplement the above with an opioid, e.g. morphine, and an anxiolytic sedative, e.g. midazolam, both regularly and p.r.n.

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# Depression

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*Sadness and tears on their own, even if associated with transient suicidal thoughts, do not justify the diagnosis of depression or the prescription of an antidepressant; many are part of an adjustment reaction and will improve with time. Other patients are demoralised rather than medically depressed and respond to symptom management and psychosocial support.*

## Evaluation

- 1 **Screening:** about 5–10% of patients with advanced cancer develop a major depression. Cases will be missed unless specific enquiry is made of all patients:

‘What has your mood been like lately?... Are you depressed?’

‘Have you had serious depression before? Are things like that now?’

- 2 **Assessment interview:** if depression is suspected, explore the patient’s mood more fully by encouraging the patient to talk further with appropriate prompts. Symptoms suggesting clinical depression include:

- *sustained* low mood (i.e. most of every day for several weeks)
  - *sustained* loss of pleasure/interest in life (anhedonia)
  - diurnal variation (i.e. worse in mornings and better in evenings)
  - waking significantly earlier than usual (e.g. 1–2h) and feeling ‘awful’
  - feelings of hopelessness/worthlessness
  - excessive guilt
  - withdrawal from family and friends
  - persistent suicidal thoughts and/or suicidal acts
  - requests for euthanasia.
- } core symptoms

- 3 **Differential diagnosis:** the symptoms of depression and cancer, and of depression and sadness overlap. If in doubt whether the patient is suffering from depression, an adjustment reaction or sadness, review after 1–2 weeks and/or obtain the help of a psychologist/psychiatrist.

- 4 **Medical causes of depression:** depression may be the consequence of:
  - a medical condition, e.g. hypercalcaemia, cerebral metastases
  - a reaction to severe uncontrolled physical symptoms
  - drugs, e.g. cytotoxics, benzodiazepines, antipsychotics, corticosteroids, antihypertensives.

## Management

- 5 **Correct the correctable:** treat medical causes, particularly severe pain and other distressing symptoms.
- 6 **Non-drug treatment:**
  - explanation and assurance that symptoms can be treated
  - depressed patients often benefit from the ambience of a Palliative Care Day Centre
  - psychological treatments available through a *Psycho-oncology Service*
  - other psychosocial professionals, e.g. chaplain and creative therapists, have a therapeutic role but avoid overwhelming the patient with simultaneous multiple referrals.

## 7 Drug treatment:

- prescribe an antidepressant if the patient is clinically depressed and is expected to live for >4 weeks (see Box)
- *the initial and continuing doses of antidepressants are generally lower in debilitated patients compared with the physically fit*
- all antidepressants can cause withdrawal symptoms if stopped abruptly: ideally withdrawal gradually over 2–3 weeks  
*except for MAOIs, when switching from one antidepressant class to another, overlap the withdrawal of the old antidepressant with the gradual introduction of the new antidepressant over 2–3 weeks.*

### Box. PCF preferred antidepressants

#### First-line antidepressants

##### **Methylphenidate (psychostimulant)**

Particularly if prognosis <3 months:

- start with 2.5–5mg b.d. (on waking/breakfast time and noon/lunchtime)
- if necessary, increase by daily increments of 2.5mg b.d. to 20mg b.d.
- occasionally higher doses are necessary, i.e. 30mg b.d. or 20mg t.d.s.

##### **Sertraline (SSRI)**

Particularly if prognosis >2–3 months, and if associated anxiety:

- no antimuscarinic effects
- may cause an initial increase in anxiety; prescribe diazepam o.n. if necessary
- low likelihood of a withdrawal (discontinuation) syndrome
- start with 50mg o.d., preferably p.c.
- if no improvement after 2 weeks, increase dose by 50mg every 2–4 weeks
- maximum dose 200mg o.d.

*If no response after 6–8 weeks, consider switching to a second-line antidepressant.*

#### Second-line antidepressants

##### **Mirtazapine (noradrenergic and specific serotonergic antidepressant, NaSSA)**

- acts on receptors; it is *not* a mono-amine re-uptake inhibitor
- a good choice for patients with anxiety/agitation
- starting dose 15mg o.n., increasing to 30mg o.n. after 2 weeks if little or no improvement
- concurrent H<sub>1</sub>-receptor antagonism leads to sedation but this decreases *at the higher dose because of noradrenergic effects*
- fewer undesirable effects than TCAs.

*If no response after 4 weeks, consider switching to a TCA and/or seeking advice from a psycho-oncologist/psychiatrist.*

##### **Tricyclic antidepressant (TCA)**

Amitriptyline or imipramine (serotonin and noradrenaline re-uptake inhibitors):

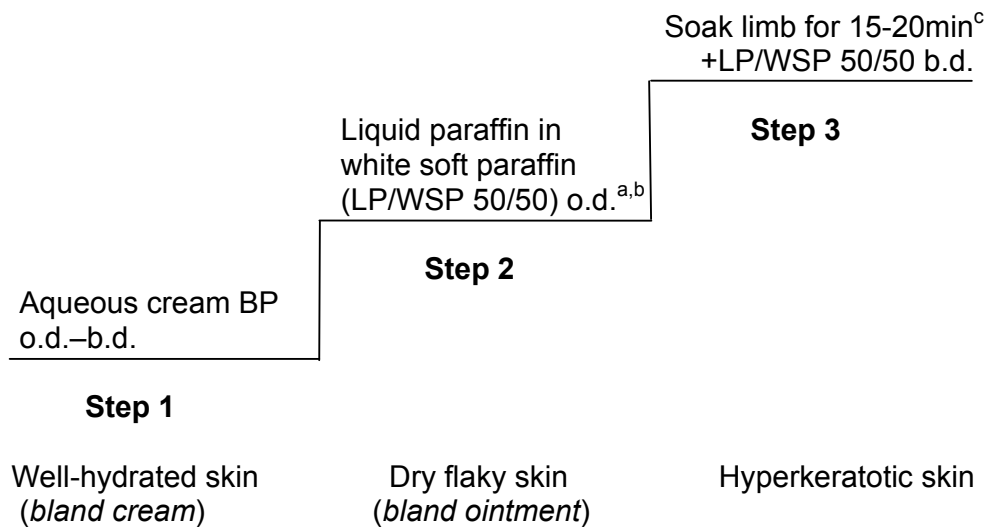
- 10–25mg o.n. initially, increasing to 25–50mg o.n. after 3–7days if tolerated
- subsequently increase dose by 25mg every 4 weeks to 75–150mg o.n. if only partial improvement
- dose escalation may be limited by undesirable effects, e.g. dry mouth and sedation.

*If no response after 8 weeks, seek advice from a psycho-oncologist/psychiatrist.*

## Dry skin in lymphoedema

Many elderly and/or malnourished patients have a dry skin – which can cause pruritus. In lymphoedema a healthy skin is crucial in prophylaxis against local infection (acute inflammatory episodes/AIE); moisturising the skin regularly is most important.

- 1 *Emollients* soothe, smooth and hydrate the skin. They are indicated for all causes of dry skin and scaling disorders. Because effects are short-lived, emollients should be applied frequently (up to q.d.s.). Less frequent use, e.g. once daily, should continue indefinitely.
- 2 The choice of emollient depends mainly on the state of the skin. The stepladder below is used in patients with lymphoedema. For patients without lymphoedema, aqueous cream b.d. may be adequate as Step 2. For normally active people, o.d. application is best at bedtime.



- a. ointments are generally not necessary for more than a few days
  - b. some people prefer *coconut oil BP* because it has a skin-cooling effect. Use the plain variety; added fragrance can cause allergic dermatitis
  - c. after soaking in a bucket of warm water (to which 15–20ml of LP/WSP 50/50 has been added) and after drying the limb, apply LP/WSP 50/50 using a circular motion; this tends to lift off hyperkeratotic skin.
- 3 Other options for hyperkeratotic skin:
    - use jacuzzi or shower spray to penetrate into the crevasses
    - to reduce bacterial and fungal colonisation in the crevasses, add sufficient *potassium permanganate tablets or granules* to achieve a rose wine colour (note: it stains skin and materials brown and tends to cause skin dryness)
    - if culture of a skin swab indicates superficial infection with *pseudomonas*, add *vinegar* 30ml/4L to the soaks
    - if there is fungal infection, apply *hydrocortisone 1% and miconazole 2%* (Daktacort) to the affected areas.

- 4 For areas resistant to treatment, consider applying LP/WSP 50/50 and covering with a hydrocolloid dressing (Comfeel, Granuflex) for 2 days and then soak etc. (see 2c).
- 5 Topical creams and ointments can cause folliculitis if massaged into the hair follicles; the likelihood of this is reduced by massaging in the direction of hair growth.
- 6 Avoid the use of emollients which:
  - contain lanolin/wool fat or are strongly scented (can cause allergic dermatitis)
  - are expensive, e.g. E45 cream (contains hypo-allergenic lanolin; 500g = £5.61), aqueous cream (500g = £1.10).
- 7 Soap should *not* be used because it dries the skin; use aqueous cream as a soap substitute.
- 8 *Emollient bath additives*: Soya containing bath oils (e.g. Balneum (soya) bath oil) are preferable to ones containing lanolin/wool fat (e.g. Oilatum emollient bath additive).
- 9 *Antipruritic emollients*: if pruritus is caused by the dry skin, rehydration of the skin will correct it. Thus, all emollients are anti-pruritic in this sense. Preparations which have more specific anti-pruritic properties include:
  - aqueous cream + 1% menthol (or 2%)
  - colloidal oatmeal cream (Aveeno); popular with children.

#### **Addendum** Topical applications

<b>Ointments</b>	<b>Creams</b>	<b>Lotions</b>
Grease-based	Water-in-oil (oily) or oil-in-water (aqueous) emulsions	Solutions or suspensions or emulsions from which water evaporates leaving a thin coating of powder
Most hydrating	Less hydrating	Only emulsions contain oil, and have an emollient effect; other lotions are drying
Messy to apply; difficult if skin very hairy	Massage well into skin; cosmetically more acceptable	Shake well before use; apply to the skin without friction

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## Hydration (parenteral) in palliative care

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- 1 Generally, all the following criteria should be met:
  - the patient is experiencing symptoms, e.g. thirst, malaise, postural hypotension, delirium
  - increased oral intake not feasible
  - anticipation that parenteral hydration will relieve the symptoms, e.g. in patients with severe dysphagia, vomiting or diarrhoea
  - the patient's underlying physical condition is relatively good, e.g. some patients with head and neck cancer
  - the patient is willing to have parenteral hydration
  - the patient and relatives understand that the purpose is to relieve symptoms and not to cure.
- 2 It is advisable to agree a time point for assessing for benefit of parenteral hydration, e.g. 2–3 days and, if unhelpful, that it will be discontinued.
- 3 Contra-indications:
  - the patient requests not to have an invasive procedure
  - the sum of the burdens of parenteral hydration outweigh the likely benefits
  - the patient is moribund for reasons other than dehydration
- 4 If it is not in the patient's best interests, parenteral hydration should not be introduced simply to satisfy relatives who insist that 'something must be done'.

### Procedure relating to CSCI of fluids

- 5 Preferred fluids are saline 0.9% or glucose 4% with saline 0.18%; generally, glucose 5% is not as readily absorbed and hypertonic or hypotonic solutions should be avoided.
- 6 Up to 3L may be administered in 24h; in palliative care 1–2L will often suffice.
- 7 Appropriate sites are the thigh, abdomen and chest wall.
- 8 The administration rate should be 1–2ml/min.
- 9 Record the time of administration on the patient's drug chart. Check the flow approximately every hour and record the time of completion.
- 10 It is preferable to change the site of infusion for every litre of fluid that is being administered and at least every 24h.

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## Nausea and vomiting in palliative care

- 1 After clinical evaluation, document the most likely cause(s) of the nausea and vomiting in the patient's case notes, e.g. gastric stasis, intestinal obstruction, biochemical, drugs, raised intracranial pressure.
- 2 Ask the patient to keep a record of symptoms and response to treatment, preferably using a diary.
- 3 Correct correctable causes/exacerbating factors, e.g. drugs, severe pain, infection, cough, hypercalcaemia. (*Correction of hypercalcaemia is not always appropriate in a dying patient.*) Anxiety exacerbates nausea and vomiting from any cause and may need specific treatment.
- 4 Prescribe the most appropriate anti-emetic stat, regularly and p.r.n. (see below). Give by SC injection or CSCI if continuous nausea or frequent vomiting.

### Commonly used anti-emetics

#### **Prokinetic anti-emetic** (about 50% of prescriptions)

*For gastritis, gastric stasis, functional bowel obstruction (peristaltic failure):*

metoclopramide 10mg PO stat & q.d.s. or 10mg SC stat & 40–100mg/24h CSCI, & 10mg p.r.n. up to q.d.s.

#### **Anti-emetic acting principally in chemoreceptor trigger zone** (about 25% of prescriptions)

*For most chemical causes of vomiting, e.g. morphine, hypercalcaemia, renal failure:*

haloperidol 1.5–3mg PO stat & o.n. or 2.5–5mg SC stat & 2.5–10mg/24h CSCI, & 2.5–5mg p.r.n. up to q.d.s.

Metoclopramide also has a central action.

#### **Antispasmodic and antisecretory anti-emetic**

*If bowel colic and/or need to reduce gut secretions:*

hyoscine butylbromide 20mg stat, 80–200mg/24h CSCI, & 20mg SC hourly p.r.n.

#### **Anti-emetic acting principally in the vomiting centre**

*For raised intracranial pressure (in conjunction with dexamethasone), motion sickness and in organic bowel obstruction:*

cyclizine 50mg PO stat & b.d.–t.d.s or 50mg SC stat & 100–150mg/24h CSCI, & 50mg p.r.n. up to q.d.s.

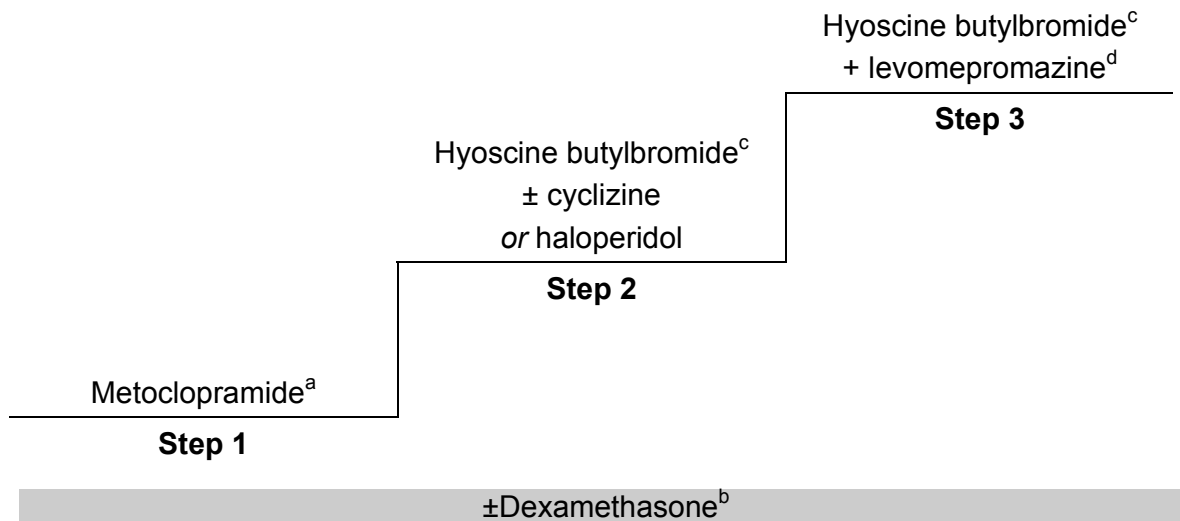
#### **Broad-spectrum anti-emetic**

*For organic bowel obstruction and when other anti-emetics are unsatisfactory:*

levomepromazine 6–12.5mg PO/SC stat, o.n. & p.r.n. up to q.d.s.

- 5 Review anti-emetic dose daily, taking note of p.r.n. use and the patient's symptoms.
- 6 If little benefit despite optimizing the dose, have you got the cause right?
  - if no, change to an alternative anti-emetic and optimize
  - if yes, add or substitute a second anti-emetic.

- 7 Anti-emetics for bowel obstruction are best given by CSCI, but levomepromazine can be given as a single SC dose o.n.:



- if colic, *omit* step 1
- the place of dexamethasone in inoperable bowel obstruction is controversial; for dose see below
- alternatively use glycopyrronium 600–1200microgram/24h
- if levomepromazine too sedative, consider using olanzapine 1.25–2.5mg o.d. PO instead; or revert to step 2 but give both cyclizine and haloperidol.

- 8 In patients who fail to respond to the commonly used anti-emetics, consider:
- corticosteroid (*adjuvant anti-emetic for bowel obstruction and when all else fails*), e.g. dexamethasone 8–16mg PO/SC stat & o.m.; consider reducing the dose after 7 days
  - 5HT<sub>3</sub>-receptor antagonist (use when massive release of 5HT/serotonin from enterochromaffin cells or platelets, e.g. chemotherapy, abdominal radiation, bowel obstruction/distension, renal failure), e.g. granisetron 1–2mg PO/SC stat & o.d.
  - somatostatin analogue (*an anti-secretory agent without antispasmodic effects; use in obstruction if hyoscine inadequate*), e.g. octreotide 100microgram stat, 300–600microgram/24h CSCI, & 100microgram p.r.n. up to q.d.s.

- Some patients with nausea and vomiting need more than one anti-emetic.
- Antimuscarinic drugs (e.g. cyclizine, hyoscine) block the cholinergic pathway through which prokinetics act; concurrent use antagonizes the prokinetic effect of metoclopramide and is best avoided.
- Continue anti-emetics unless the cause is self-limiting.
- Except in organic bowel obstruction, consider changing to PO after 72h of good control with CSCI.

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## **Guidelines for the relief of cancer pain in adults**

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The Mid-Trent Cancer Services guidelines for the relief of cancer pain are available in full in separate publications:

Palliative Care Cancer Pain Standards, Guidelines and Patient Information for Hospitals (3rd Ed.) July 2005.

Palliative Care Cancer Pain Standards and Guidelines for the Community (3rd Ed.) July 2005.

The front of the guidelines is identical across the Network; the rear contains contact region-specific resource information. The Nottingham hospital version is included here as an example; for sources of advice in other regions, please make use of the obtaining advice section at the beginning of this book.

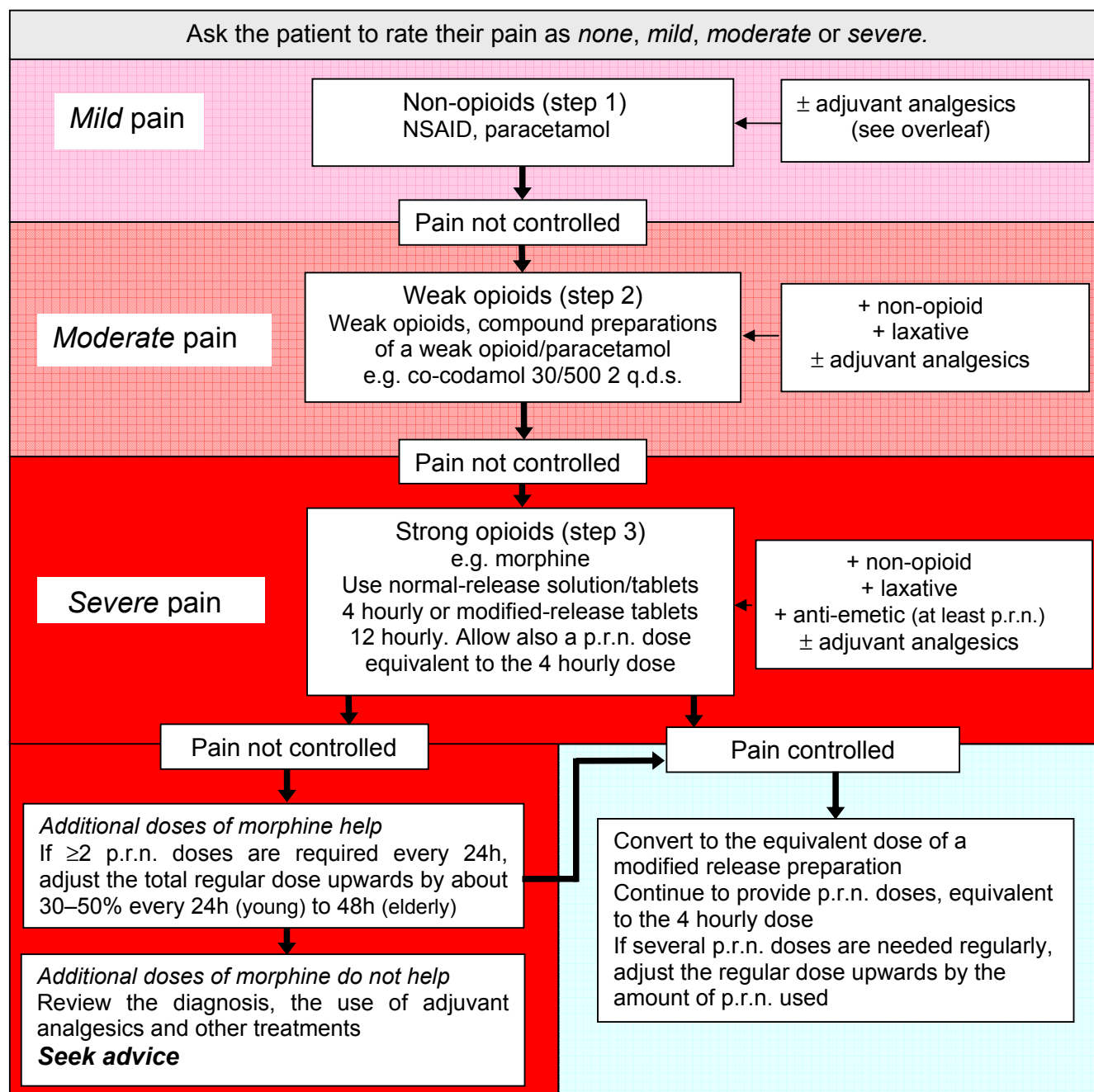


## Guidelines for the relief of cancer pain in adults

These guidelines, based on the WHO analgesic ladder, have been produced by the Mid Trent Cancer Network Palliative Care Group (0115 9627988) and are for use by all medical and nursing staff caring for adults with cancer pain. *If you have any questions or require clarification, please make use of the listed resources.*

Important keys to success include:

- accurate evaluation of the pain from the history (use a formal pain assessment tool), examination and appropriate investigation in order to diagnose the cause of the pain
- explanation to the patient and carers and discussing treatment options with them
- administer analgesics regularly
- individualize drug and non-drug approaches and the setting of realistic goals
- regular reassessment of the pain
- referral to the specialist palliative care team if the pain is not being progressively relieved.



### Additional notes

For information regarding the use and dose of specific NSAIDs, weak and strong opioids see the Palliative Care Formulary (2002), Twycross, Wilcock Charlesworth and Dickman, Radcliffe Medical Press, Abingdon. Also available on the website [www.palliativedrugs.com](http://www.palliativedrugs.com).

### Morphine prescribing

- usual starting dose is 10mg 4 hourly, titrated every 24h; the elderly and/or those with renal impairment may only require a starting dose of 2.5–5mg 4–6 hourly titrated every 48h or more
- the dose for breakthrough pain is equivalent to the 4 hourly dose i.e. 1/6 of the total 24h dose
- 50% of patients experience nausea, prescribe an anti-emetic for the first 3–5 days, e.g. haloperidol 1.5–3mg immediately, at night and p.r.n.
- regular laxatives are necessary, a preparation combining a stimulant and a softener is preferred, e.g. co-danthramer.

### Alternative strong opioids

Morphine is the strong opioid of choice. Alternative opioids, e.g. *oxycodone*, *hydromorphone*, *transdermal fentanyl*, *methadone* are generally used when there are unacceptable adverse effects with morphine. Each has its own advantages and disadvantages. *Seek guidance*.

### Adjuvant analgesics, for use in

- *neuropathic pain*, e.g. anticonvulsants, antidepressants, corticosteroids
- *skeletal muscle cramp*, e.g. benzodiazepines
- *smooth muscle spasm/colic*, e.g. antimuscarinics
- *raised intracranial pressure*, e.g. corticosteroids
- *bone pain*, e.g. bisphosphonates (usually only after NSAID + strong opioid + radiotherapy).

### Additional measures

- radiotherapy, particularly for bone pain
- nerve blockade, particularly for localised pain or neuropathic pain
- non-drug approaches, e.g. modification of lifestyle, aids for daily living, relaxation, distraction, addressing the psychological, social and spiritual dimensions of the 'total pain' experience.

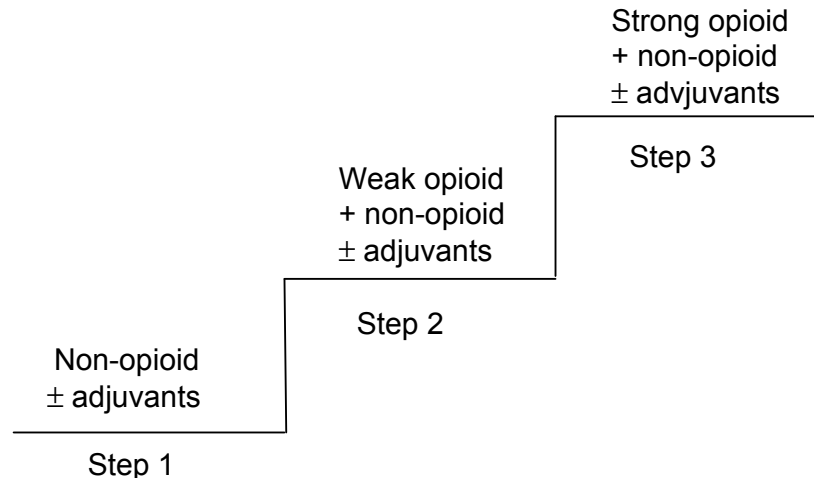
If there is no progressive control of pain contact the Specialist Palliative Care Team for advice

### Resources for Nottingham

	Nottingham City Hospital	Queen's Medical Centre
<i>Palliative Care Link Nurse and Resource file, available on each ward</i>		
Hospital Palliative Care Team	0115 9691169 Ext 46619 or air call via switchboard	0115 9249924 Ext 44119 or air call via switchboard
Palliative Medicine Consultants	Dr V Crosby Ext 47085 Dr A Wilcock Ext 46450 Dr P Costello Ext 34163 Dr B El Khoury Ext 39469	Dr V Crosby Ext 42585
<i>24 hour advice is available from Hayward House Specialist Palliative Care Cancer Unit 0115 9627619</i>		
Pain Anaesthetists	Dr A Ravenscroft Ext 45639 Dr V Hodgkinson Ext 45635	Dr Z Hussein Ext 41194 Dr G Hobbs Ext 41194
Other sources of drug information	Ext 47164	Ext 44185

## Starting a patient on oral morphine

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### WHO analgesic ladder for cancer pain

- 1 Oral morphine is indicated in patients with pain which does not respond to the optimised combined use of a non-opioid and a weak opioid.
- 2 The starting dose of morphine is calculated to give a greater analgesic effect than the medication already in use:
  - if the patient was previously receiving a weak opioid (e.g. codeine 120mg/24h or equivalent) give 10mg q4h or m/r 20–30mg q12h
  - if changing from an alternative strong opioid (e.g. fentanyl, methadone) a much higher dose of morphine may be needed
  - if the patient is frail and elderly, a lower dose helps to reduce initial drowsiness, confusion and unsteadiness, e.g. 5mg q4h
  - because of cumulation of an active metabolite, a lower and/or less frequent regular dose may be preferable in renal failure, e.g. 5–10mg q6h.
- 3 If the patient takes two or more p.r.n. doses in 24h, the regular dose should be increased by 30–50% every 2–3 days.
- 4 Upward titration of the dose of morphine stops when either the pain is relieved or intolerable undesirable effects supervene. In the latter case, it is generally necessary to consider alternative measures. The aim is to have the patient free of pain and mentally alert.
- 5 *Because of poor absorption, m/r morphine may not be satisfactory in patients troubled by frequent vomiting or those with diarrhoea or an ileostomy. M/r morphine should be used with caution if there is renal impairment.*
- 6 Supply an anti-emetic in case the patient becomes nauseated, e.g. haloperidol 1.5mg stat & o.n.
- 7 Prescribe laxatives, e.g. co-danthramer (see opioid-induced constipation guideline); adjust the dose as necessary. Suppositories and enemas continue to be necessary in about one third of patients. *Constipation may be more difficult to manage than the pain.*
- 8 Warn patients about the possibility of initial drowsiness.

- 9 If swallowing is difficult or there is persistent vomiting, morphine may be given PR by suppository; the dose is the same as PO. Alternatively give half the oral dose by injection, or one third as diamorphine, preferably by continuous SC infusion.
- 10 For outpatients, write out the drug regimen in detail with times, names of drugs and amount to be taken; arrange for follow-up.

**Scheme 1: ordinary (normal-release) morphine tablets or solution**

- morphine given q4h 'by the clock' with p.r.n. doses of equal amount
- after 1–2 days, recalculate q4h dose based on total used in previous 24h (regular + p.r.n. use)
- continue q4h and p.r.n. doses
- increase the regular dose until there is adequate relief throughout each 4h period, taking p.r.n. use into account
- a double dose at bedtime obviates the need to wake the patient for a dose during the night.

**Scheme 2: ordinary (normal-release) morphine and modified-release (m/r) morphine**

- begin as for Scheme 1
- when the q4h dose is stable, replace with m/r morphine q12h, or o.d. if a 24h preparation is prescribed
- the q12h dose will be *three times* the previous q4h dose; a daily dose will be *six times* the previous q4h dose, rounded to a convenient number of tablets or capsules
- continue to provide ordinary morphine tablets or solution for p.r.n. use; give the equivalent of a q4h dose, i.e. 1/6 of the total daily dose.

**Scheme 3: m/r morphine and ordinary (normal-release) morphine**

- generally start with m/r morphine 20–30mg b.i.d. or 40–60mg o.d. (24h preparation)
- use ordinary morphine tablets or solution for p.r.n. medication; give about 1/6 of the daily dose
- if necessary, increase the dose of m/r morphine every 2–3 days until there is adequate relief throughout each 12h period, guided by p.r.n. use.

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## Switching opioids

- 1 It is sometimes necessary to switch strong opioids because of neurotoxicity (severe drowsiness, delirium, hallucinations, myoclonus, hyperalgesia, allodynia), poor compliance or intractable constipation.

### Oral, sublingual and transdermal routes

- 2 Multiply the dose of opioid by its potency ratio to determine the dose of morphine.

**Table** Approximate PO opioid potency ratios (morphine = 1)

<i>Analgesic</i>	<i>Potency ratio with morphine</i>	<i>Duration of action (hours)<sup>a</sup></i>
Codeine	1/10	3–6
Dihydrocodeine		
Propoxyphene		
Pethidine	1/8	2–4
Tramadol	1/5 <sup>b</sup>	4–6
Oxycodone	1.5 <sup>b</sup> (2) <sup>c</sup>	3–4
Methadone	5–10 <sup>d</sup>	8–12
Hydromorphone	4–5 (7.5) <sup>c</sup>	4–5
Buprenorphine (sublingual)	80	6–8
Fentanyl (transdermal)	100 (150) <sup>c</sup>	72

a. dependent in part on severity of pain and on dose; often longer lasting in very elderly and those with renal dysfunction

b. tramadol and oxycodone are both relatively more potent by mouth because of high bio-availability; parenteral potency ratios with morphine are 1/10 and 3/4 respectively

c. the numbers in parenthesis are the manufacturers' preferred ratios; for explanation of divergence, see [www.palliativedrugs.com](http://www.palliativedrugs.com)

d. a single 5mg dose of methadone is equivalent to morphine 7.5mg, but a variable long plasma half-life and broad-spectrum receptor affinity result in a much higher than expected potency ratio when administered regularly (see methadone guidelines, p.61).

- 3 Because of its more complicated pharmacokinetics, a separate strategy is necessary when switching to methadone (see methadone guidelines, p.61).

### Injections

- 4 The following conversion ratios are approximate and should be regarded only as a general guide. Subsequent adjustment up or down may be necessary:
  - PO → SC/IV morphine, give 1/2–1/3 the PO dose
  - PO morphine → SC diamorphine, give 1/3 of the PO dose.

### Switching at high doses

- 5 When switching from high doses of morphine, e.g. >1g/24h PO, reduce the calculated dose arbitrarily by 33–50% because of 'incomplete cross-tolerance'. Rely on p.r.n. doses to make up any deficit while re-titrating to a satisfactory dose of the new opioid.
- 6 In a comparably cautious way, when there has been a recent rapid dose escalation of the first opioid, use the pre-escalation dose to calculate the initial dose of the second opioid.



## Use of transdermal fentanyl patches

These guidelines differ from the manufacturer's recommendations in that, instead of using a dose conversion ratio for morphine to fentanyl of 150:1, they use 100:1 (as in Germany). Note: pain not relieved by morphine will generally not be relieved by fentanyl. If in doubt, seek specialist advice before prescribing TD fentanyl.

- Indications for using TD fentanyl instead of morphine include:
  - intolerable undesirable effects with morphine, e.g. nausea and vomiting, constipation, hallucinations, dysphagia
  - renal failure (fentanyl has no active metabolite)
  - 'tablet phobia' or poor compliance with oral medication
  - high risk of tablet misuse/diversion.
- TD fentanyl is *contra-indicated* in patients with acute (short-term) pain and in those who need rapid dose titration for severe uncontrolled pain. TD fentanyl is best reserved for patients already on a stable dose of morphine (or other opioid analgesic) for  $\geq 1$  week.
- TD fentanyl patches are available in 5 strengths: 12, 25, 50, 75 and 100microgram/h for 3 days. Although licensed only as an aid to titration, there is no pharmacological reason for not using the 12microgram/h patch as the starting dose for TD fentanyl.
- Use the following table to decide a safe starting dose for TD fentanyl, and an appropriate rescue dose. Patients taking a weak opioid should start on 12microgram/h.
- For patients taking a dose of morphine that is not the exact equivalent of a fentanyl patch, it will be necessary to opt for a patch which is either slightly more or slightly less than the morphine dose. Thus, if the patient still has pain, round up to a higher patch strength; if pain-free and frail, round down.

**Table** Comparative doses of morphine, diamorphine and TD fentanyl (based on dose ratio 100:1)

<i>Morphine PO</i>		<i>Morphine SC/IV</i>		<i>Diamorphine SC/IV</i>		<i>Fentanyl patch</i>	
mg/24h	p.r.n mg <sup>a</sup>	mg/24h <sup>b</sup>	p.r.n mg <sup>a</sup>	mg/24h	p.r.n. mg <sup>a</sup>	microgram/h	mg/24h
30	5	15	2.5	10	2.5	12	0.3
60	10	30	5	20	2.5	25	0.6
120	20	60	10	40	5	50	1.2
180	30	90	15	60	10	75	1.8
240	40	120	20	80	15	100 <sup>c</sup>	2.4

a. using traditional 1/6 of total daily dose as p.r.n. dose

b. assuming potency ratios of morphine SC/IV to PO of 2:1 and diamorphine SC/IV to PO of 3:1

c. for combinations of patches, add the p.r.n. doses together, e.g. 100 + 75microgram/h patches = 15 + 10mg diamorphine SC/IV = 25mg diamorphine SC/IV, but can round up to 30mg or down to 20mg for convenience.

- Apply the patch to dry, non-inflamed, non-irradiated, hairless skin on the upper arm or trunk; body hair may be clipped but not shaved. If the skin is washed beforehand, use only water; *avoid soaps, oils or lotions*. Press patch firmly in place for at least 30 seconds. Micropore® or Tegaderm® may be necessary to ensure adherence.

- 7 Systemic analgesic concentrations are generally reached within 12h. If converting from:
  - *4-hourly PO morphine*, give regular doses for the first 12h after applying the patch
  - *12-hourly m/r morphine*, apply the patch and the final m/r dose at the same time
  - *24-hourly m/r morphine*, apply the patch 12h after the final m/r dose
  - *CSCI/CIVI*, continue the syringe driver for about 12h after applying the patch.
- 8 Steady-state plasma concentrations of fentanyl are generally achieved after 36–48h; the patient should use p.r.n. doses liberally during the first 3 days, particularly during the first 24h. Safe rescue doses of PO morphine are given in the table above.
- 9 After 48h, if a patient continues to need 2 or more rescue doses of morphine a day, the strength of the next patch to be applied should be increased by 12–25microgram/h. (Note: when using the manufacturer's recommended starting doses, about 50% of patients need to increase the patch strength after the first 3 days.)
- 10 About 10% of patients experience opioid withdrawal symptoms when changed from morphine to TD fentanyl. These manifest with symptoms like gastric flu and last for a few days; p.r.n. doses of morphine will relieve troublesome symptoms.
- 11 Fentanyl is less constipating than morphine; halve the dose of laxatives when starting fentanyl and re-titrate. Some patients develop diarrhea; if troublesome, control with rescue doses of morphine, and completely stop laxatives.
- 12 Fentanyl probably causes less nausea and vomiting than morphine but, if necessary, prescribe haloperidol 1.5mg stat & o.n.
- 13 In febrile patients, the rate of absorption of fentanyl increases, and occasionally causes toxicity, principally drowsiness. Absorption may also be enhanced by an external heat source over the patch, e.g. electric blanket or hot-water bottle; patients should be warned about this. Patients may shower with a patch but should not soak in a hot bath.
- 14 Remove patches after 72h; change the position of the new patches so as to rest the underlying skin for 3–6 days.
- 15 A reservoir of fentanyl cumulates in the body, and significant blood levels persist for at least 24h after discontinuing TD fentanyl.
- 16 TD fentanyl is unsatisfactory in <5% of patients. However, discontinuation is more common when TD fentanyl is used in strong opioid-naïve patients.
- 17 In moribund patients, continue TD fentanyl and give additional SC (dia)morphine p.r.n. (see Table above). If >2 p.r.n. doses are required/24h, give (dia)morphine by CSCI, starting with a dose equal to the sum of the p.r.n. doses over the preceding 24h. If necessary, adjust the p.r.n. dose taking into account the total opioid dose (i.e. TD fentanyl + CSCI (dia)morphine).
- 18 Used patches still contain fentanyl; after removal, fold the patch with the adhesive side inwards and discard in a sharps container (hospital) or flushed down the toilet (home), and wash hands. Ultimately, any unused patches should be returned to a pharmacy.

## \*Use of methadone for cancer pain

Methadone has both opioid and non-opioid properties, and a long variable half-life (approximately 8–80h vs. 2.5h for morphine). Thus there is no single potency ratio for methadone and other opioids. When switching from morphine, the eventual 24h dose of methadone is typically 5–10 times smaller than the dose of morphine, sometimes 20–30 times smaller, and occasionally even smaller. Inevitable cumulation is the reason for the week-long intervals between dose adjustments. Switching must be closely supervised, generally as an inpatient with specialist guidance.

### Indications for use

- neuropathic or mixed nociceptive-neuropathic pain not responding to an NSAID + morphine + adjuvant analgesics, e.g. an antidepressant ± an anti-epileptic
- neurotoxicity with morphine at any dose (e.g. myoclonus, allodynia, hyperalgesia) which does not respond to a reduction in morphine dose and switching to another easier-to-use opioid (e.g. fentanyl, hydromorphone, oxycodone) is not possible
- the strong opioid of choice, instead of morphine
- end-stage renal failure.

### Dose titration

- 1 When prescribing methadone PO as first-line strong opioid:
  - start with methadone 5mg (2.5mg in the elderly) q12h regularly and q3h p.r.n.
  - if necessary, titrate the regular dose upwards *once a week*, guided by p.r.n. use
  - continue with 5mg p.r.n., or 2.5mg in the elderly
  - with doses  $\geq 30$ mg q12h, increase the p.r.n. dose to 1/6–1/10 of the q24h dose.
- 2 If the patient is already receiving morphine, use the following method.

### PO Morphine to PO methadone

*Morphine is stopped abruptly when methadone is started.*

If switching from:

- normal-release morphine, give the first dose of methadone  $\geq 2$ h (pain present) or 4h (pain-free) after last dose of morphine
- m/r morphine, give the first dose of methadone  $\geq 6$ h (pain present) or 12h (pain-free) after the last dose of a 12h preparation, or  $\geq 12$ h (pain present) or 24h (pain-free) after the last dose of a 24h preparation.

Give a single loading dose of PO methadone 1/10 of the previous total 24h PO morphine dose, up to a maximum of 30mg.

Give q3h p.r.n. doses of methadone 1/3 of the loading dose, up to a maximum of 30mg.

*Example 1: Morphine 300mg/24h PO = loading dose of methadone 30mg PO, and 10mg q3h p.r.n.*

*Example 2: Morphine 1200mg/24h PO = loading dose of methadone 120mg PO, and 40mg q3h p.r.n.; however, both are limited to the maximum of 30mg.*

For patients in severe pain who need more analgesia in  $< 3$ h, see point 6 below.

On Day 6, the amount of methadone taken over the previous 2 days is noted and divided by 4 to give a regular q12h dose, with 1/6–1/10 of the 24h dose q3h p.r.n., e.g. *methadone 80mg PO in previous 48h → 20mg q12h and 5mg PO q3h p.r.n.*

If  $\geq 2$  doses/day of p.r.n. methadone continue to be needed, the dose of regular methadone should be increased once a week, guided by p.r.n. use.

- 3 If using another strong opioid, calculate the morphine equivalent daily dose and then follow the guidelines for morphine.
- 4 If converting from methadone PO to methadone SC/IV, or from another opioid CSCI/CIVI, see the respective boxes below.
- 5 If there has been recent rapid escalation of the pre-switch opioid dose, calculate the initial dose of methadone using the pre-escalation dose of the opioid.
- 6 For patients in severe pain and who need more analgesia in <3h, options include:
  - taking the previously used opioid q1h p.r.n. (50–100% of the p.r.n. dose used before switching)
  - if neurotoxicity with the pre-switch opioid, use an appropriate dose of an alternative strong opioid
  - ketamine.
- 7 The switch to methadone is successful (i.e. improved pain relief and/or reduced toxicity) in about 75% of patients.
- 8 If a patient:
  - becomes over-sedated, reduce the dose generally by 33–50% (some centers monitor the level of consciousness and respirations q4h for 24h)
  - develops opioid abstinence symptoms, give p.r.n. doses of the previous opioid to control these.

#### **Methadone PO to methadone SC/IV or CSCI/CIVI**

To convert PO methadone to methadone SC/IV, halve the PO dose, e.g. methadone 10mg/24h PO = 5mg/24h SC/IV. This is a safe conversion ratio; for some patients the SC/IV dose = PO dose.

Due to its long half-life, methadone (10mg/ml) can be given SC q8h–q12h. If SC injection is painful or causes local inflammation, give by CSCI/CIVI instead.

If CSCI methadone causes a skin reaction:

- administer as a more dilute solution in a 20ml or 30ml syringe
- change the syringe q12h, and the site daily.

For additional rescue doses of methadone SC/IV, give 1/6–1/10 of the 24h SC/IV dose q3h p.r.n., e.g. methadone 20mg CIVI/24h = 2mg q3h p.r.n. SC/IV.

If  $\geq 2$  p.r.n doses/day continue to be needed, the 24h SC/IV dose should be increased once a week, guided by p.r.n. use.

For patients in severe pain who need more analgesia in <3h, see point 6 above.

#### **Other opioids CSCI/CIVI to methadone CSCI/CIVI**

The safest approach is to follow the method for PO switching, using bolus injections of methadone SC/IV instead of PO doses.

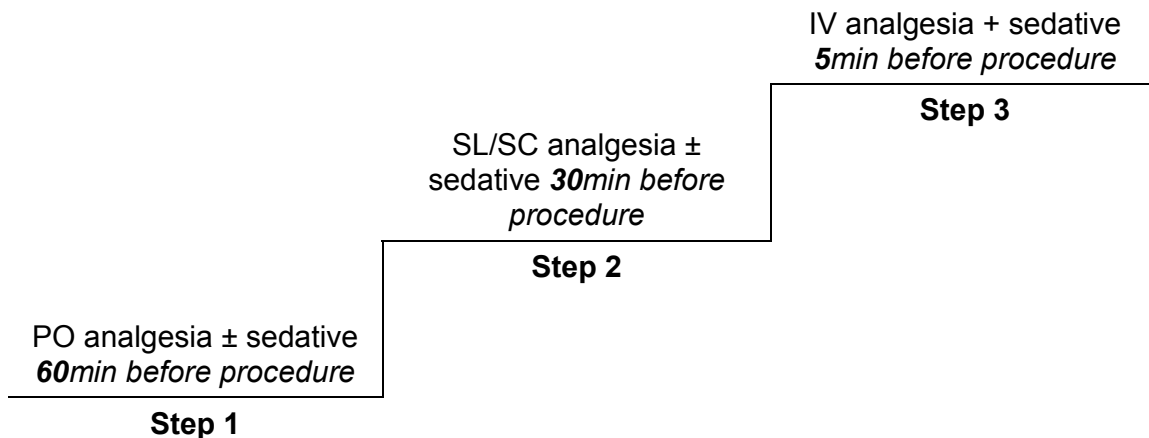
Convert the opioid 24h CSCI/CIVI dose to its PO equivalent and determine the methadone PO dose (Dose titration, point 2).

The SC/IV dose of methadone is half the PO dose; the maximum initial dose of methadone SC/IV will be 15mg. This is a safe conversion ratio; for some patients the SC/IV dose = PO dose.

## Management of procedure-related pain

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- 1 Palliative care patients may experience pain while undergoing procedures, e.g.:
  - position change
  - investigation, e.g. MRI
  - wound dressing change
  - venous cannulation
  - urethral catheterization
  - insertion of nasogastric tube
  - insertion/removal of central line
  - insertion/removal of spinal line
  - drainage of chest/abdomen
  - treatment, e.g. radiotherapy.
- 2 The goal is adequate pain relief without undesirable effects. What is appropriate depends on the anticipated pain severity, procedure duration, current opioid use, and the patient's past personal experience. Thus, severe procedure-related pain may necessitate parenteral analgesia and sedation as first-line therapy.
- 3 Always include non-drug approaches:
  - discuss past experiences of procedure-related pain, identify what was helpful or unhelpful, and clarify present concerns
  - explain the procedure thoroughly before starting
  - assure that you will stop immediately if requested
  - as far as possible, choose the most comfortable position for the patient
  - distract and relax, e.g. through talking, music, hypnosis and other relaxation techniques.
- 4 Use a local anesthetic when a cannula, urinary catheter or tube is inserted transdermally, e.g.
  - EMLA cream for venous cannulation, if needle phobic or if requested (wait 60min)
  - always use lidocaine gel for urethral catheterization (wait 5min)
  - always use lidocaine tissue infiltration for chest aspiration (wait 5min).
- 5 Consider nitrous oxide-oxygen (Entonox®) inhalation if the procedure is short and the patient is able to use the mask or mouthpiece effectively.
- 6 Give analgesia from the appropriate step of the ladder. (General anesthetic approaches are beyond the scope of these guidelines.)



## Examples of analgesia for procedure-related pain

### Step 1: If anticipating mild–moderate pain

*Give 60min before the procedure:*

PO morphine, give the patient's usual rescue dose for episodic (breakthrough) pain.

If necessary, combine with:

- PO diazepam 5mg *or*
- SL lorazepam 500–1000microgram *or*
- an alternative sedative.

### Step 2: If anticipating moderate–severe pain

*Give 30min before procedure:*

SC morphine, give 50% of the patient's usual PO morphine rescue dose.

If necessary, combine with:

- SL/SC midazolam 2.5–5mg *or*
- SL lorazepam 500–1000microgram *or*
- an alternative sedative.

### Step 3: If anticipating severe–excruciating pain

*Give 5min before procedure:*

IV morphine, give 50% of the patient's usual PO morphine rescue dose *or*

IV diamorphine, give 33% of the patient's usual PO morphine rescue dose *or*

IV ketamine 0.5–1mg/kg (typically 25–50mg). Combine with:

- IV midazolam 2.5–5mg *or*
- an alternative sedative.

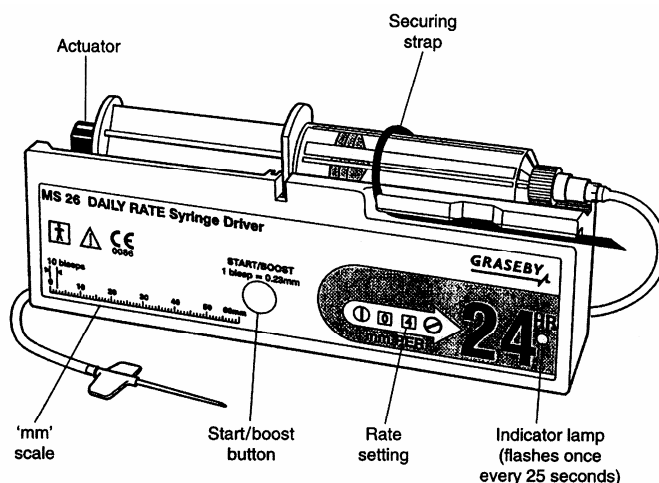
### Alternatives to SC/IV (dia)morphine

- fentanyl citrate (OTFC) 200microgram or more transmucosally
- alfentanil 250–500microgram SL (*from ampoule for injection*) or SC/IV
- fentanyl 50–100microgram SL (*from ampoule for injection*) or SC/IV
- sufentanil 12.5–25microgram SL (*from ampoule for injection*) or SC/IV.

- 7 If pain relief inadequate, give a repeat dose and wait again; if still inadequate, move to the next step.
- 8 If a sedative or sedative analgesic is used, monitor the patient to ensure that the airway remains patent, and consider intervention if the patient becomes cyanosed because of severely depressed respiration, e.g. rate  $\leq 8$  per min.
- 9 An opioid antagonist (naloxone) and a benzodiazepine antagonist (flumazenil) should be available in case of need. To prevent the complete reversal of any background regular opioid analgesic therapy, use naloxone 20–100microgram IV, repeated every 2min until the respiratory rate and cyanosis have improved.
- 10 If the procedure is to be repeated, give analgesia based on previous experience, e.g. drugs used and the patient's comments.

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## Use of syringe drivers



The Graseby Medical MS26 battery-driven portable syringe driver

### General information

- 1 Battery-driven portable syringe drivers are used to deliver medication generally SC over 24h when oral administration is unreliable or impossible due to:
  - persistent nausea and vomiting
  - intestinal obstruction
  - dysphagia
  - patient moribund.

The epidural (ED) or intrathecal (IT) routes are occasionally used for intractable pain. There are advantages and disadvantages of CSCI (Box).

#### Box Advantages and disadvantages of CSCI

##### Advantages

Increased comfort for the patient because there is less need for repeated injections.

Control of multiple symptoms with a combination of drugs.

Round-the-clock comfort because plasma drug concentrations are maintained without peaks and troughs.

Independence and mobility maintained because the device is lightweight and can be worn in a holster under or over clothes.

Generally needs to be loaded only o.d.

##### Disadvantages

Training necessary for staff.

Possible inflammation and pain at the infusion site.

Lack of flexibility with o.d. prescription.

- 2 The drugs most commonly given by CSCI infusion are:
  - (dia)morphine (*analgesic*)
  - midazolam (*sedative/anti-epileptic*)
  - metoclopramide (*anti-emetic*)
  - levomepromazine (*anti-emetic/antipsychotic*)
  - haloperidol (*anti-emetic/antipsychotic*)
  - cyclizine (*anti-emetic*)
  - hyoscine butylbromide (*antispasmodic/antisecretory*).

Because antimuscarinics block the prokinetic effect of metoclopramide, cyclizine and metoclopramide should not be prescribed concurrently

- 3 Most drugs are diluted in Water for Injections (WFI); a few are diluted in 0.9% saline:
  - ketamine
  - ketorolac
  - levomepromazine/methotrimeprazine
  - octreotide.
- 4 Drugs with a long duration of action do not need to be infused but can be given o.d. by separate SC injection:
  - dexamethasone
  - haloperidol (*but in practice it is often given by infusion*)
  - levomepromazine/methotrimeprazine (*if given by infusion, dilute in saline*)
  - granisetron.
- 5 In ED/IT analgesia, the following are often given concurrently:
  - diamorphine/morphine
  - bupivacaine
  - clonidine.

### Incompatibility

- 6 It is common practice to combine 2–3 different drugs in the same syringe driver, sometimes more and drug compatibility needs to be considered. In addition to the notes below *see also PCF2 pp 297–314 and [www.palliativesdrugs.com](http://www.palliativesdrugs.com)*.
- 7 Cyclizine may precipitate at concentrations above 20mg/ml or at temperatures above 37.5°C, or in the presence of saline, or as the concentration of diamorphine relative to cyclizine increases. Mixtures of diamorphine and cyclizine are also liable to precipitate after 24h.
- 8 Cyclizine generally precipitates if mixed with metoclopramide, but should not be combined because its antimuscarinic properties block the intestinal action of metoclopramide.
- 9 Mixtures of haloperidol and diamorphine are liable to precipitate after 24h if the concentration of haloperidol is above 2mg/ml.
- 10 Dexamethasone often causes compatibility problems and should always be the last drug added to an already dilute combination of drugs.

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## Guidelines for symptom control in the last days of life

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The Mid-Trent Cancer Services Network has adopted the nationally recommended Liverpool Care of the Dying Pathway, with modifications to the treatment algorithms.

The Nottingham Community version is included here as an example. The guidelines may vary slightly in presentation and recommendations between hospital and community settings and contact information is region-specific. For sources of advice in other regions, please make use of your locally produced Pathway documentation or the obtaining advice section at the beginning of this book.

Note. Because of the shortage of diamorphine, these guidelines recommend the use of parenteral morphine.

To convert PO morphine to 24h CSCI *morphine*, divide total 24h PO dose by 2,

e.g. 30mg/24h PO → 15mg/24h CSCI.

If diamorphine becomes freely available, use the following:

To convert PO morphine to 24h CSCI *diamorphine*, divide total 24h PO dose by 3,

e.g. 30mg/24h PO → 10mg/24h CSCI.



## Guidelines for symptom control in the last days of life (Community)

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- 1 At this stage, the focus of treatment is comfort.
- 2 The patient may have difficulty in swallowing medication, have an altered level of consciousness and much reduced or no food and fluid intake. It is therefore essential to review current medication and discontinue any medication that is no longer necessary, e.g.:

antihypertensives	diuretics
antibiotics	haematinics
anti-arrhythmics	hormone therapy
anticoagulants	oral hypoglycaemics
corticosteroids	vitamin preparations
- 3 Medication should be prescribed to manage distressing symptoms, and given by the most appropriate route and dose for each patient. The most common symptoms during the last days of life are:
  - pain
  - nausea
  - agitation / restlessness
  - noisy breathing (death rattle).
- 4 Even if these symptoms are not already present, all dying patients should have p.r.n. SC medication prescribed for the above symptoms.
- 5 Medication needs to be reviewed at least every 24h. If  $\geq 2$  doses of a p.r.n. medication are given, consider the use of a syringe driver.
- 6 The attached guidelines are to help you manage distressing symptoms.

**You still need to exercise your own clinical judgement with each patient**

For advice contact:

- Hayward House, 0115 969 1169 and ask switchboard to bleep the palliative care doctor on call, or
- Community Macmillan Nurses, 0115 993 4976 (08.30–17.00h).

Also see the Palliative Care Formulary (2e) and Palliative Care Pocketbook (2e)

### Abbreviations

b.d.	bis die (twice daily)
CSCI	continuous subcutaneous infusion
PO	per os, by mouth
p.r.n.	pro re nata (as needed, when required)
q4h	quarta quaque hora (every 4 hours); or other specified time q6h, q8h etc.
q.d.s	quater die sumendus (four times a day)
SC	subcutaneous
TD	transdermal



## Pain guidelines for the last days of life

---

### For patients already receiving regular strong opioids

#### 1 Commence syringe driver

Convert PO morphine to 24h CSCI morphine by dividing total 24h PO dose by 2, e.g. 30mg/24h PO → 15mg/24h CSCI

#### 2 Provide pain relief p.r.n.

Calculate the p.r.n. dose of morphine by dividing the 24h CSCI dose by 6, e.g. 15mg/24h CSCI → 2.5mg SC. Prescribe q1h p.r.n. If the patient currently has pain, give a stat dose.

### For patients *not* already receiving strong opioids

#### 1 Provide pain relief p.r.n.

Prescribe morphine 2.5–5mg SC q1h p.r.n. If the patient currently has pain, give an immediate stat dose.

#### 2 Review after 24h

If  $\geq 2$  p.r.n. doses given then commence a syringe driver containing the total p.r.n. morphine dose given in last 24h.

### For all patients

Review analgesia at least every 24h. If  $\geq 2$  p.r.n. doses have been required, adjust 24h CSCI accordingly; recalculate and increase the p.r.n dose.

#### **Example**

Patient on morphine 30mg/24h CSCI

Required morphine 5mg SC p.r.n. x 2 doses in last 24h:

new regular dose = morphine 40mg/24h CSCI

new p.r.n. dose = morphine 5–7.5mg SC q1h

If patient on oxycodone, hydromorphone, methadone or fentanyl TD, or if symptoms persist, ask for advice from:

- Hayward House, 0115 969 1169 and ask switchboard to bleep the palliative care doctor on call, or
- Community Macmillan Nurses, 0115 993 4976 (08.30–17.00h).

## Breathlessness guidelines for the last days of life

### Non-drug management

- i. Non-drug approaches include:
1. explanation
  2. a reassuring and calming approach
- 3 repositioning, e.g. upright, may prefer a chair to a bed
- 4 electric fan/cool draft of air
- 5 relaxation techniques.

### Trial of oxygen therapy

- 2 If  $\text{SaO}_2 < 90\%$  give oxygen 2–4L/min using nasal cannula. Evaluate benefit and titrate dose to alleviate respiratory distress.

### Drug management

- 3 Evaluate the effect of a p.r.n. opioid:
- if opioid-naïve prescribe 2.5–5mg morphine SC p.r.n. q1h
  - if already on an opioid use 1/6th of 24h dose p.r.n. q1h
  - if associated anxiety/distress combine with midazolam 2.5–5 mg SC p.r.n. q1h
- 4 If  $\geq 2$  p.r.n doses are given in 24h or the relief of breathlessness is unsatisfactory, commence regular CSCI opioid:
- if not on regular morphine give the total p.r.n. morphine dose given in last 24h
  - if on regular morphine convert PO morphine to 24h CSCI morphine by dividing total 24h PO dose by 2 and add the total p.r.n. morphine dose given in last 24h
  - add midazolam 10mg/24h CSCI to the above
  - continue p.r.n.
- 5 Review medication at least every 24h. If  $\geq 2$  p.r.n. doses have been required, adjust 24h CSCI doses of morphine and midazolam accordingly; recalculate and increase the p.r.n doses

#### Example

Patient on morphine 30mg + midazolam 10mg/24h CSCI

Required morphine 5mg + midazolam 2.5mg SC p.r.n. x 2 doses in last 24h:

new regular dose = morphine 40mg + midazolam 15mg/24h CSCI

new p.r.n. dose of morphine = 5–7.5mg SC q1h;

p.r.n. dose of midazolam = 2.5–5mg SC q1h (unchanged)

### Other treatments

- 6 Also consider:
- furosemide 20–40mg SC/IM/IV p.r.n. q2h, for pulmonary oedema
  - hyoscine butylbromide 20mg SC stat & p.r.n. q1h, for respiratory tract secretions
  - salbutamol 2.5–5mg nebulised q2h p.r.n., for bronchospasm.

If patient on oxycodone, hydromorphone, methadone or fentanyl TD, or if symptoms persist, ask for advice from:

- Hayward House, 0115 969 1169 and ask switchboard to bleep the palliative care doctor on call, or
- Community Macmillan Nurses, 0115 993 4976 (08.30–17.00h).

## Nausea and vomiting guidelines for the last days of life

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### Cause of nausea and vomiting known ± relieved by existing medication

- 1 If the patient has obtained relief from existing anti-emetics, continue these parenterally, e.g.:
  - cyclizine 50mg PO q8h → cyclizine 150mg/24h CSCI (use WFI as diluent)
  - metoclopramide 10mg PO q.d.s. → metoclopramide 40mg/24h CSCI
  - haloperidol 1.5–3mg PO b.d. → haloperidol 2.5mg/24h CSCI

### Cause of nausea and vomiting unknown ± unrelieved by existing medication

2. Use levomepromazine, a broad spectrum anti-emetic:
  - starting dose 6.25–12.5mg PO/SC stat , o.n. & p.r.n. q1h
  - titrate dose according to response; generally effective at 25–50mg/24h
  - doses ≥25mg/24h are often associated with sedation (less of an issue in the terminal stage).
- 3 Review medication at least every 24h. If ≥2 p.r.n. doses have been required, adjust 24h SC/CSCI dose of levomepromazine accordingly; recalculate and increase the p.r.n dose.

If symptoms persist seek advice from:

- Hayward House, 0115 969 1169 and ask switchboard to bleep the palliative care doctor on call, or
- Community Macmillan Nurses, 0115 993 4976 (08.30–17.00h).

## Agitation/delirium guidelines for the last days of life

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### Non-drug management

- 1 Consider correctable causes, e.g.:
  - pain
  - urinary retention
  - faecal impaction.

### Drug management

2. Use levomepromazine, a phenothiazine:
  - starting dose 6.25–12.5mg SC stat , o.n. & p.r.n. q1h
  - titrate dose according to response, typically 25–75mg/24h CSCI; maximum dose 300mg/24h, occasionally more.
3. If necessary, combine with midazolam, a benzodiazepine:
  - starting dose midazolam 5–10mg SC stat & p.r.n. q1h and 10–30mg/24h CSCI
  - titrate dose according to response; typically 30–60mg/24h CSCI; maximum dose 240mg/24h.

If symptoms persist seek advice from:

- Hayward House, 0115 969 1169 and ask switchboard to bleep the palliative care doctor on call, or
- Community Macmillan Nurses, 0115 993 4976 (08.30–17.00h).

## Respiratory tract secretions guidelines for the last days of life

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- 1 Death rattle occurs in about 50% of patients near the end of life and is caused by fluid pooling in the upper airway arising from one or more sources:
  - saliva (most common)
  - respiratory tract infection
  - pulmonary oedema
  - gastric reflux.

### Non-drug management

2. Explanation is important, particularly as secretions are relieved in only 50% of patients, e.g. “The noisy breathing is due to the presence of secretions in the airways and throat, which the patient is generally no longer aware of or bothered by, similar to snoring..”
- 3 Reposition:
  - if related to saliva or purulent secretions, semiprone to encourage postural drainage
  - if related to pulmonary oedema or gastric reflux, upright or semirecumbent.

### Drug management

4. Because they do not dry existing secretions, an antimuscarinic antisecretory drug needs to be given promptly as soon as the onset of death rattle is detected, e.g:
  - hyoscine butylbromide 20mg SC stat & p.r.n. q1h and 40–80mg CSC/24h
  - titrate dose according to response, occasionally 120mg/24h required.
- 5 In a semiconscious patient, if rattling breathing appears to be causing laboured breathing ± distress, supplement the above with an opioid, e.g. morphine, and an anxiolytic sedative, e.g. midazolam, both regularly and p.r.n.
- 6 If failing to respond, consider:
  - *pulmonary oedema*, consider furosemide 20–40mg SC/IM/IV q2h p.r.n. Note: beware precipitating urinary retention.
  - *gastric reflux*, consider metoclopramide 20mg SC/IV q3h p.r.n., but do not use concurrently with an antimuscarinic because the latter blocks the prokinetic effect of the former.
  - *respiratory tract infection*, occasionally it is appropriate to prescribe an antibiotic in an imminently dying patient if death rattle is caused by profuse purulent sputum associated with an underlying chest infection, e.g.:
    - ceftriaxone, mix 1g ampoule with 2.1ml lidocaine (lignocaine) 1%, and give 250–1000mg SC/IM o.d.
    - some centers use larger volumes of lidocaine (lignocaine) and administer a divided dose at separate SC/IM sites o.d. or give b.d.

If symptoms persist seek advice from:

- Hayward House, 0115 969 1169 and ask switchboard to bleep the palliative care doctor on call, or
- Community Macmillan Nurses, 0115 993 4976 (08.30–17.00h).



## Appendix 1: Opioid dose conversion ratios

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### General approach

- 1 This appendix provides a summary of opioid dose conversion ratios. These can be used to calculate equivalent doses of opioids when switching from a weak opioid to morphine, or from one strong opioid to another. Caution is always necessary.
- 2 Conversion ratios can never be more than an approximate guide because of:
  - wide interindividual variation in opioid pharmacokinetics
  - other variables such as nutritional status and concurrent medication
  - data derived from single dose rather than chronic dose studies.
- 3 Careful monitoring during conversion is necessary to avoid both underdosing and excessive dosing. This is particularly the case if:
  - switching at high doses
  - there has been a recent rapid escalation of the first opioid
  - switching to methadone.
- 4 When switching from high doses of morphine, e.g. >1g/24h PO, reduce the calculated dose arbitrarily by 33–50% because of ‘incomplete cross-tolerance’. Rely on p.r.n. doses to make up any deficit while re-titrating to a satisfactory dose of the new opioid.
- 5 In a comparably cautious way, when there has been a recent rapid dose escalation of the first opioid, use the pre-escalation dose to calculate the initial dose of the second opioid.

### Determining the dose of the second opioid

- 1 Select the appropriate Table based on the routes of administration:

<i>Route</i>	<i>Table</i>	<i>Page</i>
PO to PO	1	78
PO to TD	2	79
PO to SC/IV	3	80
SC/IV to SC/IV	4	81

- 2 The Tables relate mainly to switching to or from morphine. If switching from an opioid other than morphine to another opioid, it will be necessary to convert the dose of the first opioid to morphine equivalents, and then use that quantity to determine the dose of the second opioid.
- 3 With any switch:
  - round the calculated dose up or down to the nearest convenient dose of the preparation concerned, e.g. tablet, TD patch, ampoule
  - decide on an appropriate p.r.n. dose.
- 4 The conversion ratios in this Appendix are based on referenced sources given in the Palliative Care Formulary. Where these differ significantly from the manufacturer’s recommended ratios, the latter are included for comparison.

**Table 1** Approximate dose conversion ratios: PO to PO

<i>Conversion and ratio</i>	<i>Calculation</i>	<i>Example</i>
Codeine to morphine 10:1	Divide 24h codeine dose by 10	Codeine 240mg/24h PO → morphine 24mg/24h PO
Dihydrocodeine to morphine 10:1	Divide 24h dihydrocodeine dose by 10	Dihydrocodeine 240mg/24h PO → morphine 24mg/24h PO
Hydrocodone to morphine 1.5:1	Divide 24h hydrocodone dose by 1.5 (decrease dose by 1/3)	Hydrocodone 60mg 24h PO → morphine 40mg/24h PO
Tramadol to morphine 5:1	Divide 24h tramadol dose by 5	Tramadol 400mg/24h PO → morphine 80mg/24h PO
Morphine to hydromorphone 5:1 <sup>a</sup>	Divide 24h morphine dose by 5	Morphine 60mg/24h PO → hydromorphone 12mg/24h PO
7.5:1 <sup>b</sup>	<i>Divide 24h morphine dose by 7.5</i>	<i>Morphine 60mg/24h PO → hydromorphone 8mg/24h PO</i>
Morphine to methadone Variable ratio	See methadone guidelines	
Morphine to oxycodone 1.5:1	Divide 24h morphine dose by 1.5 (decrease dose by 1/3)	Morphine 30mg/24h PO → oxycodone 20mg/24h PO
2:1 <sup>b</sup>	<i>Divide 24h morphine dose by 2</i>	<i>Morphine 30mg/24h PO → oxycodone 15mg/24h PO</i>

a. for converse, some use 1:4, e.g. hydromorphone 8mg/24h PO → morphine 32mg/24h PO

b. italicized entries = manufacturers' recommendations.

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**Table 2** Approximate dose conversion ratios: PO to TD

<i>Conversion and Ratio</i>	<i>Calculation</i>	<i>Example</i>
Morphine to buprenorphine 80–100:1	Multiply 24h morphine dose in mg by 10 to obtain 24h buprenorphine dose in microgram; divide answer by 24 to obtain microgram/h patch strength	Morphine 300mg/24h PO → buprenorphine 3000microgram/24h → 125microgram/h; <i>round up</i> to 70microgram/h x 2 or <i>round down</i> to 70 + 35microgram/h patches
Morphine to fentanyl 100:1	Multiply 24h morphine dose in mg by 10 to obtain 24h fentanyl dose in microgram; divide answer by 24 to obtain microgram/h patch strength	Morphine 300mg/24h PO → fentanyl 3000microgram/24h → 125microgram/h; give as 100 + 25microgram/h patches
<i>150:1<sup>a</sup></i>	<i>Use the chart in the manufacturer's SPC</i>	<i>The doses will inevitably be smaller than those obtained with the PCF preferred dose conversion ratio</i>

a. italicized entry = manufacturer's recommendation.

For determining the appropriate p.r.n. morphine dose for patients receiving TD fentanyl see transdermal fentanyl guidelines p.59.

**Table 3** Approximate dose conversion ratios; PO to SC/IV

<i>Conversion and Ratio</i>	<i>Calculation</i>	<i>Example</i>
Hydromorphone to hydromorphone 2:1	Divide 24h hydromorphone dose by 2	Hydromorphone 32mg/24h PO → hydromorphone 16mg/24h SC/IV
Methadone to methadone 2:1 <sup>a</sup>	Divide 24h methadone dose by 2	Methadone 30mg/24h PO → methadone 15mg/24h SC/IV
Morphine to alfentanil 30–40:1	Divide 24h morphine dose by 30–40	Morphine 40mg/24h PO → alfentanil 1mg/24h SC/IV
Morphine to diamorphine 3:1	Divide 24h morphine dose by 3	Morphine 30mg/24h PO → diamorphine 10mg/24h SC/IV
Morphine to hydromorphone 10–15:1	Divide 24h morphine dose by 10–15	Morphine 30mg/24h PO → hydromorphone 2mg/24h SC/IV
Morphine to methadone Variable ratio	See methadone guidelines, p.61	
Morphine to morphine 2:1	Divide 24h morphine dose by 2	Morphine 30mg/24h PO → morphine 15mg/24h SC/IV
Morphine to oxycodone 2:1	Divide 24h morphine dose by 2	Morphine 60mg/24h PO → oxycodone 30mg/24h SC/IV
Oxycodone to oxycodone 1.5:1	Divide 24h oxycodone dose by 1.5 (decrease dose by 1/3)	Oxycodone 30mg/24h PO → oxycodone 20mg/24h SC/IV
<i>2:1<sup>b</sup></i>	<i>Divide 24h oxycodone dose by 2</i>	<i>Oxycodone 30mg/24h PO → oxycodone 15mg/24h SC/IV</i>

a. because the mean oral bio-availability is 80% (range 40–100%), some centers use 1:1, e.g. methadone 30mg/24h PO → methadone 30mg/24h SC/IV

b. italicized entry = manufacturer's recommendation.

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**Table 4** Approximate dose conversion ratios; SC/IV to SC/IV

Conversion and Ratio	Calculation	Example
Morphine to alfentanil 15–20:1	Divide 24h morphine dose by 15–20	Morphine 40mg/24h SC/IV → alfentanil 2mg/24h SC/IV
Morphine to buprenorphine 30–40:1	Divide 24h morphine dose in mg by 30–40	Morphine 40mg/24h SC/IV → buprenorphine 1mg /24h SC/IV
Morphine to hydromorphone 5:1	Divide 24h morphine dose by 5	Morphine 30mg/24h SC/IV → hydromorphone 6mg/24h SC/IV
Morphine to methadone Variable ratio	See methadone guidelines, p.61	
Morphine to oxycodone 1:1	Use same dose as 24h morphine dose	Morphine 30mg/24h SC/IV → oxycodone 30mg/24h SC/IV

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## Appendix 2: Taking controlled drugs to other countries

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- 1 Some patients receiving palliative care travel to other countries and they will need to take their medicines with them. Practitioners can help ensure a trouble-free trip by advising them, if relevant, about controlled drugs. Travellers need to consider two sets of law, the law of the country they are in and the law of the country or countries to which they are travelling.
- 2 The following is general advice, based on regulations current in the UK in the first half of 2006, but should not be regarded as formal legal advice. Detailed advice can be obtained from the regulatory authorities in the relevant countries.
- 3 Although Schedule 2, 3 and 4 Part 1 controlled drugs are normally subject to stringent import and export licensing requirements, the UK Home Office has an Open General Licence which lists the permitted maximum quantities of controlled drugs which can be taken out of and brought into the UK for personal use without a specific export/import licence
- 4 The Table gives some examples but it is not the full list. If you are uncertain about the status of a drug, advice should be obtained directly from the Home Office:  
The Home Office  
Drugs Licensing Section  
6th Floor, Peel Building  
2, Marsham Street,  
London. SW1P 4DF. UK.  
Tel: 020 7035 0472  
Fax: 020 7035 6161.  
e-mail: [licensing\\_enquiry.aadu@homeoffice.gsi.gov.uk](mailto:licensing_enquiry.aadu@homeoffice.gsi.gov.uk)  
website: [www.drugs.gov.uk](http://www.drugs.gov.uk)  
personal licence form: [www.drugs.gov.uk/drugs-laws/licensing/personal](http://www.drugs.gov.uk/drugs-laws/licensing/personal)
- 5 For patients travelling with less than the permitted limit, a letter listing the drug regimen from their general practitioner or other involved doctor is sufficient.
- 6 For patients travelling with more than the permitted limit a personal drugs import/export licence will be required. An application form can be obtained from the above website or address. This must be completed by the patient's doctor and submitted with a covering letter on the doctor's headed note-paper to confirm that the details are correct. Alternatively, applications may be made by a letter from the patient's doctor stating:
  - the patient's name and address
  - names and quantities of drugs to be taken out of/brought into the UK
  - strength and form of the drug preparations
  - dates of travel from and back to the UK.
- 7 Ten days should be allowed for processing the application. Once issued, the licence lasts for 3 months; if the patient is overseas for longer, or receives further prescriptions for controlled drugs while overseas, they should contact the Home Office on the telephone number above to arrange for a renewed licence to be faxed to them so that they can import the new supplies on their return to the UK.
- 8 Licences are issued to comply with the Misuse of Drugs Act and facilitate passage through UK customs control. Covering letters, licences and medicines contained in their original packaging should all be carried in the patient's hand luggage in case the UK customs want to examine them.

9 Drugs Export Licences have no legal status outside the UK. Before travelling, *patients should check with the relevant Embassy or High Commission about any requirements relating the import of controlled drugs for all the countries in which they will have to pass through customs.* The quantities they are allowed to import/export may differ from those on the UK Open General Licence list. A list of Embassy contact details can be downloaded from the Home Office Drugs website.

**Table** Some of the controlled drugs and their permitted quantities on the Open General Licence list

Amfetamine	300mg
Buprenorphine hydrochloride (Temgesic®)	24mg
Dexamfetamine sulphate	900mg
Dextromoramide tartrate	900mg
Diamorphine hydrochloride ampoules <sup>a</sup>	1.35g
Diazepam	900mg
Dihydrocodeine tartrate <sup>b</sup>	3.6g
Dipipanone	600mg
Fentanyl	45mg
Hydrocodone	675mg
Hydromorphone	360mg
Ketamine	900mg
Methadone <sup>c</sup>	500mg
Metamfetamine	900mg
Methylphenidate	900mg
Morphine	1.2g
Oxycodone	900mg
Phenobarbital	2.7g
Phenobarbital sodium	1.2g
Temazepam	900mg

a. medicinal diamorphine is available only in the UK. The following countries do not permit patients from the UK to bring in their own supply: Australia, Greece, Italy, Germany, France, Japan, the Netherlands, South Africa, the USA and Zimbabwe.

b. controlled only if injectable, or if tablets contain >100mg.

c. if >2g, the Home Office requires a written statement by the patient's doctor confirming that the travel documents (e.g. air tickets) have been seen.

See also [www.palliativedrugs.com](http://www.palliativedrugs.com) April / May 2006 newsletter.

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