The Palliative Care Handbook
Guidelines for clinical management and symptom control

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THE PALLIATIVE CARE HANDBOOK

GUIDELINES FOR CLINICAL MANAGEMENT AND SYMPTOM CONTROL

6TH EDITION 2012

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Foreword

Palliative care has come a long way since the inception of the modern hospice movement in the UK in the 1960s. It is now recognised as an integral and important part of health care in over 100 countries throughout the world. In New Zealand the growth of the speciality has been significant and now people throughout New Zealand should expect that those who care for people at the end of life should have access to the best quality of care.

This handbook – which started life as a small pocket book written by Rod MacLeod and Jane Vella-Brincat in Bath, England in 1994 has now grown to become an invaluable resource for practitioners throughout the country. Its popularity stems from the ease of use, the basic layout and the uncomplicated explanations of how to manage challenging symptoms that the authors have developed. The format has been utilised in other handbooks in Tasmania, Australia and Wessex in England.

This handbook finds its place in all areas where palliative care happens; it gives confidence to those who use it and hopefully therefore comfort to those approaching death so that they live every moment.

Mary Schumacher
Hospice New Zealand
Wellington
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Many of the medications listed are being used outside their product licence. Prescription of a drug (whether licensed use/route or not) requires the prescriber, in the light of published evidence, to balance both the potential good and the potential harm which might ensue. Prescribers 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 the licence, prescribers must be fully informed about the actions and uses of the drug, and be assured of the quality of the particular product (www.palliativedrugs.com/using-licensed-drugs-for-unlicensed-purposes/). Care has been taken to ensure accuracy of information at time of printing. This information may change and final responsibility lies with the prescriber.

Abbreviations

sc subcutaneous CNS central nervous system
od once daily LFTs liver function tests
bd twice daily MAOIs monoamine oxidase inhibitors
tds three times daily NSAIDs nonsteroidal anti-inflammatory drugs
qds four times daily

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INTRODUCTION

The first section of this book is a set of guidelines for the alleviation of symptoms commonly encountered in palliative care. Drug therapy is included.

The second section (the pharmacopoeia) contains drug information:

- It is in alphabetical order by generic drug name although trade names can be found at the top of the page.
- Unlicensed uses are included; these are uses for which the manufacturer has not received a product license. Full responsibility for use lies with the prescriber.
- Information about availability and PHARMAC funding is given for each drug which changes frequently and it is suggested that clinicians check the current situation with the Pharmaceutical Schedule.
- The interactions listed include discussion about enzymes responsible for drug metabolism commonly known as Cytochrome P450 (CYP) enzymes. There are many CYP enzymes some of which are genetically controlled. The interactions listed are based mainly on theory, are subject to change as more is learnt about the CYP enzyme system and are meant to be used as a guide to potential interactions only. Only commonly used palliative care drugs have been included but interactions with other drugs may also occur.
- There is also information about the use of syringe drivers.

PALLIATIVE CARE AIMS

- to achieve the best possible quality of life for patients and their families
- to understand and address patients’ physical, psychological, social and spiritual suffering
- to be applicable from early on in the course of the illness

THE WORLD HEALTH ORGANISATION DEFINED PALLIATIVE CARE AS:

"An approach that improves the quality of life of patients and their families facing the problems associated with a life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual."

Palliative care:

- provides relief from pain and other distressing symptoms
- affirms life and regards dying as a normal process
- intends neither to hasten or postpone death
- integrates the psychological and spiritual aspects of patient care
- provides support to help patients live as actively as possible
- provides support to the family during the illness and bereavement
- uses a multidisciplinary team approach
- enhances quality of life and influences the course of the illness
- is applicable early in the course of illness alongside therapies that are intended to prolong life (e.g. chemotherapy, radiotherapy) and diagnostic investigations

GENERAL SYMPTOM MANAGEMENT PRINCIPLES

- accurate and meticulous assessment is essential
- assess and address non-physical as well as physical issues
- difficult to control symptoms may require several different approaches
- aim for highest possible quality of life
- use risk vs benefit assessments when side-effects of therapy occur
- explain issues as much as possible to the patient and their carers
- use a multidisciplinary approach
- reassess continuously
PAIN

The assessment and management of pain and other symptoms are the cornerstones of effective palliative care. There are different types of pain and many patients have more than one.

PHYSICAL ASSESSMENT
• listen to the patient’s story and the language used
• ask about the site(s) of pain
• measure intensity with a validated tool to assess changes:
  — a visual analogue scale (some patients find this hard to use)
  — a numerical rating scale - perhaps the commonest method used - patients rate their pain on a scale of 0 (no pain) to 10 (the worst pain they can imagine)
  — colour charts
  — facial expression charts
• ask about the nature (e.g. stabbing, aching) and duration of the pain - this will determine management
  — identifies the type and source of pain
    > somatic nociceptive is usually constant and localised
    > visceral is usually described as deep or aching (capsular stretch pain) or intermittent and gripping (colicky pain)
    > bone pain is usually deep or boring
    > neuropathic pain is usually burning, shooting or stabbing
• ask about what relieves the pain (body position, heat, cold) and what exacerbates the pain (movement, position, heat)
  — ask about the significance of the pain
  — ask how much of a nuisance it is
  — discuss its significance
• explain the likely causes - often helpful in allaying fears or anxieties and can significantly contribute to the relief of pain
• examine the part(s) that are painful - look, touch and move
• consider further investigation such as X-ray, CT or MRI but only if the result is going to influence management
• document all findings to compare and communicate
• review regularly - essential after any therapeutic intervention

OTHER ASSESSMENT FACTORS
In a bio-medical model of practice it is tempting to assume that pain has a predominant physical component. Often, physical pain is only part of the symptom complex (through direct or indirect tumour effects or non-malignant processes). Psychological, spiritual and sociological elements will also be identifiable in many people with pain. Fear, anxiety, sadness, anger, frustration and isolation are but a few of the feelings that can contribute to the total perception of pain. All of these elements help to build up a realistic picture of the overall impact of pain on the individual’s quality of life.

MANAGEMENT

Analgesics
• several countries now recommend that all opioids be prescribed by their trade names rather than their generic names to minimise medication errors
• some pains may not respond completely to opioids
• co-analgesics are useful when response to opioids is poor
• switching route can sometimes help e.g. from oral to subcutaneous
• in prescribing analgesics use a step-wise approach:

| morphine or oxycodone or fentanyl or methadone |
| codeine or dihydrocodeine or tramadol |
| regular paracetamol |
| paracetamol or NSAIDs e.g. diclofenac, naproxen |
| co-analgesics, specific therapies e.g. radiotherapy |

• regular paracetamol may be useful in opioid induced hyperalgesia although use should be continued only if effective as up to 8 tablets per day adds significantly to the tablet burden
• there is some debate over the second step in this ladder
  — most palliative care practitioners go to step 3 either after step 1 or initially depending on the severity of the pain
  — pain relief from codeine may be from the active metabolite, morphine
  — the place of tramadol in palliative care remains unclear - it can be extremely emetogenic

Initiating morphine in opioid naïve patients
• start with small regular oral (if possible) immediate release doses
• titration with slow release morphine is less effective than immediate release and is not recommended
• prescribe morphine elixir (immediate release) (2.5 to 5mg) every four hours regularly and titrate
• prescribe ‘when required’ doses of 1/5th to 1/6th of the regular 24 hour dose for ‘breakthrough’, ‘episodic’ or ‘incident’ pain
• document the amount of morphine taken
• once a stable dosing regimen is achieved (2 to 3 days) convert to a long-acting preparation
  — calculate the total 24 hour dose of immediate release morphine required from ‘breakthrough’ and regular dosing, divide by two and give twice daily
  — ‘when required’ doses of 1/5th to 1/6th of the regular 24 hour dose should be prescribed as immediate release once again for pain between doses
• if the patient can no longer swallow
  — give ½ the total 24 hour oral dose by continuous subcutaneous infusion
  — ‘when required’ doses of 1/5th to 1/6th of the regular 24 hour dose should be prescribed once again for pain between doses
• consider reducing dose if another mode of pain relief is used (e.g. radiotherapy, ketamine)

Initiating oxycodone in opioid naïve patients
• start with small regular oral (if possible) doses
• prescribe oxycodone immediate release capsules or liquid (OxyNorm™) every 4 to 6 hours and titrate
• prescribe ‘when required’ doses of 1/10th to 1/12th initially (although many practitioners use 1/5th to 1/6th) of the regular 24 hour dose for ‘breakthrough’, ‘episodic’ or ‘incident’ pain
• document the amount of oxycodone taken
• once a stable dosing regimen is achieved (2 to 3 days) convert to a long-acting preparation (OxyContin™)
  — calculate the total daily dose of oxycodone required from ‘breakthrough’ and regular dosing, divide by two and give twice daily
  — ‘when required’ doses of 1/10th to 1/12th initially (although many practitioners use 1/5th to 1/6th) of the regular 24 hour dose should be prescribed as immediate release for pain between doses
• consider reducing dose if another mode of pain relief is used (e.g. radiotherapy, ketamine)
• the long acting preparation has a layer of immediate acting drug round it
• if the patient can no longer swallow
  — give ½ the total 24 hour oral dose by continuous subcutaneous infusion
  — ‘when required’ doses of 1/5th to 1/6th initially (although many practitioners use 1/5th to 1/6th) of the regular 24 hour dose should be prescribed once again for pain between doses
• consider reducing dose if another mode of pain relief is used (e.g. radiotherapy, ketamine)

Initiating fentanyl patches in opioid naïve patients
• don’t - fentanyl patches should only be used in patients who have already been exposed to opioids

Initiating methadone in opioid naïve patients
• as methadone has a long and variable half life it should be commenced at low dosage e.g. 1mg to 2.5mg bd and consideration should be given to dose reduction once at steady state (minimum 5 days)
• should be used under advice of a palliative care physician only

Adverse effects of opioids
• all opioids are associated with the following adverse effects but the incidence (incidences over are for morphine) and severity vary from opioid to opioid (e.g. fentanyl is less constipating than morphine)
• tolerance to some of these adverse effects can develop e.g. nausea/vomiting but not to others e.g. constipation
  — constipation - 95% of patients (less with fentanyl (50%) and the naloxone/ oxycodone combination product) - prescribe a laxative prophylactically
  — nausea/vomiting - 30-50% of patients - usually in the first 10 days until tolerance develops
  — drowsiness - 20% of patients - usually in the first 3 to 5 days until tolerance develops
  — confusion - 2% of patients - either reduce the dose, change to a different opioid or consider adding haloperidol
  — hallucinations/nightmares - 1% of patients - give haloperidol or change to a different opioid
  — hyperalgesia - usually to touch as a result of too high a dose of opioid which may improve on dose reduction
  — hyperkatafexia - emotional lability induced by long-term opioid use

Opioid rotation
• opioid rotation (or changing from one opioid to another) is often used when tolerance to the analgesic effects of opioids (stimulation of NMDA receptors) or severe adverse effects occur
• works because of the difference in the mix of opioid receptors stimulated by each individual opioid in each individual patient
• most often from morphine to oxycodone, fentanyl or methadone
• rotation should only occur under supervision and by a specialist as conversion doses are difficult to predict and are often much smaller doses than those listed below - see oxycodone, fentanyl and methadone in the second section

Opioid equivalents
• the following are ‘single dose’ equivalences i.e. ONLY equivalents in healthy volunteers given a single dose
• equivalence in sick patients who are chronically dosed is difficult to quantify - use care when converting from one opioid to another
• pethidine is NOT recommended in palliative care
  | codeine | 60mg oral | = | 6mg oral morphine |
  | tramadol | 100mg oral | = | 10mg oral morphine |
  | oxycodone | 5mg oral | = | 10mg oral morphine |
  | oxycodone | 5mg sc | = | 5mg sc morphine |
  | methadone | see methadone page in second section |
  | fentanyl | see fentanyl page in second section |
  | buprenorphine | see buprenorphine page in second section |
Co-analgesics

- drugs usually used for a different indication with analgesic properties (sometimes such use is outside the product license)
- can be used in combination with other analgesics or alone
- choice is determined by the types of pain
- the use of co-analgesics is probably most helpful in neuropathic pain
- **pain** - due to tumour or metastatic involvement
  - NSAIDs e.g. diclofenac - inhibit prostaglandins
  - bisphosphonates e.g. pamidronate, zoledronic acid
- **skeletal muscle spasm pain** - due to tumour involvement
  - muscle relaxants e.g. diazepam, clonazepam, baclofen
- **smooth (intestinal) muscle spasm pain** - "colic" from intestinal spasm
  - anticholinergic/antimuscarinic e.g. hyoscine butylbromide
- **tenesmus** - due to tumour or metastatic involvement of the rectal muscles
  - steroids e.g. dexamethasone, prednisone - decrease inflammation around tumour
- **raised intracranial pressure** - due to tumour or fluid
  - NSAIDs e.g. diclofenac - inhibit prostaglandins
- **liver capsule stretch pain** - from an enlarged liver
  - steroids e.g. dexamethasone - decrease inflammation

NEUROPATHIC PAIN

- often the most severe and difficult to manage of all persisting pains
- caused by damage to the nervous system
- involves NMDA receptor stimulation to some extent
- severity cannot usually be linked to the amount of damage
  - "trivial" lesions can produce severe pain

**Causes**

- peripheral nerve damage - post-surgical, post-trauma or compression
- herpetic nerve invasion
- amputation - phantom limb pain
- Chronic Regional Pain Syndrome (CRPS)
- nerve root injury - traumatic avulsion, post-spinal surgery
- epidural scarring, arachnoiditis
- spinal cord injury and disease
- stroke
- diabetes
- chemotherapy e.g vincristine, oxaliplatin, taxanes, cisplatin

**Characterisation**

- characterised by description and by cause
  - the pain is not always within the distribution of a dermatome or a peripheral nerve
- includes alldynia (pain in an area of altered sensitivity) and other sensory symptoms
- generally continual and of varying intensity
  - variability in intensity is spontaneous and often has a paroxysmal component not necessarily related to stimulation
- descriptive terms include burning, cutting, stabbing/shooting cramping, aching, throbbing, crushing
- episodic pain, which can be present on top of the continuous pain, may itself be brief but often a long-lasting aching pain remains for several hours

**Management**

- a multidisciplinary approach is useful
- behavioural modification - any treatment will be of only limited value unless certain behaviours are changed so address cognitive, mood and behavioural aspects of the patient’s pain individually or in a group
- drugs
  - opioid analgesics (first line for neuropathic pain) should be trialed but doses may increase rapidly - some opioids may be more useful than others e.g. methadone which has NMDA blocking activity
  - centrally acting agents reduce spinal hyperexcitability
  - some drugs have an effect on nociceptor neuromodulators, neurotransmitters and cell membrane stability
  - efficacy is highly variable between drugs so tailor the drug to the patient
    > anticonvulsants e.g. valproate
    > gabapentin/pregabalin
    > benzodiazepines e.g. clonazepam
    > tricyclic antidepressants e.g. nortriptyline - limited efficacy in palliative care
    > SSRIs e.g. escitalopram, sertraline - limited efficacy in palliative care
    > other antidepressants e.g. venlafaxine, mirtazapine
    > antiarrhythmics e.g. mexiletine
    > muscle relaxants e.g. baclofen
    > NMDA antagonists e.g. ketamine
    > alpha-adrenoergic agents e.g. clonidine
    > calcium channel blockers e.g. nifedipine
    > steroids e.g. dexamethasone for nerve pressure pain
    > sodium channel blockers e.g. lignocaine
    - combining an antidepressant with an anticonvulsant or similar may be more effective than either alone e.g. nortriptyline + gabapentin
    - if the above are ineffective consider intrathecal/epidural opioids, local anaesthetics and clonidine
- other analgesic modalities
  - nerve blocks
    > availability is dependent on the skills of the team
    > access to a specialist anaesthetist is not always possible
> for pain which breaks through analgesia, or is controlled at rest but not on movement or is nonresponsive
> upper abdominal pain due to pancreatic cancers may respond to coeliac plexus blocks

- others - often used in conjunction with analgesics
  > mobilisation e.g. structured stretching, progressive resistance training
  > radiotherapy/surgery
  > cytotoxic drugs
  > hormone therapy
  > spinal delivery systems
  > neuromodulation e.g. transcutaneous nerve stimulation (TENS) and, very occasionally, implanted devices such as peripheral nerve or spinal cord stimulation

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**GASTROINTESTINAL SYMPTOMS**

**NAUSEA/VOMITING**

These are common symptoms in palliative care and are often difficult to control.

- it is important to separate nausea from vomiting
  - consider how each affects the individual patient
- a vomit a day with no nausea may be more acceptable than continuous low-level nausea
  - for some patients nausea is more distressing than pain
- nausea and/or vomiting often has more than one cause
- choose a management strategy to fit the cause(s)
- antiemetics work at differing sites and receptors
- antiemetics that affect multiple receptors in multiple areas, such as levomepromazine (methotrimeprazine), may be useful choices regardless of cause
- a combination of antiemetics is useful, particularly where there are multiple causes

**Causes**

There are two distinct areas in the central nervous system (CNS), which are predominantly involved with nausea and vomiting:

- chemoreceptor trigger zone (CTZ) close to the area postrema
  - part of the central nervous system, the CTZ is thought to lie outside the blood/brain barrier and so can be affected by causes and treatment which are unable to penetrate the CNS
- the vomiting centre in the medulla oblongata
  - can be directly stimulated or inhibited by certain agents

The CTZ sends impulses to the vomiting centre, which then initiates nausea and/or vomiting. Higher centres involved with fear and anxiety also communicate with the vomiting centre, as do the peripheral vagal and sympathetic afferents and the vestibular nerve.

The causes can be summarised as:

- higher centre stimulation - fear/anxiety
- direct vomiting centre stimulation - radiotherapy to the head, raised intracranial pressure
- vagal and sympathetic afferent stimulation - cough, bronchial secretions, hepatomegaly, gastric stasis, constipation, intestinal obstruction
- chemoreceptor trigger zone stimulation - uraemia, hypercalcaemia, drugs e.g. opioids, cytotoxics
- vestibular nerve stimulation - motion
**Management**
- higher centre stimulation (emotion - fear/anxiety)
  - counselling/explanation/listening
  - a benzodiazepine
- direct vomiting centre stimulation (radiotherapy to the head, raised intracranial pressure)
  - cyclizine
  - dexamethasone
- vagal and sympathetic afferent stimulation (cough, bronchial secretions, hepatomegaly, gastric stasis, constipation, intestinal obstruction)
  - cough - see cough
  - bronchial secretions - see retained secretions
  - constipation - see constipation
  - hepatomegaly
    > dexamethasone
    > cyclizine
  - gastric stasis
    > domperidone (minimal extrapyramidal effects)
    > metoclopramide
    > erythromycin - a strong prokinetic
  - intestinal obstruction
    > cyclizine
    > levomepromazine (methotrimeprazine)
    > avoid prokinetics e.g. metoclopramide in complete obstruction although use in partial obstruction may help - see intestinal obstruction
- chemoreceptor trigger zone stimulation (uraemia, hypercalcaemia, drugs e.g. morphine)
  - haloperidol
  - levomepromazine (methotrimeprazine)
- vestibular nerve stimulation (motion)
  - cyclizine
  - hyoscine patch (scopolamine)
- other drugs which may be useful where others have failed
  - atypical antipsychotics e.g. olanzapine
  - ondansetron (may cause constipation - experience in palliative care is minimal and it is unlikely to be effective
  - aprepitant (a neurokinin 1 (NK1) antagonist from the class of drugs known as substance P antagonists) - used with steroids and ondansetron for delayed emesis following highly emetogenic chemotherapy. Its place in palliative care has not been established.
- other therapies with little evidence of efficacy include acupuncture, ginger

**Bowel Management**
- alteration in bowel function is common in terminally ill people
- constipation is more common than diarrhoea
- efficient bowel management may alleviate distress
- carefully assess bowel function on a daily basis
- regimens should be discussed, carried out and reported on daily

**Constipation**
- diagnose through an accurate history followed by examination
- it is the difficult or painful and infrequent passage of hard stools
- comparison with an individual's normal bowel habit and usual use of laxatives may highlight changes related to disease or treatment
- a record of bowel habits will help in the management
- examination of the abdomen and the rectum may exclude faecal impaction or rectal pathology

**Causes**
- metabolic disturbances e.g. hypercalcaemia
- dehydration from vomiting, polyuria, sweating, tachypnoea
- drugs
  - cytotoxics e.g. vinca alkaloids (via neuropathies)
  - opioids via opioid receptors in the GI tract and perhaps in the CNS - > 95% of people taking morphine will become constipated although other opioids may be less constipating e.g. fentanyl, methadone
  - anti-cholinergics e.g. tricyclic antidepressants
  - aluminium salts in antacids
  - iron
  - antispasmodics e.g. hyoscine butylbromide
  - anti-Parkinsonian drugs e.g. levodopa
  - anti-psychotics/anxiolytics
  - ondansetron
- immobility e.g. weakness
- low fibre diet e.g. milky/invalid foods or reduced intake
- inability to obey the call to stool
- concurrent medical problems e.g. haemorrhoids, anal fissure, diabetes, hypothyroidism
- intestinal obstruction from tumour, faeces or adhesions (abdominal X-ray may help with diagnosis)
- gastrointestinal tract nerve compression or damage or autonomic neuropathy

**Symptoms**
- anorexia
- vomiting/nausea
- abdominal discomfort or cramping
- spurious diarrhoea or overflow
• confusion
• anxiety
• bowel obstruction
• pain

Management
• prevention is the key
• if a cause (or causes) are identified remove it (or them) if possible
• exercise reduces the risk of constipation so encourage it where possible
• encourage increased fibre e.g. bran, kiwi crush or soluble fibre formulations (require activity and fluids to avoid impaction)
• laxatives
  — when opioids are prescribed anticipate constipation and prescribe an oral softener with a stimulant laxative e.g. docusate with senna or bisacodyl which may prevent the need for rectal intervention later (NB if combinations cause cramps reduce the dose or use an osmotic laxative such as Movicol™)
  — low dose opioid antagonists such as naloxone (marketed in combination with oxycodone), methylnaltrexone are effective in opioid-induced constipation without affecting analgesia
  — if constipation is already present give a bisacodyl 10mg suppository and a glycerin suppository or a sodium lauryl sulphoacetate enema (Micolette™)
  — avoid stimulant laxatives in people with signs of GI obstruction
  — if the patient has a partial obstruction use an osmotic/softener laxative e.g. docusate, and avoid stimulant laxatives
  — if the patient has a spinal cord compression where evacuation is difficult keep the bowel motion firm (avoid softeners) and use a stimulant
  — if a patient taking laxatives has no bowel motion for two days and this is not their normal bowel habit give extra laxatives and, if appropriate, kiwi fruit or prune juice
  — if a patient taking laxatives has no bowel motion for three days and this is not their normal bowel habit a rectal examination should be carried out
    > if soft faeces are found give two bisacodyl 10mg suppositories or one to two Micolette™ enemas
    > if hard faeces are found give one or two glycerine suppositories or two bisacodyl 10mg suppositories or consider Movicol™
    > if rectum is empty (or no result from first action) repeat abdominal palpation and consider an abdominal X-ray
    > suppositories must make contact with the bowel wall to work
    > methylnaltrexone
• faeces consist of approximately 50% water, 25% bacteria and 25% food residue so even if the patient is not eating there will be faeces in the bowel

DIARRHOEA
• a relatively uncommon problem in palliative care
• rotation from morphine to fentanyl may result in a sudden reduction in opioid constipating effects resulting in diarrhoea

Causes
• faecal impaction (overflow) - identify with a clinical examination (including rectal)
• colo-rectal carcinoma (also causes discharge and tenesmus)
• loss of sphincter tone and sensation e.g. from spinal cord compression
• incomplete gastrointestinal obstruction - frequent or recurrent diarrhoea suggests partial obstruction so try lower bowel evacuation
• malabsorption or food intolerance e.g. from lack of pancreatic enzymes
• concurrent disease e.g. diabetes mellitus, hyperthyroidism, inflammatory bowel disease
• radiotherapy to the torso
• cytotoxics (e.g. capecitabine)
• antibiotics - C.difficile
• bowel surgery or inflammation
• anxiety
• opioid rotation to a less constipating opioid e.g. from morphine to fentanyl

Management - dependent on cause
• assess bowel habit and faecal consistency
• consider likelihood of infection
• maintain skin integrity around anal area - use barrier creams to prevent excoriation e.g. zinc oxide
• think about overflow from impaction or partial obstruction
• use abdominal examination or X-ray to rule out obstruction
• restrict oral intake (except fluids) to rest the bowel
• withhold laxatives where appropriate
• administer antidiarrhoeal medications such as loperamide, opioids
• if impacted use manual removal followed by laxatives
• in partial obstruction diarrhoea may be very unpleasant
• in spinal cord compression a constipating drug may help e.g. codeine (although patients already receiving morphine may not benefit) followed by regular suppositories and/or manual removal
• in colo-rectal carcinoma a palliative colostomy or radiotherapy should be considered
• in malabsorption states, the addition of pancreatic enzymes at meal times will help the situation e.g. pancreatin or, in bile salt malabsorption, cholestyramine
• secretory diarrhoea (associated with carcinoid syndrome or AIDS) may respond to octreotide
• ondansetron may be worth considering especially if nausea/vomiting are also present
MOUTH CARE

Poor oral hygiene is probably the most significant factor in the development of oral disease near the end of life.

- good mouth care is essential to the well being of patients debilitated by advanced disease
- mouth problems are common - occur in up to 90% of patients
- risk factors for oral problems include
  - debility, dry mouth (drugs, mouth breathing, radiotherapy), chemotherapy, dehydration, cachexia, weight loss, ill-fitting dentures, bisphosphonates (osteonecrosis of the jaw)

Assessment/causes

- appropriate and effective oral assessment should be carried out on each patient daily using a pen torch and spatula
- remember functions of saliva – cleansing and lubrication, buffering, remineralisation, antimicrobial, digestion, maintenance of mucosal integrity
- key questions for effective mouth care are
  - is the mouth dirty, dry, painful or infected?
- also assess mental, nutritional and physical state, concurrent medications, tongue, teeth/dentures, mucous membranes, type of saliva, and lips
  - mental state will determine the patient’s ability and willingness to participate in their care
  - nutritional state will give an indication of the patient’s ability to chew and swallow as well as their general well being - a well balanced diet and adequate fluid intake are important in mouth care
  - physical state may also contribute to mouth care issues e.g. low haemoglobin increases susceptibility to infections and may be accompanied by lethargy, weakness and dyspnoea, all of which contribute to mouth care problems
  - patients in pain may require extra help with their mouth care
  - concurrent medications can affect the state of the mouth e.g. opioids, antidepressants may cause dry mouth, steroids/antibiotics may encourage oral candidiasis
  - other causes of poor mouth care include debility, reduced oral intake, inability to brush teeth, dehydration, saliva-reducing drugs, chemotherapy or radiotherapy, oxygen therapy and mouth breathing

Management - prevention is a priority

- regular tooth and denture brushing, twice daily at least
- regular use of anti-bacterial and anti-fungal mouthwash
- check fit of dentures
- regular dental checks if possible
- regular mouthcare; frequency dictated by assessment
- check for infection
- check for bone or nerve damage
- check mucosa
- reduce caffeine and alcohol, diet drinks (have a low pH)

INTESTINAL OBSTRUCTION

Intestinal obstruction is a difficult area of palliative care. There is considerable inter-individual and intra-individual variation in symptoms and optimal management.

Causes

- can be mechanical or paralytic
- blockage of intestine by intraluminal or extraluminal tumour, inflammation or metastasis
- blockage can occur at multiple sites in patients with peritoneal involvement
- may be aggravated by drugs e.g. anticholinergics, opioids
- radiation fibrosis
- autonomic nerve disruption by tumour

Management

The management of intestinal obstruction should be tailored to the individual at the time with different strategies being employed when needed.

- explain the predicament
- give dietary advice e.g. foods with minimal residue
- minimise colic by stopping osmotic/stimulant laxatives (continue softeners) and give subcutaneous hyoscine butylbromide (20mg bolus followed by 60 to 80mg sc infusion over 24 hours)
- give analgesia (commonly subcutaneous opioids)
- reduce vomiting by giving appropriate antiemetics e.g. cyclizine with or without haloperidol - metoclopramide should only be used if there is clear evidence that there is only a partial obstruction
- consider alternative measures e.g. surgery, radiotherapy
- steroids e.g. dexamethasone should be given a trial
- iv fluids and nasogastric tubes should be avoided but may be preferred where drug treatment has not worked. sc fluids may have a role in some
- somatostatin analogues (octreotide) may be used subcutaneously in specialist practice to reduce secretions and minimise symptoms
- if subacute intestinal obstruction, the aim may be to clear the obstruction using steroids e.g. dexamethasone to reduce the inflammation around the obstruction and hyoscine butylbromide to minimise secretions and colic then, at an appropriate time, to push gut contents through with a prokinetic agent e.g. metoclopramide
- the timings of each change in therapy will depend on the individual patient and their condition
- review the situation regularly
• hypersalivation may be helped with atropine eye drops 1%, 1 to 2 drops in the mouth three to four times a day, ipratropium bromide nasal spray, 1 to 2 puffs in the mouth three to four times a day, radiotherapy or botulinum toxin to salivary glands

Dirty mouths
• chlorhexidine mouthwash is a useful cleansing agent
• there is little point in cleaning the mouth if dentures are worn unless those dentures are also meticulously cleaned (including soaking overnight in $\frac{1}{4}$ strength Milton™)

Dry mouths
• salivary stimulants e.g. lime juice, fresh melon or pineapple are useful in dry mouths as is a saliva substitute (often useful to freeze fruit first); also, lozenges or mints (sorbitol, xylitol-containing gum)
• pilocarpine solution (1mg/mL, 5 to 10mL or 1-2 drops 4% eye drops rinsed three times a day) may be useful for dry mouths

Infected mouths
• nystatin suspension is useful in the treatment of oral candidiasis but may take up to two weeks to clear an infection and many candidal infections are now resistant to it
• miconazole oral gel is also useful in the treatment of oral candidiasis, usually after nystatin suspension has failed
• systemic anti-fungals e.g. fluconazole (50mg a day for 7 to 14 days or 100-150mg stat) are sometimes needed for intractable oral candidal infections
• pilocarpine may be useful for herpetic infections

Painful mouths
• may need systemic opioids
• coating agents
  — sucralfate suspension (use crushed tablets)
  — topical anaesthesia e.g. lignocaine viscous (watch for choking hazards), Cepacaine™
• benzydamine is an analgesic mouthwash for painful mouths
• topical corticosteroids e.g. triamcinolone in orabase may be useful for aphthous ulcers (not used if oral candidiasis present)
• Bonjela™ (choline salicyclate) may sooth sore gums

TASTE ALTERATION
• reduction in taste sensitivity i.e. hypogeusia
• absence of taste sensation i.e. ageusia
• distortion of taste i.e. dysgeusia

Causes
• local disease of mouth and tongue

Management
• remove or treat causes e.g. give pilocarpine for dry mouth, stop likely drugs
• zinc (but only if zinc is deficient)
• may be unresponsive to interventions

SWALLOWING DIFFICULTIES
Swallowing oral formulations of drugs often becomes difficult for palliative care patients.
• drugs which are available in the capsule form may be more easily swallowed using the ‘leaning forward’ technique
  — this involves bending the head down rather than tipping it back when swallowing capsules
  — when leaning the head down and forward the capsule floats to the back of the throat ready to be swallowed
  — the standard way of swallowing solid oral formulations - head is tipped back results in the capsule floating to the front of the mouth making swallowing the capsule difficult
  — this ‘leaning forward’ technique will not work for tablets as they do not float so use the standard tilting the head back approach
• if swallowing remains an issue consider crushing tablets or opening capsules if appropriate, oral liquids or other routes e.g. sc, intranasal, sublingual, rectal

MALIGNANT ASCITES
This is a common symptom in patients with breast, colon, endometrial, ovarian, pancreatic or gastric cancers.

Assessment
• consecutive measurements of abdominal girth
• respiratory function - shortness of breath may occur
• early fullness e.g. squashed stomach
• portable ultrasound examination

**Central Nervous System**

**Depression**

In terminal care it is important to distinguish between clinical depression and profound sadness.

- Depression is a pervasive sense of misery.
- Sadness is a normal response to loss which waxes and wanes but enjoyment and future planning are retained.
- Most terminally ill patients do not become clinically depressed.
- Prevalence is about 15% (compared with 5 to 10% in the general population), most commonly in the early cancer stages.
- Reaching a diagnosis of depression in terminal patients is difficult as the usual physical symptoms of depression in the otherwise well such as anorexia, weight loss, sleep disturbance are often already present in patients with malignant disease whether they are depressed or not.
- The psychological symptoms are more discriminative.
- Asking ‘Are you depressed?’ provides a bed-side assessment of mood.
- Suicide is rare, however, fleeting suicidal thoughts and fluctuating ‘will to live’ in cancer patients are common and not necessarily pathological.
- Requests for euthanasia and/or physician assisted suicide are more common although as for suicide this is not limited to depressed patients.
- Clinical depression is under-recognised and under-treated yet it is generally very responsive to treatment.
- The cause of depression is unknown but imbalances in neurotransmitters, especially serotonin, in the brain may play a part.

**Psychological Symptoms of Major Depression May Include**

- Hopelessness
- Anhedonia (loss of pleasure)
- Morbid guilt and shame
- Worthlessness and low self esteem
- Request for physician assisted euthanasia
- Persisting suicidal ideation
- Lowered pain threshold
- Decreased attention and concentration
- Cognitive slowing
- Impaired memory
- Indecisiveness
- Early morning wakening
- Rumination of negative thoughts
- Nihilistic and depressive delusions
- Feeling of unreality

**Causes**

- Peritoneal fluid build-up in the abdomen due to a failure of the lymph system to adequately drain.
- Tumour in the peritoneal cavity.
- Low serum albumin.
- Excess fluid production.
- Venous compression or vena cava/hepatic vein thrombosis.

**Management**

Symptoms usually appear at > 1 L of fluid in the abdomen.

- If the prognosis is short and the symptoms are not troublesome then no action may be needed.
- Explanation of the problem and likely outcomes may be enough to allay fears or anxieties.
- If the symptoms warrant further intervention, the bowel is not distended or the ascites is not loculated, consider paracentesis.
- Beware of loculation - use of ultrasound is now common.
- Suction may be used if the fluid is viscous, e.g. of ovarian origin.
- Drain no more than 2 L in the first hour then drain slowly for 12 to 24 hours (to a maximum of 5 L in 24 hours).
- Place an ostomy bag on the site once the paracentesis needle is removed to collect any residual leaking fluid.
- Check biochemistry frequently.
- Some centres advise daily measurement of girth.
- A surgical opinion, for the insertion of a peritoneo-venous shunt, may help in recurrent ascites if the patient’s life expectancy is greater than 3 months.
- Repeated drainage may be followed by rapid reaccumulation.
- Drugs
  - If the patient is fit for diuretics, give spironolactone 100mg (or more) with or without frusemide 40mg once daily although benefit is often extremely limited.
  - For gastric stasis give a prokinetic e.g. metoclopramide.
  - If there is evidence of liver capsule stretch pain use a steroid e.g. dexamethasone - see co-analgesics protocol.
**DELIRIUM**

Toxic confusional states, like delirium, are common in people who are dying.
- if irreversible, may be an indication of impending death
- can be most distressing for patients, family and staff

**Diagnosis**
- abrupt onset
- impairment of consciousness - the primary symptom which results in:
  - disorientation (to time)
  - fear and dysphoria
  - memory impairment (short term memory)
  - reduced attention span to external stimuli
  - hyperactive (frenzy) or hypoactive (retardation, torpor) but usually mixed hyperactive and hypoactive motor activity
  - reversal of sleep-wake cycle
  - perceptual disturbance (illusions, hallucinations)
  - disorganised thinking (paranoia, rambling)
  - dysgraphia (difficulties with writing)
- fluctuating symptoms (‘sundowner effect’)

**Causes**
There are often multiple organic causes but in up to 50% of cases specific causes are not found, despite investigations.
- infection
- organ failure (liver, kidney) and underlying medical conditions
- drugs
  - sedatives
  - anticholinergics
  - opioids
  - benzodiazepine or alcohol withdrawal
  - steroids
- metabolic disturbances
  - dehydration
  - hypercalcaemia
  - hyponatraemia
  - hypoglycaemia
- hypoxia
- anaemia (severe)
- vitamin deficiency
- cerebral metastases
- cerebral haemorrhage
- epilepsy - post-ictal

**Risk factors**
- inadequate symptom control - unrelieved pain, nausea
- poor quality of life
- lack of social support
- past and/or family history of depression
- older age
- misinformed prognosis
- drugs
  - steroids, cytotoxics, antibiotics, anti-hypertensives, neuroleptics, sedatives
- immobility
- advanced malignant disease

**Differential diagnosis**
- adjustment/grief reaction (sadness)
- ‘vital (physiological) exhaustion’
- demoralisation (a state of existential despair, meaninglessness and hopelessness but not of anhedonia and joylessness)
- delirium/sedation
- detachment (the terminal shedding of attachments)
- ‘giving up’ (affect neutral, rational, decisive)

**Management**
- mild to moderate depression
  - support, empathy, clarification of stressors or precipitators, explanation, cognitive therapy, symptomatic relief
- severe depression
  - supportive psychotherapy plus drug therapy
  - drug therapy - antidepressants are effective in 50 to 70% of cases
    - a therapeutic trial is usually appropriate
    - if in doubt, refer to a specialist psychiatrist
    - SSRI e.g. escitalopram, fluoxetine
      - if no response in 4 to 6 weeks try adding a tricyclic (e.g. nortriptyline) or venlafaxine, mirtazapine
    - psychostimulants e.g. methylphenidate
      - not as effective as SSRIs - may help retarded/withdrawn, frail patients for a few weeks only
      - a response may be achieved from small doses (5 to 30mg each morning) within days either alone or in combination with an SSRI - watch for additive serotonergic effects
    - modafinil may be a useful alternative to methylphenidate
Predisposing/precipitating/aggravating factors
• dementia and CNS immaturity
• pain
• fatigue
• urinary retention
• constipation
• unfamiliar excessive stimuli
• change of environment

Management
• treat the underlying organic causes if identifiable and treatable
• treat fever, hypoxia, anaemia, dehydration, constipation, fear and anxiety and pain if possible
• ensure there is a safe and secure environment - have adequate staffing, remove potentially dangerous objects, have the mattress on the floor
• prevent sensory over-stimulation - have a single room, minimise noise and staff changes and maintain a warm and comfortable environment
• psychological interventions
  — reassurance
  — orienting aids (clock, personal belongings, presence of a supportive family)
  — cognitive strategies (clarification, reality testing, validation and repetition during lucid periods)
  — emotional support (touch, empathy)
• drugs - use if symptoms are severe (in combination with above management)
  — antipsychotics (calm or pacify rather than sedate)
    > haloperidol is the drug of choice BUT not in AIDS delirium (HIV makes the CNS more sensitive to dopamine antagonists), hepatic encephalopathy or alcohol withdrawal where benzodiazepines only should be used (see haloperidol in drug section)
    > Haloperidol regimen in acute delirium:
      Oral if compliant, sc or iv if not initial dosage:
        mild 0.5 to 1.5mg orally
        severe 1.5 to 5mg orally
        very severe 10mg sc/iv
      > repeat and titrate every 30 to 40 minutes until controlled
      > maintenance - 50% of daily dose required to achieve control usually 1.5 to 20mg/day (oral)
      > add anticholinergic agent e.g. benztpine 2mg only if extrapyramidal symptoms appear
      > extrapyramidal side-effects are less pronounced with the parenteral route
        > levomepromazine (methotrimeprazine)
        > risperidone
        > olanzapine
        > quetiapine
  — sedatives (should not be used alone in most cases of delirium as they may aggravate symptoms particularly if inadequate doses are used so use with an antipsychotic)
    > benzodiazepines e.g. midazolam, clonazepam
    > barbiturates e.g. phenobarbitone
    — anaesthetics e.g. propofol (rarely indicated)
    — drug-induced delirium
      > opioid-induced - decrease dose or change opioid
      > anticholinergic-induced - treatment with cholinesterase inhibitors may be possible e.g. physostigmine

Even if the aetiology is irreversible, the symptoms of delirium may be palliated. Only 10 to 20% of patients with terminal delirium should require ongoing palliative sedation to achieve control.

DISORDERS OF SLEEP AND WAKEFULNESS
Sleep disturbance in people who are dying is a frequent occurrence and it requires careful assessment and management.
• sleep patterns change with age and with illness e.g. cancer
  — a reduction of depth and continuity of sleep and an increasing propensity for day-time naps occurs
  — many cancer patients have difficulty falling to and staying asleep
  — cytokines are implicated in these changes

INSOMNIA
This is common and distressing. It undermines coping strategies through tiredness.

Causes
• poor symptom control of
  — anxiety, depression, pain, urinary frequency, faecal incontinence, nausea, vomiting, delirium, coughing
• environmental changes
  — admission to hospital or hospice
  — disturbance by staff or family
• fear of going to sleep and never waking up
• drugs
  — stimulants e.g. methylphenidate
  — steroids (particularly if given after noon)
  — bronchodilators
  — alcohol, caffeine
• withdrawal of benzodiazepines, alcohol or tobacco

Management
• symptom control of above
• establish good sleep hygiene
  — regular bed-times
— minimise day-time napping
— reduce evening stimulants e.g. caffeine, alcohol
— comfortable bedding
— comfortable temperature

- relaxation techniques
- drugs
  - hypnotics
    > short acting benzodiazepines e.g. temazepam
    > zopiclone
  - sedative anti-depressants e.g. nortriptyline 10 to 20mg
  - sedating antipsychotics e.g. quetiapine 25 to 50mg at night may be considered if insomnia is resistant to above

**DROWSINESS/HYPERSONMIA**
These are common symptoms, particularly as the end of life approaches.

**Causes**
- organ failure e.g. renal, hepatic, cardiac, respiratory
- delirium (hypoactive)
- metabolic disturbances e.g. hyperglycaemia, hypercalcaemia
- fatigue or ‘vital exhaustion’
- infection
- raised intracranial pressure
- drugs
  - adverse effects e.g. opioids, anticholinergics, benzodiazepines, cyclizine, levomepromazine (methotrimeprazine)

**Management**
- accurate assessment
- treat/remove causes where possible
- it may be unresolvable and be a natural part of the dying process

**SLEEP PHASE (CIRCADIAN) DISORDER**
(Delayed Sleep Phase Syndrome or Sleep-Wake Reversal)
- a dysregulation of the sleep-wake cycle
  — profound initial insomnia and
  — the inability to arise at desirable hours
- particularly associated with cerebral tumours
- presents a major burden for carers

**Management**
- shifting the circadian rhythm with behavioural strategies and bright light therapy is impractical in the terminally ill
- relief care for the family and a night nurse may be necessary as this tends to be an intractable symptom

- drugs are of limited benefit
  — sedatives e.g. benzodiazepines
  — psychostimulants e.g. methylphenidate
  — sedating antipsychotics e.g. quetiapine 25 to 200mg at night
  — pericyazine 20 to 30mg at night
  — melatonin 0.5 to 6mg at night

**TERMINAL RESTLESSNESS**
This may indicate physical, psychological and/or spiritual discomfort. It is often a ‘pre-death’ event.

**Causes**
- physical discomfort
  — unrelieved pain
  — distended bladder or rectum
  — physical restraint
  — insomnia
  — uncomfortable bed or environment
- delirium (see delirium page)
- psychological discomfort
  — anger
  — fear
  — guilt
  — unfinished business
- spiritual discomfort
  — helplessness
  — hopelessness
- drugs
  — akathisia induced by dopamine antagonists e.g. metoclopramide, haloperidol

**Management**
- assess and treat/remove possible causes
- explain what’s happening to the family, patient (if appropriate) or main carers
- have the family present to reassure and support
- discuss psychological discomfort e.g. anger, fear, guilt
- drugs
  — see delirium page and anxiety and fear section
  — benzodiazepines e.g. midazolam in inadequate doses can aggravate (by disinhibition) rather than relieve restlessness in some patients
  — if levomepromazine (methotrimeprazine) with a benzodiazepine are ineffective consider phenobarbitone or dexamethasone
PALLIATIVE SEDATION
This is considered when all other symptom-relieving measures have failed and the patient is clearly distressed.

Reasons for palliative sedation
• terminal restlessness (see terminal restlessness)
• uncontrolled delirium (see delirium)
• severe breathlessness (see dyspnoea)
• massive haemorrhage (see haemorrhage)
• neurogenic or cardiogenic pulmonary oedema
• intractable distress

How palliative sedation is achieved
• the level of sedation should be titrated to removal of distress
• drugs
  — benzodiazepines e.g. midazolam, clonazepam
  — sedating antipsychotics e.g. levomepromazine (methotrimeprazine) (sc 12.5 to 200mg /24 hours)
  — barbiturates e.g. phenobarbitone (sc 600 to 1,200mg/24 hours)
  — dexmedetomidine - experience in palliative care is limited
• opioids
  > increasing doses may not result in increased sedation (opioids tend only to be sedating in the opioid naïve) and may instead induce respiratory depression or seizures

Sedation of this type may be subject to the principle of ‘double effect’ which has the dual effects of intentional relief of suffering and increased risk of hastening death. Palliative sedation itself has not been shown to hasten death.

ANXIETY AND FEAR
Anxiety (excessive uneasiness) and fear (being afraid and frightened) are common emotions in people faced with a life threatening illness.

• anxiety
  — may be a normal alerting response
  — may be a symptom of a medical condition e.g. delirium, depression, hormone-secreting tumour
  — may be the result of an adverse reaction to a drug e.g. bronchodilators, steroids, methylphenidate
  — may be a symptom of an impending medical catastrophe
  — may be a learned phobic reaction to an unpleasant event e.g. needles, chemotherapy

Common anxieties and fears centre around
• separation from loved ones, homes or jobs
• becoming dependent on others (being a ‘nuisance’ or ‘burden’)
• losing control of physical faculties

RAISED INTRACRANIAL PRESSURE
Raised intracranial pressure is a life-threatening event that needs to be carefully assessed and managed to optimise quality of life and minimise symptoms.

Symptoms
• severe headache which is worse when lying down or straining
• vomiting
• convulsions
• mental - drowsiness, delirium
• diplopia
• restlessness

Causes / Risk factors
• cerebral metastases (commoner with some primaries, e.g. lung, breast, melanoma than with others, e.g. prostate)
• primary brain tumour
• cerebral abscess
• cerebro-vascular event
• sagittal sinus thrombosis
• secondary hydrocephalus following surgery
Management
If raised intracranial pressure is suspected look for papilloedema and signs of cerebral irritation. Computerised tomography or MRI may be appropriate
- raise the head of the bed
- consider cranial radiotherapy or neurosurgery for malignancy if prognosis/status warrants it
- drugs
  - dexamethasone up to 16mg per day. Avoid doses after noon as may add to insomnia. Gradually reduce dose to minimum effective. Withdraw after 7 days if ineffective (note: some anticonvulsants can reduce effectiveness – see dexamethasone page)
  - simple analgesics e.g. codeine
  - consider anticonvulsants particularly if seizures are present
  - consider acetazolamide 250 to 500mg od to bd

CONVULSIONS
Convulsions can be distressing not only for the patient but also for the family and other carers. They should be managed effectively to reduce distress and anxiety wherever possible. It is important to have a clear history of the convulsion in order to diagnose the type (grand mal, focal, absence or status epilepticus). At times a convulsion can be mistakenly diagnosed when the true cause of loss of consciousness or absence is a syncopal attack, cardiac arrhythmia, or a transient ischaemic attack.

Causes
- previously diagnosed epilepsy, brain trauma/surgery, brain tumour/mets
- drugs
  - some lower seizure threshold e.g. phenothiazines, tricyclics
  - interactions: antiepileptics have many variable and unpredictable interactions
    - see individual drug pages
  - withdrawal e.g. of steroids, alcohol
- metabolic disturbance, e.g. hypoxia, hyponatraemia, hypoglycaemia

Management
Prophylaxis
- drugs
  - consider dexamethasone if related to raised intracranial pressure (primary brain tumour/metastases)
  - sodium valproate initially 100 to 200 mg bd to tds increasing every 3 days to 1 to 2 grams per day
  - carbamazepine initially 100 to 200mg od to bd increasing by 100 to 200mg every 2 weeks to 800 to 1200mg per day – consider therapeutic drug monitoring of plasma concentrations
  - phenytoin 200 to 300mg nocte - consider therapeutic drug monitoring of plasma concentrations
  - levetiracetam 500mg bd initially

- if oral route is not available consider
  > clonazepam 1 to 4mg/24 hours by sc infusion
  > midazolam 10 to 60mg/24 hours by sc infusion
  > consider the use of phenobarbitone if convulsions are not effectively managed by other agents

Grand mal convulsions or status epilepticus management
- make the patient safe, explain what is happening and reassure
- drugs
  - rectal diazepam 10 to 20mg
  - buccal midazolam 5 to 10 mg - between the cheek and gum
  - sc boluses of clonazepam or midazolam
  - if these measures are not effective consider the use of phenobarbitone
**Assessment**
- careful assessment of each situation to identify probable causes is an essential starting point
- pay particular attention to the descriptions the patient gives of the sensation and experience of breathlessness and ask specifically “How would you describe your breathlessness today?”
- severity and meaning for each individual is important as dyspnoea may have a variable effect on quality of life at the end of life, varying with the cause(s) and the individual’s perception of the meaning of the symptom
- in a broad sense, dyspnoea has at least five main components each of which must be attended to
  - sensation (what it feels like)
  - perception (how it is viewed in the context of the illness)
  - distress (does it cause suffering or grief?)
  - response (how individuals react)
  - reporting (the language used to relay these elements)

**Management**
- treat/remove causes where possible with treatments that are similar to those used in general medicine
  - the cancer itself together with radiation or chemotherapy
  - the complications of cancer e.g. pleural effusions, anaemia
  - concurrent non-cancer causes e.g. heart or lung disease
- non-pharmacological management
  - psychosocial support
    - address anxiety and fear by active listening and exploration of the meaning of breathlessness
    - explanation and reassurance usually helps
    - relaxation techniques
    - relearning breathing patterns and control
    - discuss coping strategies
  - positioning
  - adaptation and energy conservation which is often most effectively undertaken with the help of occupational or physiotherapists or specialist nurses
  - physiotherapy
  - drainage of effusions or ascites
  - blood transfusion may be useful if anaemia is present and it is appropriate
  - bronchial stents, brachytherapy
  - complementary therapies e.g. aromatherapy
  - music therapy and the arts
  - draughts of fresh air using fans and open windows
- at the end of life non-pharmacological interventions become less effective so that a greater reliance on drugs is common, although both may be used together
**Cough**

Cough is often associated with other symptoms such as dyspnoea, wheezing or chest tightness. It is a defensive mechanism, like pain and it can have a detrimental effect on the quality of life as it interferes with communication, food and drink intake and sleep.

**Causes and treatment**

- **acute respiratory infection**
  - antibiotic (if appropriate), physiotherapy, nebulised saline
- **airways disease**
  - bronchodilator e.g. salbutamol, inhaled or systemic corticosteroids, physiotherapy
- **malignant obstruction (tumour)**
  - as above but consider nebulised local anaesthetic
- **oesophageal reflux**
  - prokinetic agents e.g. metoclopramide, positioning, proton pump inhibitors e.g. omeprazole
- **salivary aspiration**
  - anticholinergic agent e.g. hyoscine

- **cardiovascular causes**
  - usual cardiac drugs
- **pulmonary oedema**
  - drugs which can cause cough
    - angiotensin converting enzyme inhibitors e.g. captopril - change or discontinue therapy

**Management**

- **cough with tenacious sputum i.e. a productive cough**
  - may respond to steam inhalation, nebulised saline, bronchodilators or physiotherapy
- **drugs (as above and below)**
  - cough suppressants e.g. codeine, pholcodine, morphine
    - may be useful in dry non-productive coughs
    - titrate dose to effect
    - may not be appropriate in productive coughs as retaining the mucus may encourage infection
  - Simple Linctus
    - this is a soothing syrup which may be an effective first choice
  - paroxetine (for itch of the respiratory tract)
    - may be useful in intractable cough
    - patients should be warned not to eat or drink for at least an hour after using the nebuliser to avoid accidental inhalation of food or drink
    - potential to cause bronchospasm so the initial dose should always be given under medical supervision
  - oxygen
    - may be useful in cough associated with emphysema
  - corticosteroids e.g. dexamethasone, prednisone
    - often used to treat cough associated with endobronchial tumours, lymphangitis or radiation pneumonitis

**Hiccup**

This is a respiratory reflex characterised by spasm of the diaphragm resulting in a sudden inspiration and closure of the vocal cords. Hiccup is a most distressing symptom and should be attended to with urgency. The phrenic and vagal nerves and the brain stem are involved.

**Causes**

- **gastric distension**
- **diaphragmatic irritation**
- **phrenic or vagal nerve irritation**
- **uraemia**
- **neurological disease affecting the medulla e.g. brain stem tumour, infarction, encephalitis**
- **liver disease (hepatomegaly)**
Management
- remove any correctable cause
  - e.g. reduction in gastric distension with a prokinetic - metoclopramide - if not obstructed
- pharyngeal stimulation with cold water
- elevation of pCO₂ using paper bag rebreathing or breath holding
- phrenic nerve block may be considered
- drugs
  - corticosteroids e.g. dexamethasone, prednisone
  - antipsychotics e.g. haloperidol, chlorpromazine, levomepromazine (methotrimeprazine)
  - muscle relaxants e.g. baclofen
  - benzodiazepine
  - anticonvulsants may be useful if a CNS cause is present e.g. phenytoin, valproate, carbamazepine
  - gabapentin

Several of the above may have to be tried. None are consistently reliable.

EXCESSIVE (RETAINED) SECRETIONS
This phenomenon occurs when a patient is too weak to clear respiratory secretions particularly near the end of life.
- air passing through these secretions produces a gurgling or rattling sound ("death rattle") which, although not obviously distressing to the patient may be distressing for families and carers
- reassurance that the patient is not distressed is important for families

Causes
- inability to swallow or clear secretions
  - salivary or bronchial secretions
- cessation of steroids in patients with cerebral involvement can lead to neurogenic pulmonary oedema which may not respond to the management below - consider continuation of steroids in these patients

Management
- appropriate positioning to allow postural drainage
- drugs
  - anticholinergics e.g. hyoscine butylbromide, hyoscine hydrobromide, glycopyrrolate
    > can help but are often started too late in life to effect a major change as secretions already present have to evaporate first
    > hyoscine hydrobromide may cause delirium while glycopyrrolate and hyoscine butylbromide do not get into the CNS readily
- occasionally suction is needed to remove plugs of mucus but is not always successful and should be avoided if possible

HAEMOPTYSIS
The coughing up of blood from the lungs or haemoptysis is often a frightening symptom for both patient and family.

Causes
It is not always possible to identify the cause and it has been suggested that up to 40% of cases remain undiagnosed.
- tumour erosion - lung or oesophagus
- infection
- pulmonary embolism
- clotting disorders

Management
- treat/remove the causes if appropriate
- if minor coughing up of blood i.e. flecks or spots of blood
  - not usually helpful to give any specific treatment but patient reassurance may help
- if the bleeding is persistent or is major
  - haemostatics such as tranexamic acid may be useful (1 to 1.5g two to four times daily)
  - consider radiotherapy which may have some benefit
- if the bleeding is massive
  - the normal ‘life saving’ interventions of bronchoscopy and intubation are inappropriate
  - reduce the patient’s awareness, fear and anxiety with subcutaneous midazolam (2.5 to 10mg) with or without subcutaneous morphine
  - staff should stay with the patient and family until the immediate crisis is over
SKIN

ITCH (PRURITUS)
Itching can be as unpleasant and disruptive as pain and can have just as adverse an effect on quality of life.
- nerve fibres involved in the itch process are anatomically very similar to those involved in pain with opioid receptors being involved in both pathways
- cholestatic and uraemic itch in particular are mediated via opioid receptors
- the skin can be affected by many metabolic, pharmacological, dietary, environmental and psychological factors
- an accurate history of the onset and nature of itching will help to identify a cause and examination of the skin for signs of disease is essential
- not all itch is histamine related
- serotonin and prostaglandins may also be involved
- both central (neuropathic) and peripheral (cutaneous) itch have been identified

Causes
- hepatic/renal disease (obstructive jaundice, cholestatic and uraemic itch)
- drug allergy
- drugs e.g. opioids, vasodilators
- endocrine disease
- iron deficiency
- lymphoma
- provocative sensory influences such as rough clothing
- parasites

Management
- treat/remove causes
- attempt to break the itch/scratching cycle by short clipping nails, wearing cotton gloves, applying paste bandages
- apply surface cooling agents with emollients e.g. 0.25 to 1% menthol in aqueous cream, tepid showers, humid environment
- avoid washing with soap and use emulsifying ointment instead and Alpha-keri™ as bath oil
- light therapy may help
- drugs
  - oral anti-histamines e.g. promethazine, cetirizine
  - bile sequestrant e.g. cholestyramine 4 to 8g per day
  - night sedation e.g. temazepam
  - H₂ antagonists (act on histamine receptors in the skin) e.g. cimetidine 400mg twice daily
  - NSAIDs e.g. diclofenac
  - anxiolytics e.g. benzodiazepines
  - steroids e.g. dexamethasone (lymphoma itch), topical hydrocortisone
  - rifampicin 150 to 300mg per day (chronic cholestasis)
  - 5HT₃ antagonists e.g. ondansetron (uraemic)
  - gabapentin (uraemic)
  - doxepin capsules or cream
  - thalidomide
  - paroxetine, mirtazapine (paraneoplastic itch)

Referral to a specialist dermatologist should be considered at an early stage if no alleviation of symptoms is obtained.

SWEATING
Sweating is an unpleasant and debilitating symptom that affects not only the patient but often indirectly, the carers as well. As with many other symptoms it can indicate physical, psychological and/or environmental disturbance.

Causes
- environmental temperature changes
- emotion
  - usually confined to the axillae, palms and soles
- lymphomas, hepatic metastases and carcinoid
  - may produce drenching night sweats
- intense pain precipitating or manifesting through anxiety and fear
- infection
- drugs
  - alcohol
  - antidepressants
  - opioids

Management
- treat/remove causes
- attempt to break the itch/scratch cycle by short clipping nails, wearing cotton gloves, applying paste bandages
- apply surface cooling agents with emollients e.g. 0.25 to 1% menthol in aqueous cream, tepid showers, humid environment
- avoid washing with soap and use emulsifying ointment instead and Alpha-keri™ as bath oil
- light therapy may help
- drugs
  - oral anti-histamines e.g. promethazine, cetirizine
  - bile sequestrant e.g. cholestyramine 4 to 8g per day
  - night sedation e.g. temazepam
  - cimetidine 400mg to 800mg at night
  - NSAIDs e.g. diclofenac
  - anxiolytics e.g. benzodiazepines
  - steroids e.g. dexamethasone
  - paracetamol (for night sweats)

PRESSURE AREA CARE
Pressure areas and injuries occur when the blood supply is shut down by pressure e.g. from a hard bed resulting in tissue death.

Causes
- pressure on one particular part of the body
  - sitting is riskier than lying as more of a person’s weight can press on a smaller area e.g. buttocks while sitting
• sliding patients against a surface can cause damage to skin (friction) or tissue (shear)
• wetness increases the risk of pressure area damage

Management
• avoid causes
• assess using appropriate ‘risk factor scale’ at regular intervals i.e. daily for high risk, weekly for low risk
• use pressure relieving aids and mattresses when these are available and assessed as being needed
• use aids to movement where appropriate
• discuss management with patient and home carers
• use a semipermeable adhesive dressing if at risk
• where semipermeable adhesive dressing is not practical use meticulous hygiene followed by povidone iodine spray
• higher rating pressure injuries should be treated as wounds with appropriate dressing products and techniques
• rubbing over pressure areas should be discouraged
• turn bed-fast patients every 2 to 4 hours as appropriate
• in incontinent patients protect vulnerable skin with zinc and castor oil cream and consider catheterisation
• if nutritional state is poor, get dietary advice from a dietitian
• inform primary carers of management on discharge from in-patient facility

LYMPHOEDEMA
As lymphoedema (swelling of a limb (usually) due to fluid) cannot be cured, the aim of treatment is to achieve maximal improvement and long-term control.

Causes
• damage to the lymphatic drainage system allows fluid to build up
• the protein in the initial oedema draws more fluid out of the blood
• the protein in the fluid also encourages inflammation
• infection may occur

Management
• provide analgesia if painful
• early referral to an appropriately trained professional (usually a physiotherapist) produces best results
• success requires the patient’s full cooperation, so a simple explanation of lymph flow and the cause of swelling is essential, together with instruction on daily skin care
• infections must be cleared before commencing treatment
• gentle massage of the affected area helps to shift fluid from one area to another, local practitioners in the techniques may be available
• regular measurement of both normal and affected limbs is essential to monitor progress

• in most cases containment hosiery of an appropriate size and strength should be worn all day, complemented by specific exercises and massage if possible
• if the limb is not in a suitable shape or condition to use hosiery or if the fingers are swollen, compression bandaging or taping may be necessary for approximately two weeks
• it may be possible to drain fluid using a needle in the tissues concerned
• diuretics are not usually useful (except when the patient has heart failure or hypoalbuminaemia), may be detrimental and can cause dehydration

FUNGATING WOUNDS AND TUMOURS
Fungation of wounds or tumours (smelly, exuding necrotising wounds) presents an obvious manifestation of disease that can cause major distress to patient, carers and family.
• ‘fungating’ wounds are malignant in nature and combine ulceration with proliferation
• usually seen in the area of the breast or head and neck
• as healing of the wound is rare, the aim in managing these wounds is to achieve maximum patient comfort together with a reduction in the distortion of body image
• odour is often caused by anaerobic bacterial infection of compromised tissue
• the wound may bleed as blood vessels are eroded

Causes
• primary skin tumour e.g. melanoma, squamous cell carcinoma
• invasion of nearby tissue by underlying tumour e.g. breast cancer
• metastatic involvement

Management
• ensuring that the area is as clean as possible can help to reduce smell and exudate
• many preparations are recommended for odour reduction and each practitioner will have their favourite e.g. lemon oil
• as the odour is often due to anaerobic infection, metronidazole gel applied directly to the wound can be helpful
• for excessive exudate wound dressings may be used on the advice of a local expert - disposable nappies may be an option
• bismuth iodoform paraffin paste (BIPP) may help in drying up the wound and reducing odour
• many fungating wounds are painful - use systemic analgesics
• morphine injection added to a gel in a clean environment and used topically may help (0.05 to 0.1% morphine [i.e. 0.5 to 1mg/mL] in Intrasite ™ gel, metronidazole gel or KY Jelly ™)
• radiotherapy, chemotherapy and hormone manipulation should be considered for some tumours
• if bleeding consider pressure with adrenaline 1:1000 soaked swabs
SYSTEMIC EFFECTS OF TERMINAL DISEASES

PARANEOPlastic SYNDROMES
The remote effects of cancer can be classified as paraneoplastic syndromes. They are thought to be rare affecting perhaps only 1% of people with cancer. These syndromes may be identified before the diagnosis of cancer is made.

Dermatological syndromes
There are a number of skin disorders that herald the presence of underlying malignant disease. Consultation with a specialist dermatologist is advised.

• acanthosis nigricans (treatment generally ineffective)
• dermatomyositis (treatment requires removal of the cause but symptoms may be managed with corticosteroids)
• acquired ichthyosis (treat the underlying cause)
• paraneoplastic pemphigus (use steroids and ciclosporin)

Metabolic syndromes
• hypercalcaemia - see hypercalcaemia section
• Cushing's syndrome (ectopic secretion of ACTH)
• SIADH - syndrome of inappropriate antidiuretic hormone secretion
  — results in hyponatraemia which is common near the end of life
  — symptoms appear at plasma sodium concentrations <125 mmol/L and include stupor, coma and seizures

Neurological/psychiatric syndromes
• Lambert-Eaton myasthenic syndrome (LEMS)
  — associated with small-cell lung cancer
  — manifests as muscle weakness and fatigue
  — may respond to immunosuppression, plasmapheresis and 3,4-diaminopyridine (3,4 DAP)
• sub-acute cerebellar degeneration
  — associated with ovarian and lung cancer
• motor neuropathy
  — associated with lymphoma
• peripheral neuropathy
  — associated with small-cell lung cancer
• limbic encephalitis
  — changes in mood, personality
  — memory impairment (recent more than remote)
  — seizures

Management
All of these syndromes are usually irreversible and treatment is largely symptomatic.

VENOUS THROMBOEMBOLISM
Venous thromboembolism (VTE) includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). It is a lethal disorder that is common in people with cancer and to a lesser extent in other advanced diseases.

Diagnosis/symptoms
• PE - episodic and otherwise unexplained breathlessness or confusion, tachypnoea, and pleuritic chest pain - may be difficult to interpret in the presence of other pulmonary pathology
• DVT - pain or tenderness and swelling, increased warmth, oedema and redness
• tests such as D-Dimers are generally unhelpful in advanced cancer but Doppler scans may reveal DVTs in large veins.

Causes and risk factors
• malignant disease
• recent chemotherapy or surgery
• immobility
• malignant pelvic disease
• familial (hereditary factors)
• age (over 40)
• obesity

Management
If the patient is at risk of VTE
• take into account any risk of bleeding and expected prognosis
• discuss with the patient and family whether they want to have active prophylaxis with anti-embolism stockings and low molecular weight (LMW) heparin as appropriate, balancing risks and benefits to optimise quality of life
• if the patient is in the last few days or weeks of life then thromboprophylaxis is often not appropriate, and is not routine - the best evidence in favour of thromboprophylaxis is in potentially reversible co-existing acute conditions

Treatment for VTE (DVT- includes prevention of PE and/or recurrent thrombosis)
• anticoagulation with a LMW heparin e.g. enoxaparin should be started immediately unless there is a contraindication - the preferred option because it is more effective in VTE associated with malignancy, and if dosed properly is less likely to cause bleeding
• LMW heparin followed by warfarin or dabigatrin is cheaper and perhaps more convenient, but warfarin requires blood tests (INR may be very difficult to keep stable in those with advanced disease and variable nutritional intake)
• re-assess the patient regularly to confirm the management plan is appropriate to the stage of their illness and their wishes
• if warfarin is used start at the same time as LMW heparin and continue the LMW heparin for 2 days after achieving therapeutic INR
• haemorrhagic complications occur in almost 50% of people with advanced cancer (due to drug interactions or hepatic dysfunction)

WEAKNESS/FATIGUE

• Weakness and fatigue are amongst the commonest and most debilitating symptoms at or near the end of life.
• it is often assumed that weakness is an inevitable consequence of approaching death however there are many factors that may exacerbate or precipitate weakness
• careful assessment may result in interventions that can improve quality of life
• there are often two main contributing factors
  — cachexia
    > a debilitating state of involuntary weight loss complicating chronic malignant, infectious and inflammatory diseases that contributes to mortality
  — asthenia
    > fatigue or lassitude
    > easily tired and a decreased capacity to maintain adequate performance
  > generalised weakness
  > anticipatory subjective sensation of difficulty in initiating a certain activity

Causes
Cancer related
• cachexia (see cachexia page)
• decreased food intake
  — nausea, vomiting, constipation, intestinal obstruction, diarrhoea, malabsorption, ‘squashed stomach syndrome’ in hepatomegaly, tumours, ascites, mouth and throat problems including infection, poor teeth, thrush, taste alteration
• metabolic problems
  — hyponatraemia, uraemia, liver failure, hypercalcaemia, anaemia from any cause
• emotional causes
  — anxiety, depression, fear, isolation, apathy, stress
• neuromuscular damage by tumour
  — to brain, spinal cord, peripheral nerves
• paraneoplastic syndromes e.g. Lambert-Eaton myasthenic syndrome, motor neuropathy
• radiotherapy and chemotherapy
• insomnia
• depression

Non-cancer related
• drugs
  — long-term steroids
  — some psychotropics
  — diuretics
  — antihypertensives
  — oral hypoglycaemics
  — statins
• neurovascular problems
  — transient ischaemic attacks, motor neurone disease, myasthenia gravis, Parkinson’s disease, peripheral neuropathies
• metabolic diseases
  — diabetes mellitus, Addison’s, hyper/hypothyroidism, tuberculosis, subacute bacterial endocarditis, connective tissue disorders

Management
• establish and where possible, treat or remove cause
  — review the drug regimen
  — correct metabolic abnormalities
• give dietary advice/support
  — increase calorific intake if appropriate
• exercise
  — exercise may be effective particularly in fatigue caused by radiotherapy
  — limited exercise programmes have been shown to be beneficial even in those close to the end of life
• drug therapy
  — hormones e.g. megestrol acetate, medroxyprogesterone
    > mechanism of action is unclear but dose related weight gain, improved calorie intake and improved sense of well-being have been reported
    > effect on fatigue is thought to be minimal
  — prokinetic antiemetics e.g. metoclopramide
    > decrease nausea and vomiting, increase food intake and appetite
    > no evidence of weight gain report
  — steroids e.g. dexamethasone
    > weight gain and fat deposition has been documented but with no increase in lean body mass
    > benefit may be transient
  — eicosapentaenoic acid (EPA) and nutritional support in combination with anti-inflammatory agents (COX2 inhibitors) have been used
  — stimulants e.g. methylphenidate, modafinil

Although these drugs may be effective in some patients with fatigue potential benefit should be weighed against adverse effects e.g. long-term steroids causing muscle weakness.
CACHEXIA
Cachexia can be distressing for both the patient and their family and carers. It is difficult to watch a person ‘waste away’ and is often perceived as a sign of impending death.
- cachexia (derived from the Greek kakos (bad) and hexis (condition))
- defined as a multifactorial syndrome with ongoing loss of skeletal muscle mass that cannot be fully reversed leading to progressive functional impairment
- diagnosis - weight loss greater than 5%, or 2% in individuals already showing depletion
- develops progressively through various stages - precachexia, cachexia, and refractory cachexia
- refractory cachexia or cancer anorexia cachexia syndrome - very advanced cancer (preterminal), active catabolism low performance status (WHO score 3 or 4), and life expectancy less than 3 months
- may complicate many chronic or end-stage diseases in addition to cancer
- it is not starvation, which can be reversed with nutrition
- distinct from age-related loss of muscle mass, primary depression, malabsorption syndromes and hyperthyroidism

Causes
The metabolic mechanism of the progressive wasting is uncertain.
- complex metabolic and catabolic processes occur with cytokines playing a major role
- tumour initiates an inflammatory response probably mediated by tumour-derived proinflammatory cytokines (interleukin-1, interleukin-6, interferon-gamma, tumour necrosis factor-alpha)
- cancer cachexia involves inflammation, hypermetabolism, neuro-hormonal changes, and the proteolytic and lipolytic factors
- enhanced substrate cycling (fat, carbohydrate and protein) occurs which is associated with metabolic inefficiency, weight loss and a suboptimal response to nutritional support (‘anabolic blockade’)
- neural pathways controlling energy homeostasis are disturbed (particularly the hypothalamic melanocortin system), promoting catabolic activity

Assessment
Cachexia should be considered if the patient has lost ≥ 5% of their body weight and/or has a BMI < 20kg/m² and 3 out of the following are present
- decreased muscle strength
- fatigue or reduced physical activity
- anorexia
- low fat-free mass index (low muscle mass)
- abnormal biochemistry
  - CRP > 5mg/L
  - IL-6 > 4pg/ml
  - Hb < 12g/dL
  - serum albumin < 32g/L

Treatments
- favourite foods
- un-pressured eating
- referral to a dietician
- drugs (efficacy is minimal for most)
  - dexamethasone 4mg/day for 5 days
  - medroxyprogesterone
  - megestrol
  - EPA (up to 2g per day)
  - cannabinoids
  - prokinetics e.g. metoclopramide
  - antidepressants e.g. mirtazapine
  - thalidomide
  - olanzapine

ANAEMIA
A significant proportion of people with advanced or chronic disease are anaemic.
- symptomatic anaemia usually presents when the haemoglobin is below 80g/L although, if chronic, patients may adapt to this concentration

Symptoms
- fatigue
- delirium
- dysphonia
- dizziness (postural hypotension)
- exacerbations of angina/heart failure

Causes (often multiple)
- chronic disease (normocytic)
- haemorrhage (microcytic, low iron levels)
- bone marrow failure (pancytopenic)
- malnutrition (macrocytic, folate and iron deficiencies)
- chronic renal failure (reduced erythropoietin production)

Management
- blood transfusion
  - rarely improves symptoms significantly for any length of time but may be considered prior to further active treatment or a significant family event
  - it is often easier to give a transfusion rather than deal with the negotiation involved in not treating although the latter may be more appropriate
  - time, attention to detail and information for the patient and the family are all essential in the decision making and consent process
- erythropoietin
  - expensive, not readily available and response can be slow and limited
HYPERCALCAEMIA OF MALIGNANT DISEASE
The symptoms and signs of hypercalcaemia are often insidious in their onset. It can be classified as a paraneoplastic syndrome.

- should be considered in patients who have vague symptoms
- consider appropriateness of treatment before a calcium blood test
- if the patient has a serum calcium > 2.6 mmol/L consider treatment

Symptoms

- thirst and dehydration
- increased urinary output
- constipation
- loss of appetite
- nausea and or vomiting
- fatigue
- pain - usually back and abdominal
- confusion, depression

Causes

- bone metastases
- increased bone metabolism
- decreased renal clearance of calcium
- dehydration
- enhanced absorption from the gut

Management

- make the diagnosis
- decide about the most appropriate course of action together with the patient, family and team
- consider stopping diuretics, vitamin D and calcium
- the aim is to provide symptom relief and reduce serum calcium to an acceptable level using minimal intervention
  - mild to moderate (serum calcium 2.6 to 3.0 mmol/L)
    > initially oral then, if necessary, iv rehydration
    > consider steroids
  - moderate to severe (serum calcium 3.0 to 3.5 mmol/L)
    > initially iv or sc rehydration
    > 2 to 3 L normal saline / 24 hours
    > then iv/sc bisphosphonate (may take 72 hours to work)
    > pamidronate 90mg iv infusion (can be given as a subcutaneous infusion)
    > zoledronic acid 4mg iv infusion can be used but is significantly more expensive
    > calcitonin may be useful when bisphosphonates begin to fail

ORGAN FAILURE

Renal Failure
The following does not apply to patients who are being dialysed. For information on drug dosing during dialysis consult a renal specialist or drug information service.

Symptoms

- oedema (from sodium and water retention)
- restless legs (may respond to clonazepam, very low dose gabapentin)
- itch (from raised urea or phosphate)
- nausea/vomiting (from increased toxins)
- fatigue (from anaemia)

Management

- the same as those outlined in the relevant sections e.g. nausea/vomiting
- when pain is an issue remember that
  - morphine’s metabolite is renally cleared so use fentanyl or methadone instead (or perhaps oxycodone)
  - NSAIDs increase sodium and water retention, are nephrotoxic and if urea is raised risk of GI bleed increases so avoid

Drug dosing

- as the kidneys fail creatinine plasma concentrations will rise
- many labs around New Zealand now report an estimated glomerular filtration rate (eGFR) - there is some debate as to whether this can be used to adjust the doses of renally cleared drugs
- to calculate how well the kidneys are functioning, calculate creatinine clearance in mLs/minute using the Cockcroft and Gault equation:

  \[
  \text{Cr Cl (mLs/min)} = \frac{(140 \text{- age}) \times \text{ideal body weight (kg)}}{\text{plasma creatinine (umol/L) } \times 0.8} \times 0.85 \text{ if female}
  \]

  (ideal body weight = 50kg + 0.9kg for each cm above 150cm [replace 50kg with 45 kg if female])

- the creatinine clearance is important in the dosing of renally cleared drugs e.g. gabapentin or drugs whose metabolites are renally cleared e.g. morphine (see end section)
- for drugs that are almost completely renally cleared the dose regimen is a proportion of the normal dose:

  \[
  \text{Adjusted dose} = \frac{\text{calculated creatinine clearance}}{100\text{mL/min}} \times \text{normal dose}
  \]
Liver Failure
End stage liver failure is usually seen with liver metastases, liver primary and/or past alcohol abuse/hepatitis.

Symptoms
- raised liver enzymes
- jaundice
- ascites
- itch
- encephalopathy
- low albumin and raised INR

Drug dosing
- there is no single marker for liver dysfunction but albumin concentrations and INR are a measure of how well the liver can clear drugs (its metabolic capacity)
- doses of metabolised drugs (drugs that are mainly cleared from the body by the liver rather than the kidneys i.e. approx 70% of drugs) should be adjusted in liver failure
- doses of metabolised drugs may need to be reduced by 25% in mild to moderate liver failure
- in severe liver failure (albumin of < 30g/L and an INR of > 1.2) decrease doses by approximately 50%

Management is the same as that outlined in the relevant sections.

Cardiac Failure
The treatment of patients with end stage cardiac failure centres around the relief of the accompanying symptoms -
- dyspnoea
- cough
- fatigue
- immobility
- oedema

Treatment of the symptoms is the same as for other causes in palliative care. Perhaps the most difficult part of the management of these patients is when and how to discontinue the many cardiac medications prescribed. As yet there is no clear evidence for the order or rate of discontinuation. Negotiation with patient, family and cardiologist may produce agreement on a process for this. Once swallowing becomes a problem consideration should be given to stopping medications.

PALLIATIVE CARE EMERGENCIES

HAEMORRHAGE
Haemorrhage is distressing for all concerned and should be treated with urgency.
- in many situations the sight of blood is indicative of impending death and many patients and families experience a significant increase in anxiety - use red towels if possible
- staff are often alarmed by haemorrhage, as they often feel helpless to ‘do’ anything to prevent it
- anticipation of bleeding is sometimes possible and can be discussed with the patient and family

Management
If the patient has been taking warfarin stop it and consider reversal with fresh frozen plasma or Vitamin K. If taking other anticoagulants e.g. enoxaparin or dabigatran stop them and consult a haematologist as not reversed by Vitamin K.

Haemoptysis/ENT cancers
- mild
  - re-assurance
- moderate
  - radiotherapy
  - bronchoscopy if appropriate
  - laser treatment if appropriate
- severe and rapid
  - sc midazolam and/or morphine
  - have someone stay with the patient
- severe and slower
  - suction if appropriate
  - physical touch (reassures patient)
  - drugs as for severe and rapid
- other drug therapy
  - tranexamic acid 1 to 1.5g po two to four times daily (inhibits plasminogen activation and fibrinolysis)
  - sucralfate for oral bleeding

Upper gastro-intestinal tract
- minimise causes e.g. discontinue NSAIDs
- treat gastritis and peptic ulceration
  - drug therapy (perhaps parenterally)
    > proton pump inhibitor e.g. omeprazole
    > H2 antagonist e.g. ranitidine
  - radiotherapy and/or surgery may be appropriate

Lower gastro-intestinal tract
- radiotherapy and/or surgery may be appropriate
• drug therapy
  — tranexamic acid rectally
  — rectal steroids e.g. hydrocortisone rectal foam

Haematuria
• may occur with infection so check and treat if appropriate
• radiotherapy may help if tumour is present in the urinary tract
• endoscopic surgery may be appropriate
• drug therapy
  — tranexamic acid orally (as before)

Vaginal
• often due to infection so treat with antifungals and/or antibiotics
• palliative radiotherapy may help

SPINAL CORD COMPRESSION
This is a relatively uncommon problem that requires urgent and effective management.
• it is one of the true medical emergencies in palliative care
• once paralysed 95% will not walk again

Symptoms
• pain (usually before neurological symptoms)
• weakness especially of lower limbs
• sensory disturbance
• loss of sphincter control

Management
• urgent assessment
  — history and clinical findings
  — MRI examination
• referral to radiation oncology is usually most appropriate
• as soon as the diagnosis is made or suspected
  — dexamethasone 16mg daily, for a few days then tapered down according to symptom response
  — radiation therapy should be given concurrently
• decompressive laminectomy is rarely undertaken but should be considered as an option.

Decompressive laminectomy is rarely undertaken but should be considered as an option.

DIABETES, HYPERGLYCAEMIA AND HYPOGLYCAEMIA
The pathophysiology of diabetes in the palliative care setting (and particularly in the terminal phase) may be complex as the
• control of blood sugar may be lost due to insulin resistance associated with illness and also because of erratic nutritional intake.
• certain malignancies e.g. pancreatic cancer also affect the beta cells directly which control of blood glucose concentrations is important in palliative care as both hyperglycaemia and hypoglycaemia may cause symptoms resulting in a loss in the quality of life e.g. marked hyperglycaemia may exacerbate pre-existing cachexia - in the catabolic state insulin has an anabolic effect
• management must balance treatment tolerability (including tolerability of blood glucose monitoring if required) with treatment efficacy and symptom control

Diabetes
Type 2 diabetes (previously called non insulin dependent diabetes (NIDDM))
• patients usually have some beta cell (insulin producing) function
• tight control of blood glucose concentrations is not necessary, although if it is easily achievable it may increase quality of life
• relax usual dietary restrictions and adjust insulin/hypoglycaemic agent use as appropriate
• if the patient is taking metformin consider discontinuing it to avoid the adverse effects of metformin e.g. nausea, weight loss and lactic acidosis. There may be a need to add a different drug e.g. insulin
• if the patient is taking a thiazolidinedione e.g. pioglitazone, rosiglitazone there is a risk of developing peripheral oedema so consider stopping if near to the end of life
• if the patient is taking a dipeptidyl peptidase inhibitor e.g. sitagliptin this should be continued
• weight loss reduces blood glucose concentrations so requirements for antidiabetic agents may reduce as weight is lost
  — once weight loss begins or appetite decreases, halve the dose of antidiabetic agent in previously well controlled patients
  — reduce doses further or stop as required
• on admission to a hospice oral hypoglycaemic agents will not be required unless there is an infection or other serious stress in which case
  — monitor blood glucose concentrations every two days (after the main meal if possible) and treat hyperglycaemia if symptomatic
• symptoms of HYPERGLYCAEMIA will usually appear at blood glucose concentrations of > 15 mmol/L so treatment should begin only above this concentration
  — avoid HYPOGLYCAEMIA during this treatment as it may be difficult to reverse without systemic therapy especially if the patient is vomiting or not eating
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  — give a fast acting insulin analogue e.g. lispro (Humalog™) or glulisine
— skin infection
— confusion
• at blood glucose concentrations of > 40 mmol/L
— drowsiness
— obtundation
— coma

NB Some of these symptoms may be present in terminally ill patients in the absence of high blood glucose concentrations.

**Causes**

• in diabetic patients
  — lack of insulin or hypoglycaemic agent
  — loss of dietary control
  — stress, illness
  — infection
  — myocardial infarction
  — GI motility disorders and obstruction
• in non-diabetic patients
  — malignant disease
    — over 1/3 of cancer patients will develop Type 2 diabetes (NIDDM) - an effect on metabolism
• drugs (even in non-diabetic patients)
  — corticosteroids e.g. dexamethasone, prednisone
  — diuretics (at high dose) e.g. bendrofluazide, frusemide

**Management**

• in active palliative care patients
  — closely monitor blood glucose concentrations as this may help them to retain function
• in patients who are close to death
  — aim for minimal monitoring and maximal comfort
  — ‘treat the patient rather than blood glucose concentration’
  — aim for maximum quality of life by loosening control of blood glucose and encouraging eating if appropriate
• in Type 2 diabetes (non-insulin dependent) patients
  — often rehydration will partially reverse hyperglycaemia
  — BUT insulin (often only once a day) may be necessary
• in Type 1 diabetes (insulin dependent) patients
  — give insulin at least twice a day (continue with patients usual regime if possible) basing the dose on body weight and predicted carbohydrate intake
  — withdrawal of insulin in these patients will lead to diabetic ketoacidosis (acidosis, shock then death)
  — if diabetic ketoacidosis occurs treat with rehydration and iv insulin if appropriate

Hyperglycaemia

**Symptoms**

• at blood glucose concentrations of < 15 mmol/L
  — major symptoms are rare
• at blood glucose concentrations of 15 to 40 mmol/L
  — dehydration, dry mouth
  — thirst
  — polyuria
  — lethargy
  — blurred vision
  — candidiasis

(Apidra™) insulin 2 to 4 hourly initially (usually for 24 hours) in doses determined by monitoring - usually 5 to 10 units BUT tailor dose to both the size of the patient and food intake

— once in the range 10 to 15 mmol/L convert to an intermediate or long acting insulin e.g. isophane insulin (Protaphane™) or glargine (Lantus™) once or twice daily injections at 75% of the 24 hour short acting dose. Chart a fast acting insulin analogue e.g. lispro (Humalog™) or glulisine (Apidra™) insulin to be used for breakthrough hyperglycaemia (post-prandially if eating).

— monitor fasting blood glucose concentrations daily for several days then twice per week
— discuss all management with the patient to avoid misinterpretation

Type 1 diabetes (previously called insulin dependent diabetes (IDDM)) — these are the minority of patients who are on insulin and have usually been diagnosed in childhood or early in adult life. Other patients (the majority) on insulin will have started it in later life and the following does not apply (see Type 2).

— insulin must be continued even in the terminally ill to avoid diabetic ketoacidosis. Consider capillary beta hydroxyl-butyrate monitoring - if > 1.2mmol/L ketosis is likely and should be treated if appropriate.
— tight control is not necessary
  — a blood glucose concentration of 10 to 15 mmol/L is a good target unless patient is symptomatic
• if the patient is well nourished and has a steady oral intake
  — maintain the usual dose of insulin
  — monitor blood glucose concentrations twice a day every 3 days
  — when appetite decreases, increase blood glucose concentration monitoring and decrease insulin
• if patient is vomiting, is no longer eating or has a variable appetite
  — use a base line long acting insulin e.g. glargine (Lantus™) daily and chart a fast acting insulin analogue e.g. lispro (Humalog™) or glulisine (Apidra™) insulin to be used for breakthrough hyperglycaemia (post-prandially if eating)
  — monitor frequently
• if the patient is near to death
  — discuss continuation of insulin with patient and family

Type 2 diabetes (NIDDM) — an effect on metabolism

— over 1/3 of cancer patients will develop Type 2 diabetes (NIDDM) - an effect on metabolism

— in non-diabetic patients
  — malignant disease
  — > over 1/3 of cancer patients will develop Type 2 diabetes (NIDDM) - an effect on metabolism
— in non-diabetic patients
  — corticosteroids e.g. dexamethasone, prednisone
  — diuretics (at high dose) e.g. bendrofluazide, frusemide

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Management

- treat/ remove causes where possible
- give glucose
- monitor blood glucose concentrations

**USING STEROIDS**

Steroids are often seen as cure-all/miracle drugs in palliative care. Careful consideration should be given to initiating these drugs as they have many adverse effects. Most of the use in palliative care is for unlicensed and/or non-evidence based indications e.g. spinal cord compression, nerve compression, dyspnoea (from a number of causes), SVC obstruction and inflammation following radiation therapy, pain relief, anti-cancer hormone therapy, appetite stimulation and the enhancement of well-being.

**Adverse effects**

- diabetes mellitus
- osteoporosis
- avascular bone necrosis
- mental disturbances
  - insomnia, paranoid psychosis, depression, euphoria
  - muscle wasting (predominantly proximal myopathy)
- peptic ulceration - not as severe as NSAID induced ulceration but of concern particularly in the elderly or patients with other risk factors
- skin thinning
- immunosuppression
  - infection - candidiasis, septicaemia
  - poor wound healing
- sodium and water retention - leading to oedema
- potassium loss
- hypertension
- Cushing’s syndrome
  - moon-like face
  - striae
  - acne

**Prescribing**

- a trial of 5 days at 4 to 16mg dexamethasone (dose dependent on indication) should be considered after benefit/risk has been assessed and discussed
  - dexamethasone is the preferred drug - prescribe as a single or 2 morning doses (before noon) to avoid sleep disturbance
- consider gastric protection with a PPI e.g. omeprazole particularly in the elderly
- consider blood glucose monitoring (particularly if continuing)
- higher doses may be required if the patient is taking CYP enzyme inducers e.g. phenytoin and lower doses with inhibitors e.g. fluconazole
- withdraw completely if used for less than 2 weeks and < 6 mg dexamethasone. Otherwise tail off by 2mg every 5 to 7 days until 2mg od, then by 0.5mg every 5 to 7 day

**Hypoglycaemia**

**Symptoms - CNS**

- behaviour changes, anxiety
- confusion
- fatigue
- seizures
- loss of consciousness

**Symptoms - peripheral**

- palpitations
- tremor
- sweating
- hunger
- paraesthesia
- pallor
- increased heart rate

**Causes**

- diseases
  - insulinomas (rare)
  - autoimmune disease
  - infection (sepsis)
  - carcinoid
- failure to monitor correctly
- organ failure
  - renal, hepatic, cardiac
- diet - low food intake
- drugs
  - insulin
  - hypoglycaemic agents e.g. glipizide
  - alcohol
  - quinine
  - pentamidine

**Management**

- treat/ remove causes where possible
- give glucose
- monitor blood glucose concentrations
Recognising the ending of a life may seem relatively easy or obvious but in practice the 'diagnosis of dying' may be challenging for individuals or teams. Signs may include:

- the patient becoming increasingly weak, sleepy, disinterested in getting out of bed, seeing anyone other than close family, less interested in surroundings, confused or agitated
- symptoms becoming more apparent and physical changes suggesting the body closing down becoming more noticeable (skin colour changes, skin temperature changes, slowing of respiration or Cheyne-Stokes respiration, involuntary twitching or moaning)

**Management**

- planning for the death is important
- if in an institution ensure that advance care plans indicate that the person is not for resuscitation
- ensure cultural or religious wishes are known and followed
- ensure that the patient and family are aware of the progression of disease and let them know what you expect to happen
- much anxiety near the end of life is engendered by a fear of the unknown so provide information about those things that are known to mitigate feelings of uncertainty
- anticipate what might happen rather than wait for a crisis
- anticipatory prescribing is considered to be best practice - analgesics, antiemetics, anxiolytics and antisecretory drugs should all be considered remembering that the oral route will probably be lost so use the sc route

**Common symptoms**

- **Pain** (see pain page)
  - opioids are the predominant analgesics used
  - if the oral route is not feasible then consider
    - fentanyl patches - not suitable for unstable pain but may be useful as an alternative to oral analgesic
    - sc boluses prn or continuous infusion
    - conversion from oral to sc is 2:1 for morphine and oxycodone i.e. 10mg oral = 5mg sc

- **Nausea/vomiting** (see nausea/vomiting page)
  - not usually a great problem unless there is intestinal obstruction or it has previously not been controlled

- **Agitation/distress/anxiety** (see fear, anxiety, delirium pages)
  - if are there fears/worries/tensions/spiritual issues consider what has helped in the past
  - consider and address constipation/urinary retention/pain

**Oral/buccal drugs**

- lorazepam tablets 0.5 mg to 1mg bd
- clonazepam drops (2.5 mg/mL - 0.1mg per drop)
- midazolam sublingually or buccally (between gum and cheek)

**Subcutaneous drugs**

- midazolam 10 mg over 24hrs is a usual starting dose if not on benzodiazepine previously
- clonazepam boluses may be useful

**Confusion** (see delirium page)

- **Non-pharmacological management**
  - look for reversible causes
  - aim for minimal disruption and have familiar people in the room

- **Oral drugs**
  - haloperidol drops (2mg/mL - 0.1mg per drop), initiate at 1 to 2mg prn and titrate to response (much higher doses may be required - see haloperidol page)
  - in frail or elderly patients an initial dose of 0.5 to 1mg prn may be sufficient

- **Subcutaneous drugs**
  - haloperidol by continuous infusion 1 to 10mg over 24 hours
  - boluses of 1 to 2mg may also be used

**Excess secretions** (see excessive (retained) secretions page)

- **Non-pharmacological management**
  - consider position change
  - it may be distressing to the family/carers rather than the patient

- **Drugs**
  - hyoscine (Scopaderm™) patch may be applied behind the ear although confusion and other anticholinergic side effects may occur
  - hyoscine butylbromide may be useful - 20 mg sc followed by 30 to 60mg by continuous subcutaneous infusion over 24 hours
  - secretions may become thickened and plugs may form

**After death review**

It can be helpful for teams to review what happened in order to learn from each patient and family

- What things went well and what lessons have been learned that can be carried to the next person and family?
- Did the patient and family resolve all unfinished business?
- Were all opportunities to say goodbye taken?
- Was death peaceful and dignified?
- Was everything possible done to care for the family and friends?
- How could care have been improved?
- How does each of the team of professional carers feel?
PALLIATIVE CHEMOTHERAPY

- palliative (i.e. non-curative) active treatments include surgery, chemotherapy and radiotherapy
- two thirds of all chemotherapy treatments given are with ‘palliative’ intent
- the aim is the palliation of symptoms but the benefit of treatment should exceed the adverse effect on quality of life

Benefits
- symptom management
- increase in quality and quantity of life

Adverse effects
- unrealistic hope
- avoidance of ‘death talks’ and preparations
- nausea / vomiting
- lethargy / fatigue
- loss of taste
- peripheral neuropathies e.g. with vincristine
- alopecia
- diarrhoea
- constipation
- stomatitis

ALTERNATIVE THERAPIES

Complementary and Alternative Medicines (CAM) are widely used in New Zealand.
- it is important for a drug history to include all medicines including CAMs
- CAM can sometimes adversely impact on conventional therapies
- CAM use may be influenced by cultural beliefs and behaviours
- there is no universally agreed definition of CAM but The World Health Organisation defines it as:
  ‘A broad set of health care practices that are not part of a country’s own tradition and not integrated into the dominant health care system. Other terms sometimes used to describe these health care practices include ‘natural medicine’, ‘non-conventional medicine’ and ‘holistic medicine’.
- the Medical Council of New Zealand has produced a statement on CAM that can be found at www.mcnz.org.nz

Health professionals unfamiliar with CAM therapies that their patients are taking should seek information from a drug information pharmacist.
**QUALITY OF LIFE**

The primary goal of palliative care is to optimize the quality of life for patients and their families by preventing problems, delaying their onset and reducing their severity.

There are many views on the nature of quality of life but one enduring view by Calman in 1984 (see further reading) is that quality of life “can be defined as subjective well-being reflecting differences or gaps between hopes and expectations and current experiences.”

The aim of care near the end of life is to

- provide ‘appropriate’ palliative care
- provide and maintain improvement in patients’ quality of life
- achieve a ‘good death’ for the patient and family

However, health professionals and patients often have different views on what aspects of disease and treatment are important. There are many ‘expert-derived’ tools available such as:

- McGill Quality of Life questionnaire
- Schedule for the Evaluation of Individual Quality of Life (SEIQoL)
- Missoula-VITAS quality of life index - encompasses a number of domains and is user-friendly (http://www.dyingwell.org/MVQOLI.htm)

It contains questions about

- symptoms - the level of physical discomfort and distress
- function - perceived ability to perform accustomed functions and activities of daily living and the emotional response, experienced in relation to expectations
- interpersonal aspects - degree of investment in personal relationships and the perceived quality of one’s relations/interactions with family and friends
- well-being - the individual’s internal condition i.e. a sense of wellness or unease, contentment or lack of contentment
- transcendent - degree of connection with an enduring construct, and of a meaning and purpose in life

It has also been suggested that there are a number of developmental milestones to be reached near the end of life that are helpful for practitioners and patients alike to recognise including:

- to sense completion of worldly affairs, of relationships with the community and family and friends
- to sense meaning about our own life and life in general
- to experience love of self and others
- to accept the finality of life – of one’s existence
- to sense a new self (personhood) beyond personal loss
- to surrender to the transcendent, to the unknown – letting go

**SPIRITUALITY**

Part of the “task of dying” for the patient and the family is to address spiritual concerns. Spiritual and existential concerns are important for most people at end-of-life. Spiritual care should be routinely assessed, documented and addressed just as other elements of the patient’s care are. Spiritual concerns may influence other symptoms. Spiritual care needs to be patient-led and a normal part of history taking and care plans at end-of-life.

- there is no universally agreed definition of spirituality. It includes the existential to the religious, means different things to different people and may involve a search for: ultimate beliefs/values; a sense of meaning/purpose in life; a sense of connectedness; identity and awareness; and for some people, faith and religion.
- spirituality is individually determined and culturally varied
- Spiritual paths include nature (garden, sea, wilderness), relationships (self, family, friends, God), aesthetic pursuits (art, poetry, music), metaphysical pursuits (silence, prayer, ritual, philosophy)
- spiritual distress/pain is that caused by the threats to the extinction of the being/person and their meaning of ‘self’. It is a similar construct to demoralisation, but not to clinical depression
- there is some agreement that religion and spirituality are different but related concepts with religion being within the broader category of spirituality although religion has become disconnected from spirituality for some

**Spirituality Assessment (or Discernment):**

The majority of seriously ill patients are likely to want their spirituality attended to; however there is a proportion who will find this intrusive. Questions that may initiate conversations are:

- “are you at peace?”
- “what does your illness mean to you?”
- “tell me about your faith?”
- “how is your illness challenging your relationship with your God?”
- “you must be wondering “Why me”?”
- “do you have a belief in an afterlife?”
- “what gives your life meaning?”

Alternatively a spiritual wellbeing survey may be used e.g.: FACIT sp 12 Copyright © 2010 FACIT.org

“Over is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.”
**Advance Care Planning (ACP) and Advance Directives (AD)**

- ACP is the process of discussion and planning for future health care in the context of anticipated deterioration of health. Not everyone will choose to participate in ACP.
- It involves the patient, health care professionals, and family/carers.
- It incorporates the patient’s beliefs, values, culture, preferences for care, current and anticipated medical status and treatment options.
- The patient has to be competent to participate.
- It should take place early in the course of a terminal illness but can happen at any time.
- It may result in:
  - A conversation and shared understanding between patient and health professionals.
  - Documentation of an ACP plan.
  - Writing of an Advance Directive (see below).
  - The appointment of an enduring power of attorney/surrogate decision-maker.
- It is the articulation of wishes, preferences, values, and goals.
- It respects personal autonomy and medical reality.
- It should be used to inform decision-making, even in acute medical emergencies.
- It should be regularly reviewed and updated – it is a flexible ‘living’ document.
- It is open to change, revision, and cancelation.
- It is not confined to medical issues – may include spiritual or interpersonal issues.

**Dealing with Spiritual Distress:**

- A non-judgemental approach involving presence, compassion, and empathic and contemplative listening should be used.
- The creation of space ('a safe place to suffer'), being with and listening to ('to be with and to bear witness'), touch and encouraging experiencing the natural and artistic worlds are useful approaches.
- Spiritual care is generally agreed to be the role of all those involved in care, with the need to involve a specialist as important as any other aspect of medical care.
- More specialised interventions include retreats, group therapy, meditation and religious rituals.
- Theological beliefs and conflicts should be referred to a chaplain/pastoral care worker.
- Ethical spiritual care is critical. Proselytizing is widely understood to be unethical.

**Negative Effects of Spirituality**

Not all effects associated with spirituality in the health setting are positive. The negative aspects of spirituality are mostly to do with 'religious spirituality'. These include punishment or abandonment by God, religious pressure, guilt, stress, afterlife questions, and malign spirit visitations. The latter and other unexplained phenomena are quite common and need to be heard compassionately. In most cases referral to a spiritual specialist is recommended.
**Competency or capacity**
- an individual’s ability to perform a particular task at a particular point in time e.g. a decision regarding their current or future health care includes competency and capacity
- all adults can be presumed to have capacity
- competency may fluctuate depending on the issues under consideration
- the patients needs to be able to understand information relevant to the decision, to reason and deliberate, to retain the information (even for only a short time), to communicate by any means
- capacity does not necessarily imply rationality
- if capacity is not possessed decisions must be taken by others in that person’s best interests and in the least restrictive manner possible

**Legally authorised proxy/ surrogate decision-maker**
- if the patient is incompetent an individual with enduring power of attorney (EPA) or a court-appointed welfare guardian may make decisions. Family members do not have this right (unless they hold the EPA)
- the preferable surrogate is a close and mature relative. It is a difficult role
- in the absence of a legally authorised proxy clinicians make the required decisions (but family should be included)
- all decisions must be made with patients’ best interest in mind and tend to be conservative and life-affirming
- EPAs may be for property, personal care and welfare, or both
- an AD requires a medical certificate stating mental incapacity under the Protection of Personal and Property Rights Act. EPAs are legally, not medically, determined

**Testamentary capacity**
- this is the legal and mental ability to make or alter a valid will
- the testator must have knowledge of extent and value of their property, knowledge of their natural beneficiaries, and the ability to communicate this knowledge

**Grief and Loss**
Grief is the distressing emotional response initiated by the death of a loved and attached person, or a loss.
- it is a normal, adjustment process
- spontaneous recovery occurs over time for the majority
- grief begins at loss/diagnosis
- there are not specific stages of grief. Grief is never fully resolved
- modern society is death-denying and death-defying
- symptoms include sadness, anger, waves of distress, tearfulness, initial insomnia, pining, haunting reminiscences, fleeting auditory or visual pseudo-hallucinations or a sense of presence of the departed
- mourning is the behavioural response of grieving. Culture and social norms are determinants. Mourning customs serve to organise, protect and support the grief-stricken
- grief is age-influenced. Children do not develop the capacity to appreciate the permanency of death until aged 9-10. In the elderly grief may be curtailed if the death is expected
- grief therapy may be ineffective and potentially harmful, except in distressed/complicated grievers

**Complicated grief:**
- intense and/or protracted (> 1-2 years)
- it is characterised by prolonged longing and yearning for the deceased, intrusive thoughts or images, anger, guilt, emotional numbness, avoidance of reminders and difficulties redefinition
- it occurs in 10-15% of bereaved people
- it is accompanied by increased psychological and physical morbidity, substance abuse and suicide
- risk factors include sudden, unexpected, traumatic death, pre-existing dependant or ambivalent relationship, psychological/psychiatric vulnerability, disenfranchised grief (the hidden grief of those socially unable to express their response), compounded by major depression or substance abuse

**Management of Grief**
- ‘death talk’ (anticipatory grief) and advance care planning may mitigate/moderate
- early identification of those at high risk, bereavement follow-up
- support, empathy, normalisation, offer pragmatic information/education
- encouraging adaptation and restructuring of a world without the lost one, acknowledgement of the emotional ‘scar’
- short term mild hypnotic medication if marked insomnia
- specific counselling e.g. Cognitive Behavioural Therapy if complicated grief, perhaps with antidepressant medication
- cathartic expression of distress is of minimal, if any, benefit
PHARMACOPOEIA

Drugs listed are preferred choices in palliative care.

BISACODYL
(Bisacodyl (AFT), Dulcolax™, Fleet Laxative Supp™, Lax-Tab™)
Class: laxative - stimulant
Indication: constipation
Contraindications/cautions: acute abdominal pain, intestinal obstruction
Adverse reactions: common abdominal cramps, diarrhoea, perianal irritation (usually with suppositories) less common atonic colon (on prolonged use), hypokalaemia
Metabolism/clearance: mainly excreted in faeces
Interactions:
• decreased clinical effects of antispasmodics (e.g. hyoscine butylbromide) may occur due to stimulant effects of bisacodyl
Dosing:
oral: 5 to 10mg at night or 5mg twice a day
rectal: 10mg at night
Syringe driver: not available
Mechanism of action: stimulates colonic activity via nerves in the intestinal mucosa
Onset: oral: 6 to 12 hours rectal: 20 to 60 minutes
Availability:
Tab 5mg fully funded (Lax-Tab™)
Supp 5mg, 10mg fully funded (Dulcolax™)
Cost: Approx $0.02 per tab, $0.50 per supp
Notes: May be useful in opioid induced constipation especially in combination with a softener.

BACLOFEN
(Alpha-baclofen™, Pacifen™, Lioresal™)
Class: GABA derivative musculoskeletal muscle relaxant
Indication: relief of musculoskeletal spasm
Contraindications/cautions: epilepsy, sc injection, psychosis, schizophrenia, depression, mania, GI ulceration, cerebrovascular disease, alcoholism, diabetes (may increase blood glucose concentrations), hypertension
Adverse reactions: common nausea, sedation, somnolence less common decreased cardiac output, hypotension, GI disturbance, respiratory depression, lightheadedness, personality changes, headache, insomnia, euphoria, depression, weakness, tremor, hallucinations, dry mouth, tinnitus
Metabolism/clearance: mainly excreted in urine unchanged (70%) so dose adjust in renal impairment
Interactions:
• additive drowsiness and CNS depression with other CNS depressant drugs e.g. alcohol, benzodiazepines (e.g. clonazepam), opioids
• increased muscle relaxation with tricyclic antidepressants e.g. nortriptyline
Dosing:
oral: 5 to 20mg three to four times a day (start at 5mg three times a day)
sc: not available
Mechanism of action: works in the spinal cord where it stimulates GABA-receptors which inhibit the release of glutamate and aspartate (excitatory). Also has a CNS depressant action.
Onset: variable - hours to weeks
Availability:
Tab 10mg fully funded (Pacifen™)
Inj (IT) 0.05mg/mL, 10mg/5mL not funded
Cost: Approx $0.05 per tab, $10.50-$190.80 per injection
Notes: Stopping abruptly may result in a withdrawal reaction (confusion, psychosis, tachycardia, hyperthermia and rebound spasticity).
BUPRENORPHINE
(Temgesic™, Norspan™) (in combination: Suboxone™)

Class: analgesic - opioid, partial mu agonist/kappa antagonist
Indication: moderate to severe pain
Unlicensed indications: subcutaneous injection/infusion
Contraindications/cautions: buprenorphine hypersensitivity/allergy, use with other opioids, adverse effects such as respiratory depression may not completely respond to naloxone, COPD, use with benzodiazepines
Adverse reactions: see morphine
Metabolism/clearance: metabolised by unclear pathway
Interactions:

- additive CNS depression with other CNS depressants e.g. benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), other opioids, alcohol

Dosing:
sublingual combo: not used
sc: not used
patch: 5 to 20mcg/hour (each patch lasts for 7 days)
Syringe driver: compatibility unknown so best to infuse on its own. Irritancy potential is unknown.

Mechanism of action: partially stimulates mu- and blocks kappa opioid receptors in the CNS and gastrointestinal tract
Peak effect: patch: 60 hours after initial application
Onset: 11 to 21 hours
Duration: patch: 7 days
Availability:
Patches: 5mcg, 10mcg, 20mcg/hour not funded
Injection: 300mcg/mL not funded
Sublingual Tabs with naloxone:
2mg/0.5mg, 8mg/2mg (for opioid dependence) not funded
Controlled drug form required.
Cost: Approx $1.88 per inj, approx $8.55 to $23.70 per patch
Notes:

- As buprenorphine is only a partial agonist of mu receptors and an antagonist of kappa receptors it should not be used with other opioids or within 24 hours of them as it may lead to severe opioid withdrawal.
- As patches last for 7 days and peak concentrations occur at 60 hours do not use in rapidly escalating pain.
- For acute toxicity give naloxone 2mg and repeat as required (max 10mg) over a prolonged time but be aware that full reversal of toxicity may not occur as buprenorphine binding to opioid receptors is high.
- Do not cut patches.
- Equivalence to other opioid data is sparse but 20mcg/hour patch may be equivalent to 90mg oral morphine per day.

CHOLESTYRAMINE
(Questran Lite™)

Class: anion exchange resin
Indication: hypercholesterolaemia, pruritis due to partial biliary obstruction, diarrhoea associated with ileal resection or cholerrhoeic enteropathy
Contraindications/cautions: complete biliary obstruction, diabetes, nephrotic syndrome, phenylketonuria, prolonged use, constipation
Adverse reactions: common constipation, faecal impaction, hyperchloraemic acidosis, perianal irritation, intestinal obstruction less common nausea, bloating
Metabolism/clearance: combines with bile acids and is excreted in the faeces - not absorbed
Interactions:

- decreased clinical effect/toxicity of some drugs (due to decreased absorption- see below)
- altered concentrations of some drugs that undergo enterohepatic recycling

Dosing:
oral 4 to 16g per day
Syringe driver: not available
Mechanism of action: binds bile acids which reduces plasma bile acid concentrations
Onset: pruritus: 4 to 7 days
Availability:
oral sachets 4g not funded
Cost: Approx $0.38 per sachet
Notes: As absorption of other drugs will be affected take all other drugs 1 hour before or 4 to 6 hours after cholestyramine. Sachet contents must be mixed with 100 to 150mL of fluid before administering.
**CITALOPRAM**
(Arrow Citalopram™, Celapram™, Cipramil™, Citalopram-Rex™)

**Class:** Antidepressant - SSRI (Selective Serotonin Re-uptake Inhibitor)

**Indication:** depression

**Unlicensed indications:** anxiety (chronic)

**Contraindications/cautions:** hepatic impairment, epilepsy, bleeding disorders, abrupt withdrawal

**Adverse reactions:** common nausea, sweating, tremor, diarrhoea (excessive serotonin), constipation, somnolence less common dry mouth, cough, postural hypotension, tachycardia, amnesia, taste disturbance, visual disturbances, pruritus, hyponatraemia, sexual dysfunction, QT prolongation

**Metabolism/clearance:** metabolised by metabolising enzymes CYP2C19 mainly in the liver

**Interactions:**
- increased clinical effect/toxicity of citalopram (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. fluconazole, fluoxetine, omeprazole, valproate
- decreased clinical effect/toxicity of citalopram (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. phenobarbitone, phenytoin, rifampicin
- additive risk of serotonin syndrome (potentially fatal syndrome - symptoms include sweating, diarrhoea, confusion) with other serotonergic drugs e.g. amitriptyline, carbamazepine, fluoxetine, paroxetine, tramadol, lithium
- increased risk of bleeding (antiplatelet effect) with anticoagulants

**Dosing:**
- oral: 10 to 40mg once a day
- sc/rectal: not available

**Syringe driver:** not available

**Mechanism of action:** blocks the reuptake of serotonin

**Onset:** depression 1 to 2 weeks anxiety or pain 3 to 7 days

**Peak response:** 5 to 6 weeks

**Availability:**
- Tab 20mg fully funded (Arrow Citalopram™)

**Cost:** Approx $0.03 per tablet

**Notes:**
- May not inhibit CYP2D6 to as great an extent as other SSRIs e.g. fluoxetine, paroxetine so less likely to interact with drugs that are metabolised by CYP2D6 e.g. codeine, haloperidol, ondansetron.
- Escitalopram (Loxalate™) is now available and funded as 10mg and 20mg tablets. Doses used are approximately half. May have fewer adverse effects.
- Doses of greater than 40mg per day have been associated with QT interval prolongation.

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**CLONAZEPAM**
(Rivotril™, Paxam™)

**Class:** anticonvulsant - benzodiazepine

**Indication:** epilepsy, convulsions

**Unlicensed indications:** sedation, anxiety, agitation, restless leg syndrome, neuropathic pain, dyspnoea, hiccupps, myoclonic jerks, subcutaneous injection /infusion

**Contraindications/cautions:** avoid sudden withdrawal, respiratory depression

**Adverse reactions:** common fatigue, drowsiness (at higher doses)

**Interactions:**
- increased clinical effect/toxicity of clonazepam (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. clarithromycin, fluconazole, fluoxetine, grapefruit juice, itraconazole, ketoconazole, valproate
- decreased clinical effect/toxicity of clonazepam (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. carbamazepine, dexamethasone, phenobarbitone, phenytoin, prednisone, rifampicin, St John’s wort
- additive CNS effects with other CNS depressants e.g. opioids (e.g. morphine), phenothiazines (e.g. chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), alcohol may occur with concomitant clonazepam

**Dosing:**
- oral: 10 to 40mg once a day
- sc/rectal: not available

**Syringe driver:** not available

**Mechanism of action:** may enhance the effect of GABA, an inhibitory neurotransmitter in the CNS

**Onset:**
- depression 1 to 2 weeks
- anxiety or pain 3 to 7 days

**Peak response:** 5 to 6 weeks

**Availability:**
- Tab 0.5, 2mg fully funded (Paxam™)

**Cost:** Approx $0.06 to $0.11 per tab, $0.74 per mL oral drops, $3.80 per 1mg inj

**Notes:**
- A long acting benzodiazepine so difficult to titrate to response.
- Benzodiazepines may reduce dyspnoea by anxiolytic and sedative effects.
- Approximate equivalent oral anxiolytic/sedative doses: diazepam 5mg = lorazepam 0.5 to 1mg = clonazepam 0.5mg = temazepam 10mg = midazolam 7.5mg = triazolam 0.25mg
**Pharmacological properties of benzodiazepines and other hypnotics**

<table>
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<tr>
<th>Drug</th>
<th>Anxiolytic</th>
<th>Night sedation</th>
<th>Muscle relaxant</th>
<th>Anticonvulsant</th>
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**CODEINE PHOSPHATE**

(Codeine phosphate (PSM), (Douglas), (USP, AFT))

(in combination - several different brand names)

**Class:** analgesic - opioid (metabolised to morphine)

**Indication:** step 2 in the WHO analgesic ladder, cough, diarrhoea

**Unlicensed Indication:** subcutaneous injection/infusion

**Contraindications/cautions:** avoid use with other opioid analgesics

**Adverse reactions:** as for morphine - very constipating

**Metabolism/clearance:** metabolised by metabolising enzyme CYP2D6 mainly in the liver to an active metabolite - morphine. Minor metabolism by 3A4/5/7.

**Interactions:**
- decreased clinical effect/toxicity of codeine (due to decreased blood concentrations of morphine - an active metabolite) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. bupropion, fluoxetine, paroxetine (not citalopram), quinine
- additive CNS effects with other CNS depressants e.g. benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), other opioids, alcohol may occur with concomitant codeine
- inhibition of the antidiarrhoeal effects of codeine may occur with concomitant metoclopramide/domperidone

**Dosing:**

- pain, cough and diarrhoea:
  - oral: 15 to 60mg 4 to 6 hourly (Max. 240mg in 24 hours)
  - sc: not recommended - use other opioid instead
  - rectal: not available

**Syringe driver:** available as injection but not used

**Mechanism of action:** metabolised to morphine and other active metabolites

**Peak effect:** 2 to 4 hours  **Duration:** 4 to 8 hours

**Availability:**

- Tab 15mg, 30mg, 60mg fully funded (PSM) with paracetamol tabs fully funded (ParaCode™, Relieve™)
- Inj 50mg/mL not funded

**Cost:** Approx $0.05 to $0.18 per tablet, $0.03 per combination tab, $6.26 per 50mg inj

**Notes:**
- Combination products are not recommended.
- 10% of dose is converted to morphine in “normal” metabolisers i.e. 60mg codeine = 6mg morphine.
- 5 to 10% of the Caucasian population may be unable to metabolise codeine to morphine.
- Combination with other opioids is illogical.
- Dihydrocodeine slow release is available although it is not often used in palliative care.
CYCLIZINE
(Nausicalm™, Valoid (AFT™))
Class: antiemetic - antihistaminic
Indication: nausea/vomiting (including motion sickness)
Unlicensed indications: subcutaneous injection/infusion
Contraindications/cautions: prostatic hypertrophy, narrow angle glaucoma
Adverse reactions: common drowsiness, restlessness, dry mouth, blurred vision, constipation less common insomnia, hallucinations (more common in elderly), arrhythmias
Metabolism/clearance: metabolised in the liver mainly to norcyclizine
Interactions:
• additive CNS effects with other CNS depressants e.g. benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), opioids, alcohol
Dosing:
oral:  25 to 50mg three times a day (cyclizine hydrochloride)
s:  75 to 150mg/24 hours (cyclizine lactate) (well diluted)
rectal: not available
Syringe driver: see syringe driver compatibility table.
Mechanism of action: acts on the histamine receptors in the vomiting centre in the CNS and has anticholinergic properties
Peak concentration: approx 2 hours
Availability:
Tab 50mg fully funded (Nausicalm™)
Inj 50mg/mL fully funded (Nausicalm™)
Cost: Approx $0.16 per tab and $2.99 per 50mg inj
Notes:
• Although there is a theoretical interaction with prokinetic antiemetics (prokinetics stimulate the gut while cyclizine slows it down) use together is common and may be justified on the basis of central nervous system receptors antagonism.

DANTHRON AND POLOXAMER
(Pinorax™)
Class: laxative - stimulant with faecal softener
Indication: constipation – prophylaxis and treatment in terminally ill patients only
Unlicensed indications:
Contraindications/cautions: acute abdominal pain, intestinal obstruction
Adverse reactions: common abdominal cramps, diarrhoea, perianal irritation, pink or red urine/perianal skin (can lead to excoriation in incontinent patients) less common atonic colon (on prolonged use), hypokalaemia (GI loss)
Metabolism/clearance: poorly absorbed, hydrolysed in the gastrointestinal tract
Interactions:
• decreased clinical effects of antispasmodics e.g. hyoscine butylbromide may occur with concomitant danthron/poloxamer
Dosing:
oral: (prophylaxis and treatment):
Susp 5 to 10mL at night
Susp Forte 5 mL at night
s: not available
rectal: not available
Syringe driver: see syringe driver compatibility table.
Mechanism of action: stimulates colonic activity via nerves in the intestinal mucosa (danthron) and increases fluid uptake by stools thus softening them (poloxamer)
Onset: oral 6 to 12 hours
Availability:
Oral susp: danthron 25mg, poloxamer 200mg/5mL fully funded (Pinorax™)
Oral susp: danthron 75mg, poloxamer 1g/5mL fully funded (Pinorax Forte™)
Only for terminally ill patients (due to association of danthron with tumours in rats)
Cost: Approx $0.16-$0.23 per 5mL
DEXAMETHASONE
(Dexamethasone (Biomed), (Douglas), dexamethasone sodium phos (DBL, Hospira))

Class: corticosteroid - glucocorticoid

Indication: cerebral oedema (raised intracranial pressure), allergy/anaphylaxis, replacement, shock, collagen diseases, asthma, respiratory insufficiency, leukaemia, lymphoma, rheumatic disease, psoriasis, colitis, enteritis, hypercalcaemia of malignancy

Unlicensed indications: nausea/vomiting, sweating, itch, hiccup, pain, liver capsule pain, tenesmus, subcutaneous injection

Contraindications/cautions: infections, GI bleeding

Adverse reactions: common insomnia (decrease by giving as single dose in the morning) less common sodium/fluid retention, GI ulceration, delayed wound healing, thinning of skin (on prolonged use), muscle weakness (proximal myopathy), Cushing’s syndrome, weight gain, mania, depression, delirium, hyperglycaemia, osteoporosis

Metabolism/clearance: metabolised by metabolising enzyme CYP3A4/5/7 (major) mainly in the liver

Interactions:
- increased clinical effect/toxicity of dexamethasone (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. clarithromycin, fluconazole, fluoxetine, grapefruit juice, itraconazole, ketoconazole, valproate
- decreased clinical effect/toxicity of dexamethasone (due to decreased blood concentrations) may occur with some CYP metabolising enzyme inducers (see above) e.g. carbamazepine, phenobarbitone, phenytoin, prednisone, rifampicin, St John’s wort
- decreased clinical effect/toxicity of other drugs metabolised by CYP enzymes (due to induction of their metabolism by dexamethasone) may occur e.g. aprepitant, carbamazepine, clonazepam, diazepam, domperidone, fentanyl, itraconazole, ketoconazole, methadone, midazolam, ondansetron, prednisone, quetiapine, triazolam
- increased risk of GI bleed/ulceration when given with NSAIDs (e.g. diclofenac)

Dosing:
oral: 4 to 32mg in 24 hours
sc: 4 to 16mg/24 hours
rectal: not available

Syringe driver: see syringe drivers BUT best given as a morning bolus by sc injection/short infusion


Onset: 8 to 24 hours

Availability:
Tab 1mg, 4mg fully funded (Dexamethasone (Douglas))
Oral liquid 1mg/mL fully funded (Dexamethasone (Biomed))
Inj 4mg/mL 1mL, 2mL fully funded (Hospira)

Tablets and liquid must be endorsed by a specialist.

Cost: Approx $0.16 to $0.62 per tab, $1.60 per mL liq and $4.30 to $6.20 per inj

Notes:
- Antiinflammatory effect: 0.75mg dexamethasone = 5mg prednisone = 20mg hydrocortisone.
- On discontinuation decrease dose slowly (taper) unless the patient has been taking it for less than five days in which case dose tapering is not necessary.
- Alteration in mood is not usually seen below 6mg dexamethasone (40mg prednisone) per day.
- Corticosteroid-induced insomnia responds to benzodiazepines (e.g. temazepam) but not to zopiclone.
- Corticosteroid induced mood disorder is usually depression and rarely mania.
- The use of steroids in palliative care is common and sometimes, particularly at high dose, consideration should be given to the appropriateness of their use.
- The use of 0.5 to 1mg dexamethasone in a syringe driver may reduce the risk of irritation at the subcutaneous site but adverse effects can occur even at low dose.
DICLOFENAC
(Apo-Diclo™, Cataflam™, Diclax SR™, Flameril™, Sandoz, Voltaren™)

Class: non-steroidal anti-inflammatory drug (NSAID)

Indication: pain associated with inflammation

Unlicensed indications: itch, sweating

Contraindications/cautions: GI ulceration, asthma (in sensitive patients), renal, cardiac or hepatic impairment

Adverse reactions: common GI ulceration (more common if elderly, on steroids or aspirin), diarrhoea, indigestion, nausea less common dizziness, rash, nephrotoxicity, hepatitis, oedema, hypertension, headache, tinnitus, proctitis (rectal administration)

NB inhibits platelet aggregation - may prolong bleeding time.

Metabolism/clearance: metabolised by metabolising enzyme CYP2C9 mainly in the liver

Interactions:
- increased clinical effect/toxicity of diclofenac (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. fluconazole, fluoxetine, omeprazole, valproate
- decreased clinical effect/toxicity of diclofenac (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. phenobarbitone, phenytoin, rifampicin
- increased risk of renal toxicity and hyperkalaemia with ACE inhibitors (e.g. enalapril)
- increased risk of gastro-intestinal bleed with corticosteroids (e.g. dexamethasone)
- increased clinical effect/toxicity of lithium, digoxin, methotrexate, warfarin may occur with concomitant diclofenac so monitor
- decreased clinical effects of diuretics (e.g. frusemide), antihypertensives (e.g. propranolol) may occur with concomitant diclofenac

Dosing:
oral: 50 to 150mg per day in three divided doses for normal release and two divided doses (sometimes just one) for long acting preparations.
sc: inj available but not for sc injection as too irritant
rectal: as for normal release oral

Syringe driver: not recommended

Mechanism of action: inhibits prostaglandin synthesis - prostaglandins are involved in inflammation and pain

Peak effect: oral (normal release): 0.3 to 2 hours

Duration: oral (normal release): 6 to 8 hours

Availability:
Tab sugar coated 12.5 mg, 25mg not funded
Tab EC 25mg, 50mg (normal release) some fully funded (Sandoz)
Tab dispersible 50mg (normal release) not fully funded (Voltaren D Disp™)
Tab sustained release 75mg, 100mg some fully funded (Diclax SR™)
Supp 12.5mg, 25mg, 100mg fully funded (Voltaren™)
Inj 25mg/mL fully funded (Voltaren™)

Special Authority applies to dispersible tablets.

Cost: Approx $0.24 to $0.26 per sugar coated tab, $0.03 to $0.04 per EC tab, $0.07 per dispersible tablet, $0.06 to $0.13 per SR tab, $0.18 to $0.63 per supp and $2.40 per inj

Notes:
- Co-analgesic often used with opioids in bone and soft tissue pain.
- NSAID of choice in palliative care.
- Patients at risk of gastro-intestinal bleeds should be prescribed gastric protection (e.g. omeprazole) prophylactically.
DOMPERIDONE  
(Motilium™)

Class: antiemetic - prokinetic, dopamine antagonist  
Indication: dyspeptic symptom complex including gastro-oesophageal reflux oesophagitis, epigastric sense of fullness, feeling of abdominal distension, upper abdominal pain, eructation, flatulence and heartburn, nausea, vomiting  
Contraindications/cautions: complete intestinal obstruction  
Adverse reactions: common hyperprolactinaemia, breast tenderness less common abdominal cramps, diarrhoea, dry mouth, headache, dizziness  
Metabolism/clearance: metabolised by metabolising enzyme CYP3A4/5/7 mainly in the liver and gut  
Interactions:  
- increased clinical effect/toxicity of domperidone (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. clarithromycin, fluconazole, fluoxetine, grapefruit juice, itraconazole, ketoconazole, valproate  
- decreased clinical effect/toxicity of domperidone (due to decreased blood concentrations) may occur with some CYP metabolising enzyme inducers (see above) e.g. carbamazepine, phenobarbitone, phenytoin, prednisone, rifampicin, St John's wort  
- decreased prokinetic effect of domperidone may occur with anticholinergic drugs (e.g. amitriptyline, hyoscine)  

Dosing:  
oral: 10 to 20mg three to four times a day  
rectal: not available  
Syringe driver: not available  

Mechanism of action: similar to metoclopramide - blocks dopamine receptors in the upper gastrointestinal tract, chemo-receptor trigger zone (CTZ) and the CNS (minimal effect on CNS therefore less likely to cause extrapyramidal side-effects than metoclopramide)  
Peak concentration: 30 to 110 minutes  
Availability:  
Tab 10mg fully funded  
Supp 10mg not funded, not licensed  
Costs: Approx $0.08 per tab  
Notes:  
- Main advantage over metoclopramide is less extrapyramidal side-effects but not available in injectable form.  
- Useful in nausea and vomiting associated with gastric stasis.
FENTANYL
(Sublimaze™, Durogesic™, Fentanyl (AstraZeneca, DBL, Hospira, Goldshield, Biomed, Boucher and Muir), Mylan fentanyl patch™)
Class: analgesic - opioid
Indication: step 3 on the WHO ladder for severe pain, anaesthetic premed
Unlicensed indications: subcutaneous injection/infusion
Contraindications/cautions: fentanyl hypersensitivity/allergy (not nausea/hallucinations)
Adverse reactions: see morphine - less constipating (reduce dose of laxatives when converting from morphine), perhaps less sedating and less emetogenic than other opioids.
Metabolism/clearance: metabolised by metabolising enzyme CYP3A4/5/7 mainly in the liver.
Interactions:
• increased clinical effect/toxicity of fentanyl (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. clarithromycin, fluconazole, fluoxetine, itraconazole, ketoconazole, valproate
• decreased clinical effect/toxicity of fentanyl (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. carbamazepine, phenobarbitone, phenytoin, prednisone, rifampicin, St John’s wort
• additive CNS depression with other CNS depressants e.g. benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), other opioids, alcohol
Dosing:
oral: not available
sc: treatment (of DVT etc): 1.5mg/kg once a day or 1mg/kg twice a day (lower in the obese and renal failure patients)
prophylaxis: 20 to 40mg once or twice a day
Syringe driver: not available
Mechanism of action: has high anti-Xa activity
Peak anti-Xa activity: 3 to 5 hours post inj
Availability:
Syringe 20mg/0.2mL, 40mg/0.4mL, fully funded as below
60mg/0.6mL, 80mg/0.8mL, fully funded as below
100mg/1mL, 120mg/0.8mL, fully funded as below
150mg/mL, fully funded as below
Available on Special Authority
Costs: Approx $3.92 to $19.20 per syringe
Notes:
• As the coagulation ability of cancer patients is altered it may be that low molecular weight heparins are a better choice in these patients than oral anticoagulants.

ENOXAPARIN
(Clexane™)
Class: anticoagulant - low molecular weight heparin
Unlicensed indications: duration of more than 30 days treatment
Contraindications/cautions: heparin allergy, active bleeding, recent haemorrhagic stroke, low platelets, renal impairment (adjust dose), spinal/epidural medication, prosthetic heart valve, history of gastrointestinal ulceration/bleed
Adverse reactions: common haemorrhage, haematoma, elevated LFTs less common allergic reactions, skin necrosis, thrombocytopenia
Metabolism/clearance: metabolised but cleared mainly by the kidneys so adjust dose in renal failure
Interactions:
• increased effect of enoxaparin may occur with other drugs that decrease blood clotting e.g. aspirin, clopidogrel, warfarin, heparin
• increased risk of bleeding when combined with NSAIDs e.g. diclofenac
• decreased effect of enoxaparin may occur with haemostats e.g. tranexamic acid, phytonadione (vitamin K)
Dosing:
oral: not available
sc: treatment (of DVT etc): 1.5mg/kg once a day or 1mg/kg twice a day (lower in the obese and renal failure patients)
prophylaxis: 20 to 40mg once or twice a day
Syringe driver: not available
Mechanism of action: has high anti-Xa activity
Peak anti-Xa activity: 3 to 5 hours post inj
Availability:
Syringe 20mg/0.2mL, 40mg/0.4mL, fully funded as below
60mg/0.6mL, 80mg/0.8mL, fully funded as below
100mg/1mL, 120mg/0.8mL, fully funded as below
150mg/mL, fully funded as below
Available on Special Authority
Costs: Approx $3.92 to $19.20 per syringe
Notes:
• As the coagulation ability of cancer patients is altered it may be that low molecular weight heparins are a better choice in these patients than oral anticoagulants.
**FLUCONAZOLE**
(Diflucan™, Fluozole™, fluconazole (Pacific, Mylan), Canesten Fluconazole™, m-Fluconazole™, Ozole™, Fluconazole-Claris™)

**Class:** antifungal - triazole

**Indication:** fungal infections – cryptococcosis, candidiasis, prophylaxis, dermatomycoses

**Contraindications/cautions:** renal impairment, hepatic impairment

**Adverse reactions:**
- common: gastrointestinal upset, headache
- less common: rash, blood disorders, arrhythmias, dizziness, convulsions, hypokalaemia

**Metabolism/clearance:** mainly excreted by the kidneys (fraction excreted by the kidneys unchanged = 0.8) so care in renal failure

**Interactions:**
- increased clinical effect/toxicity of some drugs (see below) (due to increased blood concentrations of them) may occur due to inhibition of metabolising enzymes by fluconazole e.g. amitriptyline, aprepitant, carbamazepine, citalopram, clonazepam, dexamethasone, diazepam, domperidone, fentanyl, itraconazole, ketoconazole, methadone, midazolam, NSAIDs (e.g. diclofenac), omeprazole, ondansetron, phenobarbitone, phenytoin, prednisone, quetiapine, triazolam, warfarin
- decreased clinical effect of amphotericin may occur with concomitant fluconazole

**Dosing:**
- oral:
  - vaginal candidiasis: 150mg as a single dose
  - cryptococcal infections/ systemic candidiasis: 200 to 400mg once a day for 7 days
  - oropharyngeal candidiasis: 50 to 100mg once a day for 7 days
  - prophylaxis in malignancy: 50mg once a day
  - not usually used sc, iv: refer to package insert

- rectal: not available

**Syringe driver:** not applicable

**Mechanism of action:** inhibits fungal cell membrane formation

**Availability:**
- Cap 50mg, 150mg, 200mg: fully funded (Pacific, Ozole™)
- Susp 50mg/5mL: fully funded as below
- Infusion 2mg/mL 50mL: not funded

**Special Authority required for suspension.**

**Cost:** Approx $0.17 to $0.68 per cap, $0.99 per mL of suspension, $5.68 per 100mg infusion

Caps only available from a ‘hospital only’ pharmacy and on specialist endorsement.

**Notes:**
- Useful in severe or recurrent fungal infections.
- May be less likely to interact with other CYP metabolised drugs (see above) than ketoconazole.

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**Conversion Chart:**

<table>
<thead>
<tr>
<th>Oral morphine (mg/24 hours)</th>
<th>Fentanyl patch (mcg/hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>12.5</td>
</tr>
<tr>
<td>60-134</td>
<td>25</td>
</tr>
<tr>
<td>135-224</td>
<td>50</td>
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<tr>
<td>225-314</td>
<td>75</td>
</tr>
<tr>
<td>315-404</td>
<td>100</td>
</tr>
<tr>
<td>405-494</td>
<td>125</td>
</tr>
<tr>
<td>495-584</td>
<td>150</td>
</tr>
<tr>
<td>585-674</td>
<td>175</td>
</tr>
<tr>
<td>675-764</td>
<td>200</td>
</tr>
<tr>
<td>765-854</td>
<td>225</td>
</tr>
<tr>
<td>855-944</td>
<td>250</td>
</tr>
<tr>
<td>945-1,034</td>
<td>275</td>
</tr>
<tr>
<td>1,035-1,124</td>
<td>300</td>
</tr>
</tbody>
</table>
Notes:
- Fluoxetine has a half life of 48 hours but its active metabolite (norfluoxetine) has a half life of 11 days.
- Watch for serotonin syndrome if switching antidepressants as it takes four to five half lives to clear a drug from the body i.e. 44 to 55 days for fluoxetine/norfluoxetine.
- Withdrawal symptoms on stopping fluoxetine are unlikely to occur.
- Tablets are dispersible in water allowing dosing increments of < 20mg. Capsule contents are also dispersible in water.

FLUOXETINE
(Prozac™, Fluox™)

Class: antidepressant - SSRI (Selective Serotonin Re-uptake Inhibitor)
Indication: depression and associated anxiety, bulimia nervosa, obsessive-compulsive disorder, premenstrual dysphoric disorder

Unlicensed indications: neuropathic pain

Contraindications/cautions: epilepsy, bleeding disorders (decreases platelet aggregation)

Adverse reactions: common nausea, sweating, tremor, diarrhoea (excessive serotonin), taste disturbance, sexual dysfunction less common dry mouth, cough, constipation, postural hypotension, tachycardia, somnolence, anamnesis, visual disturbances, pruritus, hyponatraemia

Metabolism/clearance: metabolized by metabolising enzyme CYP2D6 and 2C9 mainly in the liver

Interactions:
- increased clinical effect/toxicity of fluoxetine (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. paroxetine (not citalopram), quinine
- decreased clinical effect/toxicity of fluoxetine (due to decreased blood concentrations) may occur with some CYP metabolising enzyme inducers (see above) e.g. phenobarbitone, phenytoin, rifampicin
- increased clinical effect/toxicity of some drugs (due to increased blood concentrations of them) may occur with fluoxetine due to metabolising enzyme inhibition by fluoxetine e.g. aprepitant, amitriptyline, buspirone, carbamazepine, clonazepam, codeine (decreased morphine concentrations so decreased clinical efficacy of codeine), dexamethasone, diazepam, haloperidol, itraconazole, ketoconazole, midazolam, NSAIDs (e.g. diclofenac), phenobarbitone, phenytoin, prednisone, promethazine, triazolam, warfarin
- additive risk of serotonin syndrome (potentially fatal syndrome - symptoms include sweating, diarrhoea, confusion) with other serotonergic drugs e.g. carbamazepine, citalopram, tricyclic antidepressants (e.g. amitriptyline), lithium, tramadol

Dosing:
oral: 20 to 80mg in the morning
sc: not available
rectal: not available

Syringe driver: not available

Mechanism of action: blocks the reuptake of serotonin, a neurotransmitter, in the CNS

Onset: depression/anxiety: 1 to 2 weeks pain: 3 to 7 days

Peak response: 5 to 6 weeks

Availability:
Cap 20mg some fully funded (Fluox™)
Disp. Tab 20mg some fully funded (Fluox™)

Cost: Approx $0.03 per cap and $0.08 per tab
**Glycopyrrolate**  
*(Robinul™)*  
**Class:** anticholinergic - antisecretory/antispasmodic  
**Indication:** antisecretory premedication, adjunctive peptic ulceration treatment  
**Unlicensed indications:** ‘death rattle’, subcutaneous injection/infusion  
**Contraindications/cautions:** urinary retention, cardiac disease, glaucoma  
**Adverse reactions:**  
- common: dry mouth, tachycardia  
- less common: urinary retention, visual problems, dizziness, constipation, drowsiness  
**Metabolism/clearance:** excreted in the bile and unchanged by the kidneys  
**Interactions:**  
- additive anticholinergic effects (e.g. dry mouth, urinary retention) with other drugs which have anticholinergic effects e.g. cyclizine, amitriptyline, haloperidol, phenothiazines (e.g. chlorpromazine)  
- decreased clinical effect (prokinetic effects) of metoclopramide /domperidone may occur with concomitant glycopyrrolate  
**Dosing:**  
- oral: not available (not absorbed orally)  
- sc: 200 to 600 micrograms/24 hours  
- rectal: not available  
**Mechanism of action:** blocks cholinergic receptors  
**Initial response:** (im): 30 to 45 minutes  
**Duration:** (im): 7 hours  
**Availability:** Inj 0.2mg/mL 1mL not funded  
**Cost:** Approx $1.40 per 1mL inj  
**Notes:**  
- May be a useful alternative to hyoscine particularly in the elderly because it is less likely to cause CNS adverse effects as it does not readily cross the blood brain barrier.

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**Gabapentin**  
*(Neurontin™, Nupentin™)*  
**Class:** anticonvulsant  
**Indication:** partial seizures, including secondarily generalised tonic-clonic seizures, initially as add-on therapy in patients who have not achieved adequate control with standard antiepileptic drugs, neuropathic pain  
**Contraindications/cautions:** renal disease (reduce dose), absence seizures, encephalopathy  
**Adverse reactions:**  
- common: easy bruising (purpura), increased blood pressure, dizziness, ataxia, somnolence, blurred vision  
- less common: fatigue, headache, anxiety, GI effects, sexual dysfunction, oedema, twitching  
**Metabolism/clearance:** not metabolised, mainly excreted unchanged by the kidneys (fu = 0.8) so care and adjust dose in renal dysfunction  
**Interactions:**  
- decreased clinical effect/toxicity of gabapentin with antacids e.g. Mylanta™ due to decreased absorption of gabapentin  
- additive CNS depression with other CNS depressants e.g. benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), opioids, alcohol  
**Dosing:**  
- oral: epilepsy 900 to 1,800mg/day in divided doses max 2,400mg  
  neuropathic pain 900 to 3,600mg/day in divided doses  
- sc: not available  
- rectal: not available  
**Mechanism of action:** may act through effects on the synthesis of GABA in the CNS  
**Availability:**  
- Cap 100mg, 300mg, 400mg fully funded as below  
- Tab 600mg fully funded as below  
**Special Authority available.**  
**Cost:** Approx $0.07 to $0.15 per cap, $0.67 per tab
HALOPERIDOL
(Serenace™, Haldol™-depot inj)

Class: antipsychotic - butyrophenone

Indication: psychotic disorders, acute alcoholism, intractable nausea and vomiting, neuroleptanalgesia

Unlicensed indications: hiccup, subcutaneous injection/infusion

Contraindications/cautions: hepatic encephalopathy, epilepsy, Parkinson's

Adverse reactions: common extrapyramidal symptoms (usually at 5 to 20mg/24 hours) e.g. oculogyric crisis, dystonia, tremor, abnormal movements, restlessness - may be less with parenteral route less common hyperprolactinaemia, dry mouth, sedation, arrhythmias, QT prolongation

Metabolism/clearance: metabolised by metabolising enzyme CYP2D6 and perhaps 3A4/5/7 (minor) and 1A2 mainly in the liver

Interactions:
- increased clinical effect/toxicity of haloperidol (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. aprepitant, bupropion, ciprofloxacin, clarithromycin, fluconazole, fluoxetine, grapefruit juice, itraconazole, ketoconazole, paroxetine, valproate
- decreased clinical effect/toxicity of haloperidol (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. carbamazepine, dexamethasone, phenobarbitone, phenytion, prednisone, rifampicin, smoking, St John's wort
- increased clinical effect/toxicity of some drugs (due to increased blood concentrations of them) may occur with haloperidol due to metabolising enzyme inhibition by haloperidol e.g. amitriptyline, codeine (decreased morphine concentrations so decreased clinical efficacy of codeine), fluoxetine, nortriptyline, oxycodone, paroxetine, promethazine
- additive CNS effects with other CNS depressants e.g. benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), opioids, alcohol
- enhanced extrapyramidal side-effects may occur with lithium
- additive anticholinergic effects (e.g. dry mouth, urinary retention) may occur with other drugs which have anticholinergic effects e.g. cyclizine, amitriptyline, phenothiazines

Dosing:
oral: parenteral = 3 : 2
nausea/vomitting
oral: 1.5 to 3 mg once a day oral: 1.5 to 20mg per 24 hours
sc: 1 to 2mg/24 hours sc: 1 to 15mg/24 hours
iv: 2 to 5mg (at 1mg/minute)

Syringe driver: see syringe driver compatibility table

Mechanism of Action: nausea/vomiting - blocks dopamine receptors in the chemoreceptor trigger zone thus blocking input into the vomiting centre; delirium - may rebalance the unbalanced cholinergic/dopaminergic systems seen in delirium

Peak effect: oral: 2 to 6 hours im/sc: 20minutes

Duration: up to 24 hours
HYOSCINE BUTYLBROMIDE
(Buscopan™, Gastro-Soothe™)
Class: antispasmodic - gastrointestinal tract
Indication: GI spasm/colic
Unlicensed indications: some action as anti-emetic and antisecretory, sialorrhoea, ‘death rattle’
Contraindications/cautions: megacolon, stenosis, glaucoma, tachycardia, urinary retention
Adverse reactions: common dry mouth less common urinary retention, tachycardia, visual problems, dizziness, constipation
Metabolism/clearance: metabolised but also some excreted unchanged by the kidneys so care in renal dysfunction
Interactions:
- additive anticholinergic effects (e.g. dry mouth, urinary retention) may occur with other drugs which have anticholinergic effects e.g. cyclizine, amitriptyline, phenothiazines (e.g. chlorpromazine)
- decreased clinical effect (prokinetic effects) of metoclopramide /domperidone may occur with concomitant hyoscine butylbromide
Dosing:
oral: 20mg four times a day
sc: 40 to 100mg/24 hours
rectal: not available
Syringe driver: see syringe driver compatibility table
Mechanism of action: blocks the effect of acetylcholine on gastrointestinal smooth muscle causing relaxation
Onset: oral: 1 to 2 hours sc: 5 to 10 minutes
Duration: oral: 2 hours or less
Availability:
Tab 10mg some fully funded (Gastro-Soothe™)
Inj 20mg/mL fully funded (Buscopan™)
Cost: Approx $0.07 per 10mg tab and $1.91 per 20mg inj
Notes:
- May be useful with steroids in intestinal obstruction.
- Doesn’t cross the blood-brain barrier so doesn’t cause drowsiness or have a central antiemetic action.
- Only 8 to 10% absorbed orally.

HYOSCINE (HYDROBROMIDE)
(hyoscine hydrobromide BP (DBL, Hospira, Mayne), hyoscine- Scopaderm™)
Class: anticholinergic - antisecretory
Indication: premedication for sedation/amnesia, nausea/vomiting from motion sickness
Unlicensed indications: ‘death rattle’
Contraindications/cautions: elderly, urinary retention, cardiac disease, glaucoma
Adverse reactions: common dry mouth, tachycardia, hypotension (especially with morphine) less common urinary retention, tachycardia, visual problems, dizziness, constipation, drowsiness, hallucinations (commoner in the elderly)
Interactions:
- additive anticholinergic effects (e.g. dry mouth, urinary retention) may occur with other drugs which have anticholinergic effects e.g. cyclizine, amitriptyline, phenothiazines (e.g. chlorpromazine)
- decreased clinical effect (prokinetic effects) of metoclopramide /domperidone may occur with concomitant hyoscine
Dosing:
oral: not available
sc (as the hydrobromide): 0.4 to 2.4mg/24 hours (usually 0.8 to 1.2mg stat)
rectal: not available
patch: 1 patch (1.5 mg)/72 hours (behind the ear)
Syringe driver: see syringe driver compatibility table
Mechanism of action: blocks cholinergic receptors in CNS and the gastrointestinal tract
Peak response: im: 1 to 2 hours (antisecretory)
Duration: im: 8 hours
Availability:
Inj 0.4mg/mL (hydrobromide) some fully funded (Mayne)
Patch 1.5mg fully funded as below
Special Authority required for patches.
Cost: Approx $1.33 per inj and $5.98 per patch
Notes:
- Thought to cross the blood brain barrier more easily then hyoscine butylbromide.
- Risk of confusion in the elderly is high.
- May be particularly useful in nausea and vomiting related to motion.
KETAMINE
(Ketalar™, ketamine (Biomed))

Class: anaesthetic

Indication: general anaesthesia (400–700mg im)

Unlicensed indications: severe pain (at sub-anaesthetic doses), opioid tolerance reversal, neuropathic pain, subcutaneous injection/infusion

Contraindications/cautions: hypertension, tendency to hallucinations, alcohol abuse, epilepsy

Adverse reactions: common hallucinations (see notes below), delirium, tachycardia, hypertension less common hypotension, bradycardia, laryngospasm, diplopia, respiratory depression

Metabolism/clearance: may be metabolised in the liver by CYP metabolising enzymes. Active metabolite - norketamine

Interactions:
- additive CNS effects with other CNS depressants e.g. benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), opioids, alcohol

Dosing:
oral: injection has been given orally, capsules and lozenges are available as below
sc: 100 to 500mg in 24 hours as a ‘pulse’ over 5 days. Give a test dose of 10mg before starting infusion.
rectal: not available

Syringe driver: see syringe driver compatibility table

Peak effect: iv: 10 to 15 minutes
Duration: iv: 15 to 30 minutes

Availability:
Inj: 200mg/2mL not funded
Infusion syringes 100 mg/10 mL, 100 mg/50 mL, 200 mg/50 mL not funded
Infusion bags 100 mg/100 mL not funded

Cost: Approx $39.00 per 200mg inj, $14.00 to $25.00 per infusion syringe, $33.50 per infusion bag

Notes:
- May be useful in opioid tolerance/intolerance, in ‘wind-up’ (or rapidly escalating doses) and may allow a reduction in opioid dose.
- May be useful in neuropathic pain although ‘pulse’ therapy has been shown to be no better than placebo in a recent study.
- If hallucinations occur reduce the dose of ketamine and give a benzodiazepine (e.g. diazepam 5mg orally, midazolam 5mg subcutaneously) or haloperidol 2 to 5mg orally or subcutaneously.
- Has been effective when used topically.
- ‘Pulse’ therapy (increasing subcutaneous doses over 3 to 5 days) may be sufficient to ‘reset’ the NMDA/opioid receptors. Give 100mg/24 hours then 200mg/24hrs then 300mg/24hrs for 3 days then consider discontinuation.
- Oral administration usually involves lower doses e.g. 25 to 50mg three times a day as more norketamine is produced due to first pass metabolism. Norketamine is active and may be more potent than the parent ketamine.
- Oral formulations include the injection given orally either straight or made up into a syrup (see www.palliativedrugs.com for formula), oral lozenges and oral capsules (from Pharmaceutical Compounding in Auckland - not licensed or funded).
- Sublingual use of the injection may also be effective.
LEVOMEPROMAZINE (METHOTRIMEMPRAZINE)  
(Nozinan™)

Class: antipsychotic/neuroleptic - phenothiazine  
Indication: psychosis, severe ‘terminal’ pain with anxiety/distress/restlessness, schizophrenia, with other analgesics for pain, anxiety and distress  
Unlicensed indications: nausea/vomiting  
Contraindications/cautions: hepatic dysfunction, encephalopathy, Parkinson’s disease  
Adverse reactions: common somnolence, asthenia, infection, GI disturbance, blurred vision, hostility, pruritus, pain  
Metabolism/clearance: metabolised by hydrolysis. Fraction excreted unchanged in the urine is 0.7.  
Interactions:  
• increased clinical effect/toxicity of levetiracetam may occur with other drugs that are excreted by active tubular secretion e.g. probenecid  

Dosing:  
oral: 500mg twice daily initially (reduce in renal impairment)  
sc: not available  
rectal: not available  
Syringe driver: not available  
Mechanism of Action: suppresses sensory impulses in the CNS via various neurotransmitters.  
Onset: peak concentrations at 1.5 hours  
Availability:  
Tab 25mg, 50mg, 75mg fully funded  
Tab 1000mg not funded  
Cost: Approx $0.40 to $2.50 per tab  

LEVETIRACETAM  
(Keppra UCB Pharma™, Levetiracetam-Rex™)

Class: anticonvulsant  
Indication: seizure control  
Contraindications/cautions: monitor for behavioural changes, hepatic and renal impairment  
Adverse reactions: common somnolence, asthenia, infection, GI disturbance, blurred vision, hostility, pruritus, pain  
Metabolism/clearance: metabolised by hydrolysis. Fraction excreted unchanged in the urine is 0.7.  
Interactions:  
• increased clinical effect/toxicity of levetiracetam may occur with other drugs that are excreted by active tubular secretion e.g. probenecid  

Dosing:  
oral: 500mg twice daily initially (reduce in renal impairment)  
sc: not available  
rectal: not available  
Syringe driver: not available  
Mechanism of Action: inhibits Ca²⁺ currents and reduces the release of Ca²⁺ from intraneuronal stores. Reverses the reductions in GABA- and glycine-gated currents induced by zinc and β-carbolines.  
Onset: peak concentrations at 1.5 hours  
Availability:  
Tab 250mg, 500mg, 750mg fully funded  
Tab 1000mg not funded  
Cost: Approx $0.40 to $2.50 per tab  

Notes:  
• Only phenothiazine with analgesic properties.  
• Doses of less than 25mg are associated with minimal sedation.  
• Benztropine 2mg may be useful in alleviating extrapyramidal side-effects.  
• May be a useful option in patients with multiple symptoms.  
• For smaller doses disperse tablets in water and give a fraction of it.
LOPERAMIDE
(Diamide™, Imodium™, Nodia™)
Class: antidiarrhoeal - peripheral opioid receptor agonist
Indication: diarrhoea, reduce number of stools in ileostomy and colostomy patients
Contraindications/cautions: diarrhoea due to infection or antibiotics
Adverse reactions: common flatulence, constipation, abdominal distension, abdominal pain, bloating less common giddiness, dry mouth
Metabolism/clearance: transported out of cells by P-glycoprotein which stops it crossing the blood-brain barrier. Metabolised by oxidation but 50% excreted unchanged in faeces.
Interactions:
• decreased clinical effect of loperamide with prokinetics e.g. metoclopramide / domperidone
• CNS adverse effects may occur with P-glycoprotein inhibitors e.g. grapefruit juice, itraconazole, ketoconazole, tamoxifen
Dosing:
oral: 2mg after each loose stool (max. of 16mg/24 hours)
sc: not available
rectal: not available
Syringe driver: not available
Mechanism of Action: binds to opioid receptors in gastrointestinal tract. May also affect cholinergic receptors.
Onset: 1 to 3 hours
Availability:
Tab 2mg fully funded (Nodia™)
Cap 2mg fully funded (Diamide Relief™)
Cost: Approx $0.02 per tab or cap
Notes:
• May not be of benefit if patient is already taking morphine.
• Absorbed but doesn’t normally cross the blood-brain barrier BUT may become active in the CNS as an opioid if given with P-glycoprotein inhibitors e.g. itraconazole.

LORAZEPAM
(Ativan™)
Class: anxiolytic - short acting benzodiazepine
Indication: anxiety, insomnia, premedication
Unlicensed indications: muscle spasm, nausea/vomiting (anxiety related)
Contraindications/cautions: respiratory failure
Adverse reactions: common sedation, dizziness, unsteadiness
less common respiratory depression (high dose), disorientation, depression, disinhibition, amnesia, excitement
Metabolism/clearance: Mainly metabolised by glucuronidation
Interactions:
• additive CNS effects with other CNS depressants e.g. other benzodiazepines (e.g. midazolam), phenothiazines (e.g. chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), opioids, alcohol
Dosing:
oral: 1 to 3mg/day in 2 to 3 doses (max. 10mg/24 hours)
sc: injection available (unregistered) but difficult to obtain
rectal: not available
Syringe driver: not available
Mechanism of Action: may enhance the effect of GABA, an inhibitory neurotransmitter in the CNS
Onset: oral: 20 to 30 minutes sublingual: shorter onset
Duration: oral: 6 to 8 hours Half life: 10 to 20 hours
Availability:
Tab1mg, 2.5mg fully funded
Inj 4mg/mL not funded (Section 29)
Cost: Approx $0.07 to $0.11 per tab, $11.00 per 4mg inj
Notes:
• Lorazepam is a short acting benzodiazepine.
• Tablets may be tried sublingually.
• Not metabolised by metabolising enzymes CYP450 so less likely to interact with other drugs compared with other benzodiazepines.
• Theoretically most appropriate benzodiazepine to use in hepatic failure.
• For approximate equivalent oral anxiolytic/sedative doses see clonazepam page.
• For pharmacological properties of benzodiazepines and other hypnotics see clonazepam page.
As affects NMDA receptors may prevent ‘wind up’ (rapidly escalating doses) on long term use and is useful in neuropathic pain.

• Renal and hepatic impairment are rarely a problem.
• Subcutaneous injection/infusion may be irritant.
• Some centres use low dose methadone alongside other opioids.
• In opioid naïve patients starting doses are usually 2.5 to 5mg twice a day with 3 hourly prn breakthrough doses. Titrate dose weekly.

Conversion to methadone

There are various methods advocated in the literature for converting from other opioids to methadone. The most commonly used method has been the Morley and Makin model (see below) which has now been modified (www.palliativedrugs.com):

Morley and Makin model

When converting to oral methadone stop the original opioid and calculate the dose of methadone as follows:

• Give 3 hourly as required doses of oral methadone which are 1/10th of the previous 24 hour oral morphine (or equivalent) dose, up to a maximum of 30mg.

As methadone has a long half life after several days of therapy a dose reduction may be possible without loss of analgesia to reduce adverse effects such as drowsiness.

Toombs/Ayonide method (preferred)
This method uses a nomogram and has begun to be used as an easier method. Loading of the body is missed using this method meaning that a stable dose may not be reached as quickly as with the Morley and Makin model, but it may be safer.

- Convert total daily oral dose of morphine (or equivalent) to equivalent predicted total daily dose of methadone using the nomogram over
- Divide the predicted total daily dose of methadone by 3 and give this dose 8 hourly e.g. total daily dose of 300mg oral morphine (or equivalent) = total daily oral dose of methadone of 30mg i.e. 10mg 8 hourly.
- Breakthrough - methadone 1/10th the total daily methadone 2 hourly i.e. 10mg 8 hourly breakthrough dose of 3mg or continue with the original opioid for breakthrough
- Based on ratios by Ayonide, 2000:

<table>
<thead>
<tr>
<th>mg oral morphine</th>
<th>ratio of morphine : methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>3:1</td>
</tr>
<tr>
<td>101-300</td>
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<td>301-600</td>
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<td>601-800</td>
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<td>801-1000</td>
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<td>&gt;1001</td>
<td>20:1</td>
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METHYLPHENIDATE
(Concerta™, Ritalin™, Rubifen™)
Class: central stimulant - amphetamine related
Indication: attention deficit hyperactivity disorder (Medsafe restriction), narcolepsy
Unlicensed indications: depression, neurobehavioural symptoms in brain tumours / injuries, dementia
Contraindications/cautions: anxiety, glaucoma, agitation, hyperthyroidism, cardiac problems, hypertension, epilepsy
Adverse reactions: common nervousness, insomnia, tachycardia, urticaria less common blurred vision, hallucinations, blood disorders, psychosis (very high doses), arrhythmias
Metabolism/clearance: metabolised by hydrolysis. Inactive metabolite is excreted by the kidneys.
Interactions:
- increased analgesia and decreased sedation may occur with some opioids
- hypertensive crisis may occur with concomitant MAOIs (e.g. tranylcypromine)
- decreased hypotensive effect of adrenergic blockers (e.g. terazosin) may occur with concomitant methylphenidate
- hypertension with tricyclic antidepressants (e.g. amitriptyline) may occur
Dosing:
oral: depression (max. adult dose of 1mg/kg/24 hours)
10 to 30mg a day (morning and mid-day)
sc: not available
rectal: not available
Syringe driver: not available
Mechanism of Action: acts as a stimulant in the CNS
Onset: depression 2 to 5 days
Availability:
Tab 5mg, 10mg, 20mg fully funded for below (Ritalin™, Rubifen™)
Tab SR 20mg fully funded for below (Ritalin™, Rubifen SR™)
Cap extended release fully funded for below (Concerta™)
18mg, 27mg, 36mg, 54mg fully funded for below (Concerta™)
10mg, 20mg, 30mg, 40mg fully funded for below (Ritalin™)
Special authority for full funding for narcolepsy or ADHD. Medsafe restrictions also apply. Controlled drug form required.
Cost: Approx $0.10 to $2.18 per tab/cap
Notes:
- Patients may respond to short courses of 2 to 3 weeks then withdraw.
- Methylphenidate is occasionally used to treat opioid-induced drowsiness.
- Not funded for depression.
METRONIDAZOLE
(Flagyl™, Rozex™, Trichozole™, metronidazole (AFT, Baxter), Zidoval™)
Class: antibiotic - anti-anaerobe
Indication: bacterial infections, useful in controlling malodorous wounds
Adverse reactions: common GI upset, urticaria, metallic taste, furry tongue less common drowsiness, headache, dizziness, urine darkening, blood disorders, muscle/joint pain
Metabolism/clearance: metabolised in the liver partially by the metabolising enzyme CYP2D6 to inactive metabolites which are mainly excreted with some parent drug by the kidneys
Adverse reactions: less common tardive dyskinesia - usually on prolonged use, extrapyramidal reactions e.g. Parkinsonism, akathisia (usually at doses > 30mg/24 hours - switch to domperidone which enters the CNS to a lesser extent), diarrhoea, restlessness
Interactions:
• disulfiram-like reaction (nausea, vomiting, sweating) may occur with concomitant alcohol
• increased toxicity of lithium may occur with metronidazole
Dosing:
oral: 800mg stat then 400mg three times a day
sc: injection available but not usually used sc
iv: 500mg three times a day (infusion)
rectal: 1g three times a day for 3 days then twice a day
topical: apply twice a day
Syringe driver: not applicable
Mechanism of Action: in malodorous wounds kills anaerobes responsible for the smell
Availability:
Tabs 200mg, 400mg fully funded (Trichozole™)
Oral liq 200mg/5ml fully funded (Flagyl-S™)
Supp 500mg fully funded (Flagyl™)
Inj 500mg not funded
Topical Gel 0.5% not funded (Rozex™)
Topical Cream 7.5mg/g not funded (Rozex™)
Vaginal Gel 0.75% not funded
Cost: Approx $0.09 to $0.17 per tab, $2.45 per supp, $0.25 per mL liq, $2.46 per inf, $8.69 per 10g tube of gel, $16.67 to $21.80 per 30 to 50g gel/cream, $25.88 per 40g vaginal gel
Notes:
• ‘High dose’ metoclopramide may work via 5HT3 antagonism (like ondansetron) but is associated with severe extrapyramidal effects.
• Most effective for nausea/vomiting due to gastric stasis. Some clinicians believe that metoclopramide is no better than placebo as an antiemetic but is useful as a prokinetic.
• Benztropine 2mg may be used as an antidote.
MICROLAX™/MICOLETTE™
(Sodium citrate 450mg, sodium lauryl sulphoacetate 45mg, sorbitol 3.125g, sorbic acid 5mg, water to 5mL)
Class: rectal laxative - stimulant, faecal softener and osmotic
Indication: constipation, bowel evacuation
Dosing:
oral: not available
sc: not available
rectal: 1 tube as required
Syringe driver: not available
Mechanism of Action: may stimulate colonic activity via nerves in the intestinal mucosa (sodium citrate) and increased fluid uptake by stools thus softening them (sodium lauryl sulphoacetate, sorbitol)
Onset: almost immediate
Availability:
Enema 5mL fully funded (Micolette™)
Cost: Approx $0.50 per enema

MICONAZOLE
(Daktarin™, Resolve™, Tinasolve™, miconazole (Multichem), Micreme™)
Class: antifungal - imidazole
Indication: fungal infection - topical, oral, GI, vaginal
Contraindications/cautions: hepatic impairment
Adverse reactions: common oral gel - GI upset less common oral gel - hepatitis, topical/vaginal- burning, itching
Metabolism/clearance: metabolised by the liver
Interactions: Oral gel/vaginal preparations (absorption is likely)
  • decreased clinical effect of amphotericin may occur with miconazole
  • May affect INR of patients taking warfarin. Monitor even if only using oral gel.
Dosing:
mouth (topical): 50mg four times a day for 7 days
sc: not available
rectal: not available
topical: apply twice a day
vaginal: use at night
Syringe driver: not available
Mechanism of Action: increases fungal cell membrane permeability
Availability:
Oral gel 2% 40g fully funded (Daktarin™)
Topical cream 2% some fully funded (Multichem)
Topical lotion 2% not funded
Powder 2% 20g not funded
Tincture 2% 30mL not funded
Vaginal cream 2% not funded
Cost: Approx $8.70 per 40g oral gel, $0.46 per 15g cream, $4.36 per 30g lotion, $8.50 per 30g powder, $4.36 per 30mL Tinct, $2.75 per 40g vaginal cream
MIDAZOLAM
(Hypnovel™, midazolam (Pfizer))
Class: sedative - benzodiazepine
Indication: sedation, anaesthetic induction agent, nasal route
Unlicensed indications: subcutaneous injection/infusion, hiccups, epilepsy, muscle spasm, dyspnoea, insomnia
Contraindications/cautions: avoid sudden withdrawal, respiratory depression
Adverse reactions: common fatigue, drowsiness, amnesia less common respiratory depression (high dose), aggression, confusion, hypotension
Metabolism/clearance: metabolised by metabolising enzyme CYP3A4/5/7 (major) mainly in the liver
Interactions:
- increased clinical effect/toxicity of midazolam (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. aprepitant, clarithromycin, fluconazole, fluoxetine, grapefruit juice, itraconazole, ketoconazole, valproate
- decreased clinical effect/toxicity of midazolam (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. carbamazepine, dexamethasone, phenobarbitalone, phenytoin, prednisone, rifampicin, St John’s wort
- additive CNS effects with other CNS depressants e.g. other benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), opioids, alcohol
Dosing:
oral: not available
sc: 5 to 60mg/24 hours (up to 150mg in sedation at the end of life)
rectal: not available
intrasanal: use inj in empty sodium chloride nasal spray bottle (0.5mg/spray): 1 to 2 sprays in each nostril prn for anxiety related dyspnoea only
Syringe driver: see syringe driver compatibility table
Mechanism of Action: may enhance the effect of GABA, an inhibitory neurotransmitter in the CNS
Peak concentrations: oral 20 to 50 min sc 5 to 10 min intranasal 10 mins
Duration: 15 minutes to several hours Half life: 2 to 5 hours
Availability:
Tab 7.5mg not fully funded
Inj 1mg/mL 5mL, 5mg/mL 3mL fully funded (Hypnovel™)
Cost: Approx $0.10 per tab and $1.07 to $2.38 per inj
Notes:
- Midazolam is a very short acting benzodiazepine so dose titration to response is easier than with longer acting benzodiazepines e.g. clonazepam.
- iv administration can result in hypotension and transient apnoea.
- Benzodiazepines may reduce dyspnoea by anxiolytic and sedative effects.
- For approximate equivalent oral anxiolytic/sedative doses see clonazepam page.
- For pharmacological properties of benzodiazepines and other hypnotics see clonazepam page.
- May be used intranasally for breathlessness (anxiety). (See above)

MIRTAZAPINE
(Avanza™, Apo-mirtazapine™)
Class: antidepressant – central presynaptic alpha 2 and 5HT antagonist
Indication: major depression
Unlicensed indications: nausea
Contraindications/cautions: bipolar depression, epilepsy, cardiac disease, prostatic hypertrophy, diabetes, abrupt withdrawal
Adverse reactions: common increased appetite, dizziness, headache, dry mouth less common convulsions, tremor, nightmares, mania, syncope, hyponatraemia, nausea
Metabolism/clearance: metabolised by metabolising enzyme CYP2D6, 1A2 and 3A4/5/7 mainly in the liver to at least one active metabolite (b CYP3A4/5/7)
Interactions:
- increased clinical effect/toxicity of mirtazapine (due to increased blood concentrations of parent) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. bupropion, aprepitant, ciprofloxacin, clarithromycin, fluconazole, fluoxetine, grapefruit juice, itraconazole, ketoconazole, paroxetine, quinine, valproate
- decreased clinical effect/toxicity of mirtazapine (due to decreased blood concentrations of parent) may occur with some CYP metabolism enzyme inducers (see above) e.g. carbamazepine, dexamethasone, phenobarbitalone, phenytoin, prednisone, rifampicin, smoking, St John’s wort
- additive risk of serotonin syndrome (potentially fatal syndrome - symptoms include sweating, diarrhoea, confusion) with other serotonergic drugs e.g. amitriptyline, carbamazepine, fluoxetine, paroxetine, tramadol, lithium
Dosing:
oral: 15 to 45mg at bed-time
sc: not available
Syringe driver: not available
Mechanism of Action: blocks presynaptic alpha 2 and 5HT2 and 5HT3 receptors increasing central noradrenaline and serotonin (blocking 5HT2 and 5HT3 receptors allowing stimulation of 5HT3 receptors)
Peak concentrations: oral 2 hours
Half life: 20 to 40 hours
Availability
Tab 15mg, 30mg, 45mg fully funded as below
Special Authority available for severe major depression after a trial of two different antidepressants or in an inpatient who has trialled one antidepressant
Cost: Approx $0.73 to $1.17 per tab
**MORPHINE**

(m-Eslon™, RA-Morph™, Sevredol™, morphine sulphate (DBL), (Biomed), morphine tartrate (DBL), (Hospira), Arrow-morphine LA™)

**Class:** analgesic - opioid

**Indication:** step 3 on the WHO ladder for severe pain, more effective in nociceptive than in neuropathic/visceral pains, severe breathlessness, cough, diarrhoea

**Contraindications/cautions:** morphine hypersensitivity/allergy (not nausea/hallucination with opioids)

**Adverse reactions:** common nausea/vomiting in 10 to 30% of patients (usually transient for 1 to 5 days) - give haloperidol, constipation in 90% of patients - give a stimulant & softener laxative prophylactically, dry mouth, dizziness, sedation (usually transient and on initiation or dose increase)

less common respiratory depression (high doses) - pain is an antidote - give naloxone if severe, visual problems - may see things upside down/flipping, myoclonic jerking - sign of toxicity - try a different opioid, delirium in 2% of patients - give haloperidol rare hallucinations, hyperalgesia, raised intracranial pressure, biliary/urinary tract spasm, muscle rigidity, pruritus, pulmonary oedema, physical dependence (irrelevant in dying)

**Metabolism/clearance:** metabolised mainly in the liver by glucuronidation to active metabolites one of which is excreted by the kidneys so watch for accumulation in renal dysfunction

**Interactions:**
- additive CNS effects with other CNS depressants e.g. benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), other opioids
- faster onset of action of slow release morphine may occur with metoclopramide

**Dosing:**

**Pain (initially use the normal release and titrate to pain)**

- **oral:**
  - normal release: initially 5 to 10mg 4 hourly and prn
  - slow release: initially 10 to 30mg 12 hourly
- *prescribe rescue doses (normal release) of 1/5th to 1/6th of the total 24 hour dose 4 to 6 hourly
- *there is no real maximum dose but it is usually less than 200mg/24 hours. If it is >400mg/24 hours consider the aetiology of the pain and the use of co-analgesia
- *review doses regularly

- **sc:**
  - oral: sc = 2:1
- **rectal:**
  - oral: rectal = 1:1
- **epidural:**
  - sc/epidural = 10:1
- **intrathecal:**
  - sc/intrathecal = 100:1

**Breathlessness, cough**

- **oral:** normal release 5 to 10mg 4 hourly prn

**Syringe driver:** see syringe driver compatibility table

**Mechanism of Action:** stimulates mu (and other) opioid receptors in the CNS and gastrointestinal tract

**Peak effect:**
- **oral:** normal release 1 hour

**Duration:**
- **oral:** normal release 4 to 5 hours
- **oral:** slow release 8 to 12 hours

**Availability:**

<table>
<thead>
<tr>
<th>Oral liq</th>
<th>Tab normal release</th>
<th>Tab long acting</th>
<th>Inj</th>
<th>Inj 5mg/mL</th>
<th>Inj 120mg/1.5mL</th>
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<tbody>
<tr>
<td>1mg, 2mg, 5mg, 10mg/mL (RA Morph™)</td>
<td>10mg, 20mg (Sevredol™)</td>
<td>10mg, 30mg, 60mg, 100mg (m-Eslon™)</td>
<td>5mg/mL, 10mg/mL, 15mg/mL, 30mg/mL as sulphate</td>
<td>400mg/5mL as tartrate</td>
<td>400mg/5mL as tartrate</td>
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Controlled drug form required.

**Cost:** Approx $0.04 per mL to $0.11 per mL liq, $0.28 to $0.55 per normal release tab, $0.22 to $0.80 per slow release cap (m-Eslon™), $0.20 to $0.78 per long acting tab, $0.96 to $15.00 per inj

**Notes:**
- Tolerance to effect does occur but progressive disease is also a cause of dose fade.
- If dose of slow release morphine is increased remember to also increase the prescribed dose of normal release morphine for breakthrough pain/rescue.
- Toxicity: decrease in respiratory rate, mental status and blood pressure - give naloxone (see naloxone page).
- m-Eslon™ capsules can be opened and sprinkled on food or given via a PEG or nasogastric tube.
- For conversion to oxycodone, fentanyl or methadone see relevant pages.
- Morphine can affect the ability to drive. Some patients may need to be told not to drive while taking morphine. Always advise patients not to drive for several days after a dose increase.
- Topical morphine may be useful for wound pain. It is usually used as 0.05 to 0.1% morphine [i.e. 0.5 to 1mg/mL] in Intrasite™ gel, metronidazole gel or KY Jelly™.
NALOXONE
(Narcan™, naloxone (DBL), (CSL), (Mayne), (Hospira))

Class: opioid antagonist
Indication: opioid overdose
Unlicensed indications: may enhance opioid analgesia at very low dose, may attenuate opioid adverse effects e.g. nausea and vomiting at low dose

Contraindications/cautions: cardiovascular disease
Adverse reactions: common nausea, vomiting, tachycardia, sweating, raised blood pressure (opioid withdrawal)
Metabolism/clearance: metabolised mainly in the liver by glucuronidation

Interactions:
- blocks the actions of opioids e.g. morphine, fentanyl, methadone, oxycodone

Dosing:
- If respiratory rate < 8 per minute, patient unconscious or cyanosed
  iv: 0.1 to 0.2mg every 2 to 3 minutes for reversal of CNS depression post-op
  0.4 to 2mg every 2 to 3 minutes up to 10mg for opioid overdose
- oral: not available alone
- sc: see below
- rectal: not available

Syringe driver: not applicable

Mechanism of Action: blocks action of opioids at opioid receptors

Onset: iv 2 to 3 minutes sc/im 15 minutes
Duration: 15 to 90 minutes

Availability:
Inj 0.4mg/mL fully funded (Mayne)
Inj 0.02mg/mL not funded

Cost: Approx $6.60 per inj

Notes:
- Best given iv, however if not practical can be given im or sc.
- Reversal of respiratory depression will result in reversal of analgesia and withdrawal symptoms if physiologically dependent.

MOVICOL™
(Macrogol 3350, sodium chloride, sodium bicarbonate, potassium chloride, potassium acesulfame)

Class: laxative - osmotic
Indication: constipation including faecal impaction
Contraindications/cautions: intestinal obstruction or perforation, ileus and severe inflammatory conditions, cardiac disease (contains sodium and potassium)
Adverse reactions: less common abdominal distension and pain, nausea

Metabolism/clearance: not absorbed
Interactions: few as not absorbed - may affect the absorption of some drugs

Dosing:
- Movicol™:
  constipation 1 to 3 sachets per day
  faecal impaction 8 sachets per day taken within 6 hours for a max. of 3 days. If cardiovascular problems, do not take more than 2 sachets over any one hour.
  Each sachet should be dissolved in 125 mL. For faecal impaction dissolve 8 sachets in 1L of water.
- Movicol-Half™:
  constipation 1 to 6 sachets/day
  faecal impaction 16 sachets/day taken within 6 hours for a max. of 3 days. If cardiovascular problems, do not take more than 4 sachets over any one hour.
  Each sachet should be dissolved in 60mL of water.

Mechanism of action: osmotic action in the gut to increase liquid content of stools but with no net loss of sodium, potassium or water
Onset: faecal impaction most cleared after 3 days

Availability: Sachets
Movicol™ fully funded as below
Movicol-Half™ not funded
Special Authority available.
Cost: Approx $0.60 per sachet Movicol™, $0.40 per sachet of Movicol Half™

Notes:
- Effective laxative in palliative care.
- More acceptable to many than lactulose.
**NAPROXEN**
(Naprosyn™, Naxen™, Noflam™, Naprogesic™, Sonalflam™)

**Class:** non-steroidal anti-inflammatory drug (NSAID)

**Indication:** pain associated with inflammation (including bone pain), dysmenorrhea

**Unlicensed indications:** itch, sweating

**Contraindications/cautions:** GI ulceration, asthma (in sensitive patients), renal, cardiac or hepatic impairment

**Adverse reactions:** common GI ulceration (more common if elderly, on steroids or aspirin), diarrhoea, indigestion, nausea less common dizziness, rash, nephrotoxicity, hepatitis, oedema, hypertension, headache, tinnitus, proctitis (rectal administration). NB increases platelet aggregation - may prolong bleeding time.

**Metabolism/clearance:** metabolised by metabolising enzyme CYP2C9 and 1A2 mainly in the liver

**Interactions:**
- increased clinical effect/toxicity of naproxen (due to increased blood concentrations) may occur with some CYP metabolising enzyme inducers (see above) e.g. ciprofloxacin, fluconazole, fluoxetine, ketoconazole, valproate
- decreased clinical effect/toxicity of naproxen (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. broccoli like vegetables, carbamazepine, phenobarbitaline, phenytoin, rifampicin, smoking
- increased clinical effect/toxicity of lithium, digoxin, methotrexate and warfarin may occur with naproxen due to increased concentrations of these drugs via kidney excretion competition so monitor
- decreased clinical effects of diuretics (e.g. frusemide) and beta blockers (e.g. propranolol) may occur with naproxen
- increased risk of renal toxicity and hyperkalaemia with ACE inhibitors (e.g. enalapril) may occur with naproxen
- additive risk of bleeding may occur with warfarin and heparin in combination with naproxen

**Dosing:**
- oral: normal release 500 to 1,000mg per day in two divided doses or 275mg every 6 to 8 hours (max 1,375mg)
- sustained release 750 to 1,000mg per day as a single dose
- sc: not available
- rectal: not available (try diclofenac)

**Syringe driver:** not available

**Mechanism of Action:** inhibits prostaglandin synthesis which are involved in inflammation and pain

**Peak effect:** oral normal release 2 to 4 hours

**Duration:** 7 hours

**Availability:**
- Tab 250mg, 500mg fully funded (Noflam™)
- Tab 275mg not funded
- Tab long-acting 750mg, 1g fully funded (Naprosyn™)

**Cost:** Approx $0.05 to $0.10 per tab, $0.20 to $0.23 per long acting tab

**NORTRIPTYLINE**
(Norpress™)

**Class:** antidepressant - tricyclic

**Indication:** depression, smoking cessation

**Unlicensed indications:** neuropathic pain, itch

**Contraindications/cautions:** arrhythmias, recent MI, epilepsy (lowers seizure threshold), urinary retention

**Adverse reactions:** common anticholinergic - dry mouth, blurred vision, urinary retention, drowsiness (tolerance to these may develop except dry mouth) less common sweating, constipation, confusion, arrhythmias, tachycardia, postural hypotension.

**Metabolism/clearance:** metabolised by the metabolising enzyme CYP2D6 (major) mainly in the liver to active metabolites

**Interactions:**
- increased clinical effect/toxicity of nortriptyline (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. bupropion, fluoxetine, paroxetine, quinine
- increased risk of serotonin syndrome (potentially fatal syndrome - symptoms include sweating, diarrhoea, confusion) with other serotonergic drugs e.g. carbamazepine, fluoxetine
- additive drowsiness may occur with alcohol, benzodiazepines (e.g. clonazepam)
- increased risk of seizures in epileptics may occur with nortriptyline so interacts with anticonvulsants e.g. phenytoin
- additive CNS effects with other CNS depressants e.g. benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), opioids, alcohol
- additive increased risk of QT interval prolongation (cardiac adverse effect which may lead to arrhythmias) with other drugs that prolong the QT interval e.g. lignocaine, lithium, haloperidol

**Dosing:**
- oral: 25 to 100mg at night (max. of 50mg in elderly) 10 to 50mg at night
- sc: not available
- rectal: not available

**Syringe driver:** not available

**Mechanism of Action:** not really understood but thought to be through noradrenaline and serotonin in the CNS

**Onset:**
- depression 2 to 6 weeks
- pain several days

**Availability:** Tab 10mg, 25mg fully funded

**Cost:** Approx $0.06 to $0.08 per tab

**Notes:**
- Metabolite of amitriptyline, less adverse reactions (including sedation) than amitriptyline.
- 25mg nortriptyline = 75mg amitriptyline (approx).
**NYSTATIN**  
(Nilstat™, Mycostatin™)  
Class: antifungal - polyene  
Indication: fungal infections - topical, oral, gastrointestinal, vaginal  
Adverse reactions: less common nausea, vomiting, diarrhoea (at high doses), local irritation  
Dosing:  
oral: (not absorbed orally)  
gastrointestinal candidiasis: 500,000 to 1,000,000 units three times a day  
topical: not available  
vaginal: 5g of cream once or twice a day  
Syringe driver: not available  
Mechanism of Action: increases fungal cell membrane permeability  
Availability:  
Oral suspension 100,000 unit/mL, 24mL fully funded (Nilstat™)  
Tabs/Caps 500,000 units fully funded (Nilstat™)  
Topical cream 100,000 units/g, 15g not fully funded  
Vaginal cream 100,000 units/5g, 75g fully funded (Nilstat™)  
Cost: Approx $0.13 per mL liq, $0.28 per tab, $0.26 per cap, $1.00 per 15g cream, $4.71 per 75g vaginal cream  
Notes:  
• If infection is severe or recurrent use a systemic antifungal e.g. fluconazole.

**OCTREOTIDE**  
(Octreotide (DBL Hospira), Sandostatin™)  
Class: growth hormone inhibitor  
Indication: acromegaly, gastro-entero pancreatic endocrine tumours, post pancreatic surgery, emergency treatment to stop bleeding oesophageal varices  
Unlicensed indications: antisecretory in intestinal obstruction, secretory diarrhoea, high fistula output, variceal bleeds  
Contraindications/cautions: diabetes  
Adverse reactions: less common injection site reaction, gastro upset, hepatitis, gallstones, hyper/hypoglycaemia, bradycardia, dizziness, drowsiness, headache, hypothyroidism  
Metabolism/clearance: metabolised by the liver  
Interactions:  
• decreased absorption of ciclosporin may occur with octreotide  
Dosing:  
ooral: not available  
gastrointestinal candidiasis: 200 to 600 micrograms/24 hours (max. 1mg/24 hours)  
syringe driver: see syringe driver compatibility table  
Mechanism of Action: blocks somatostatin receptors  
Peak effect: 30 minutes  
Duration: 12 hours  
Availability:  
Inj 50 micrograms/mL, 1mL fully funded as below  
Inj 100 micrograms/mL, 1mL fully funded as below  
Inj 500 micrograms/mL, 1mL fully funded as below  
Inj LAR 10mg, 20mg, 30mg fully funded as below  
Full funding on Special Authority.  
Cost: Approx $5.13 to $35.00 per normal release inj, $1,772 to $2,951 per LAR inj  
Notes:  
• Long acting octreotide formulations are available. Their use in palliative care has not been established.
**Olanzapine**
(Apo-olanzapine™, Arrow Olanzapine™, Dr Reddy’s olanzapine™, Olanzaccord™, Olanzine™, Zyprexa™)

**Class:** antipsychotic, antimanic, mood stabiliser

**Indication:** acute and chronic psychoses including schizophrenia, bipolar disorder

**Unlicensed indications:** nausea and vomiting, delirium

**Contraindications/cautions:** liver dysfunction, cardiovascular and cerebrovascular disease, hypotension, seizures, blood disorders, renal dysfunction, prostatic hypertrophy, paralytic ileus, bone marrow depression, diabetes, narrow angle glaucoma, hypercholesterolaemia, Parkinson’s disease

**Adverse reactions:** common drowsiness, weight gain, dizziness, hallucinations, akathisia and other extrapyramidal side effects, elevated blood glucose and triglycerides, chest pain, oedema, constipation, dry mouth less common angioedema, urticaria, diabetic coma, hepatitis, pancreatitis, priapism, tardive dyskinesia, neuroleptic akathisia and other extrapyramidal side effects, elevated blood glucose and other metabolic side effects, increased blood pressure, pooled uterine fibroids, cardiac arrhythmias, increased risk of myocardial infarction, increased risk of suicide

**Class:** antipsychotic, antimanic, mood stabiliser

**Unlicensed indications:** nausea and vomiting, delirium

**Indication:** acute and chronic psychoses including schizophrenia, bipolar disorder

**Dosing:**
- oral tabs/disp tabs: 2.5 to 20mg per day as a single dose
- sc: inj available but recommended for im use only
- rectal: not available

**Mechanism of action:** antagonises serotonin and dopamine receptors in the CNS

**Availability:**
- Tab 2.5mg, 5mg, 10mg: fully funded
- Oral wafers 5mg, 10mg: some fully funded (Dr Reddy’s, Olanzine-D™)
- Inj 10mg: not funded

**Cost:** Approx $0.07 to $0.23 per tablet, $0.23 to $0.31 per wafer, $8.11 per inj

**Notes:**
- Lower potential for neurological adverse effects than conventional antipsychotics.
- Increasingly used in acute delirium and behavioural disturbances associated with brain tumours.

**Omeprazole**
(Losec™, Dr Reddy’s omeprazole™, Omezol Relief™)

**Class:** ulcer healing/prophylactic - proton pump inhibitor

**Indication:** duodenal/gastric ulcer, reflux oesophagitis, dyspepsia, NSAID associated gastric and duodenal ulcer/erosion treatment

**Unlicensed indications:** subcutaneous infusion/injection

**Contraindications/cautions:** renal impairment

**Adverse reactions:** common headache, nausea/vomiting, diarrhoea or constipation less common insomnia, dizziness, vertigo, pruritus, blood disorders, muscle/joint pain, dry mouth, agitation

**Metabolism/clearance:** metabolised by metabolising enzyme CYP2C19 mainly in the liver

**Interactions:**
- increased clinical effect/toxicity of omeprazole (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. ciprofloxacin, ketoconazole
- decreased clinical effect/toxicity of omeprazole (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. broccoli-like vegetables, carbamazepine, smoking, omeprazole, phenobarbital, phenytoin, rifampicin
- possible increase risk of extrapyramidal effects with dopamine antagonists e.g. metoclopramide
- additive hypotension with antihypertensives e.g. propranolol
- additive CNS effects with other CNS depressants e.g. benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), opioids, alcohol

**Dosing:**
- oral: 10 to 40mg once a day
- sc: injection and infusion available but not usually used sc. Doses of 40mg in 100mL normal saline have been given sc over 3 hours
- rectal: not available

**Syringe driver:** short infusions only

**Mechanism of Action:** inhibits gastric acid secretion via proton pump blockade

**Onset:** oral (antacid effect) 10 to 20 minutes

**Availability:**
- Caps 10mg, 20mg, 40mg: fully funded
- Inj 40mg: fully funded

**Cost:** Approx $0.03 to $0.06 per cap, $5.73 per inj

**Notes:**
- Omeprazole is considered the drug of choice for prophylaxis or treatment of NSAID-induced gastro-intestinal damage.
- Oral suspension can be made.
OXYCODONE
(OxyNorm™, OxyContin™)
Class: analgesic - opioid
Indications: step 3 in the WHO analgesic ladder
Contraindications/cautions: severe renal failure, respiratory disease
Adverse reactions: see morphine
Metabolism/clearance: metabolised by metabolising enzyme CYP2D6 mainly in the liver
Interactions:
- increased clinical effect/toxicity of oxycodone (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. bupropion, fluoxetine, paroxetine, quinine, valproate
- increased clinical effect/toxicity of oxycodone (due to increased blood concentrations) may occur with some CYP metabolising enzyme inducers (see above) e.g. broccoli-like vegetables, carbamazepine, smoking, dexamethasone, omeprazole, phenobarbitone, phentoyin, prednisone, rifampicin, St John’s wort

Dosing: (and see notes)
oral: initially in opioid naïve 1 to 3mg 4 to 6 hourly
slow release initially 5mg every 12 hours
sc: oral: sc 2:1
rectal: not available

Syringe driver: see syringe driver compatibility table

Mechanism of Action: stimulates opioid receptors in the CNS and gastrointestinal tract

Onset: oral: 20 to 30 minutes
Duration: oral (immediate release) 4 to 6 hours slow release 12 hours

Availability:
Immediate release cap 5mg, 10mg, 20mg fully funded (OxyNorm™)
Slow release tab 5mg, 10mg, 20mg, 40mg, 80mg fully funded (OxyContin™)
Oral liquid 5mg/5mL fully funded (OxyNorm™)
Inj 10mg/mL, 1mL, 2mL fully funded (OxyNorm™)
50mg/mL, 1mL not funded (OxyNorm™)

Oxycodone/naloxone slow release tabs 5mg/2.5mg, 10mg/5mg, 20mg/10mg, 40mg/20mg not funded (Targin™)

Costs: Approx $0.14 to $0.49 per immediate release cap, $0.37 to $2.90 per slow release tab, $0.04 per mL oral liq and $2.88 to $5.76 per inj, $0.85 to $2.83 per oxycodone/naloxone slow release tablet

Notes:
- May be useful in opioid rotation.
- Dose conversion from oral morphine to oral oxycodone is 2:1 i.e. 10mg oral morphine = 5mg oral oxycodone because oral availability of oxycodone is twice that of morphine.
- The slow release tablets have a coating of immediate release drug so that the last dose of immediate release does not have to be given with the first dose of slow release.

ONDANSETRON
(Zofran™, Dr Reddy’s Ondansetron™)
Class: antiemetic - 5HT3 antagonist
Indication: nausea/vomiting post chemo- or radio- therapy, post-operative nausea/vomiting
Unlicensed indications: nausea/vomiting not due to above, subcutaneous injection/infusion
Contraindications/cautions: hepatic impairment, subacute gastro-intestinal obstruction
Adverse reactions: common headache, constipation less common hiccups, injection site reaction, dizziness, cardiac effects (iv usually tachycardia, chest pain, arrhythmias), sedation, convulsions
Metabolism/clearance: metabolised by metabolising enzymes CYP3A4/5/7, 2D6 and 1A2 mainly in the liver
Interactions:
- increased clinical effect/toxicity of ondansetron (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. aprepitant, bupropion, clarithromycin, ciprofloxacin, fluconazole, fluoxetine, itraconazole, ketoconazole, paroxetine, quinine, valproate
- decreased clinical effect/toxicity of ondansetron (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. broccoli-like vegetables, carbamazepine, smoking, dexamethasone, omeprazole, phenobarbitone, phentoyin, prednisone, rifampicin, St John’s wort

Dosing:
oral: 4 to 8mg twice a day
sc: not usually used
rectal: not available

Syringe driver: compatibility unknown so don’t mix

Mechanism of Action: acts on 5HT3 receptors in the vomiting centre in the CNS and in the gastrointestinal tract

Peak concentration: oral 1 to 2 hours im (sc) 30 minutes

Availability:
Tab 4mg, 8mg fully funded (Dr Reddy’s)
Oral wafers 4mg, 8mg fully funded (Dr Reddy’s)
Inj 4mg/2mL, 8mg/4mL not funded

Cost: Approx $0.17 per tab, $0.17 to $0.20 per oral wafer, $4.93 to $10.56 per inj

Notes:
- Use in palliative care is outside the product license. May be of use in nausea and vomiting refractory to all other antiemetics.
**PAMIDRONATE DISODIUM**  
(Pamisol™)

**Class:** bisphosphonate calcium regulator

**Indication:** hypercalcaemia, metastatic bone pain, Paget’s disease

**Contraindications/cautions:** severe renal impairment, dental surgery, oral disease, ensure adequate hydration

**Adverse reactions:** less common transient flu-like symptoms, slight increase in temperature, fever, hypocalcaemia, transient bone pain, nausea, headache, osteonecrosis (particularly of jaw)

**Metabolism/clearance:** not metabolised, excreted by the kidneys after uptake into the bone

**Interactions:**
- incompatible with calcium containing infusion fluids

**Dosing:**
- oral: not available
- sc: zoledronic acid is usually used instead
- rectal: not available
- iv infusion:
  - bone pain 90mg every 3 to 4 weeks
  - hypercalcaemia 15 to 90mg depending on corrected calcium concentration
- rate of infusion should not exceed 60mg/hour (20mg/hour in renal impairment) and concentration should not exceed 90mg/250mL

**Syringe driver:** not applicable

**Mechanism of Action:** inhibits bone resorption

**Onset:** hypercalcaemia 1 to 2 days

**Duration:**
- hypercalcaemia 2 weeks to 3 months
- bone pain 3 to 4 weeks

**Availability:**
- Inj 15mg, 30mg, 60mg, 90mg fully funded (Pamisol™)

**Cost:** Approx $18.75 to $112.50 per inj

**Notes:**
- 50% of patients with metastatic bone pain may be responsive.
**PARACETAMOL**  
(Dispersol™, Ethics Paracetamol™, Lemsip™ (various), Pamol™, Panadol™, Paracare™, Parafast™, Perfalgan™, Parapaed™, Pharmacare™)  
(in combination:- many)  
**Class:** analgesic - non-opioid  
**Indication:** step 1 on the WHO analgesic ladder, co-analgesic, antipyretic  
**Contraindications/cautions:** severe hepatic impairment  
**Adverse reactions:** less common rash, pancreatitis on prolonged use, liver damage in overdose (> 6g in 24 hours) or in combination with heavy alcohol intake, nephrotoxicity  
**Metabolism/clearance:** metabolised in the liver mainly by glucuronidation  
**Interactions:**  
- increased toxicity of paracetamol may occur with alcohol  
- increased anticoagulant effect of warfarin may occur if given with concurrent paracetamol regularly for a long time so monitor INR  
- increased absorption of paracetamol may occur with metoclopramide / domperidone  
- increased risk of hepatotoxicity may occur with concurrent carbamazepine, phenytoin  
**Dosing:**  
oral: 500mg to 1g 4 to 6 hourly (max. 4g in 24 hours)  
supps: 125mg, 250mg, 500mg  
**Mechanism of Action:** thought to have a central effect on pain pathways and not anti-inflammatory  
**Onset:** 0.5 hours  
**Duration:** 4 hours  
**Availability:**  
Tab 500mg fully funded  
Supp 125mg, 250mg, 500mg some fully funded  
Liq 120mg/5mL, 250mg/5mL some fully funded  
Solu 500mg not funded  
Inf 500mg/50mL, 1g/100mL not funded  
**Cost:** Approx $0.01 per tab, $0.37 to $0.72 per supp, $0.01 per mL liq, $0.18 per sol tab, $2.57 to $3.96 per infusion  
**Notes:**  
- Give regularly rather than if required.  
- Combination preparations are not recommended.  
- Liver damage is likely to occur in overdose.  
- Useful analgesic when given regularly in combination with opioids.

**PANTOPRAZOLE**  
(Dr Reddy’s Pantoprazole™, Pantocid™)  
**Class:** ulcer healing/prophylaxis - proton pump inhibitor  
**Indication:** duodenal/gastric ulcer, reflux oesophagitis, dyspepsia  
**Contraindications/cautions:** renal impairment  
**Adverse reactions:** common headache, nausea/vomiting less common abdominal pain, flatulence, insomnia, pruritus, dizziness  
**Metabolism/clearance:** metabolised by metabolising enzyme CYP2C19 mainly in the liver  
**Interactions:**  
- increased clinical effect/toxicity of pantoprazole (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. fluconazole, fluoxetine, ketoconazole, omeprazole, valproate  
- decreased clinical effect/toxicity of pantoprazole (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. phenobarbitone, phenytoin, rifampicin  
- decreased absorption of ketoconazole, itraconazole may occur with pantoprazole  
**Dosing:**  
oral: 20 to 80mg once a day  
supps: 20 to 40mg once a day  
**Mechanism of Action:** inhibits gastric acid secretion via proton pump blockade  
**Onset:** oral (antacid effect) 2 hours  
**Availability:**  
Tabs 20mg, 40mg fully funded (Dr Reddy’s™)  
Inj 40mg fully funded (Pantocid™)  
**Cost:** Approx $0.04 to $0.05 per cap, $6.50 per injection
**PHENOBARBITONE**
(phenobarbitone (PSM, Hospira))

**Class:** anticonvulsant - barbiturate

**Indication:** seizure control, status epilepticus, pre-op anxiety

**Unlicensed indications:** terminal restlessness

**Contraindications/cautions:** acute intermittent porphyria, elderly, renal/hepatic failure

**Adverse reactions:** common drowsiness, headache less common GI upset, paradoxical excitement, pain, hypocalcaemia

**Metabolism/clearance:** metabolised by metabolising enzyme CYP2C19 mainly in the liver

**Interactions:**
- increased clinical effect/toxicity of phenobarbitone (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. fluconazole, fluoxetine, ketoconazole, omeprazole, valproate
- decreased clinical effect/toxicity of phenobarbitone (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. phenytoin, rifampicin
- decreased clinical effect/toxicity of some drugs (due to decreased blood concentrations of them) may occur with phenobarbitone due to metabolising enzyme induction by phenobarbitone e.g. aprepitant, busiprone, amitriptyline, carbamazepine, clonazepam, dexamethasone, diazepam, domperidone, fentanyl, itraconazole, ketoconazole, methadone, midazolam, NSAIEds (e.g. diclofenac), olanzapine, ondansetron, phenytoin, prednisone, quetiapine, triazolam, warfarin
- additive CNS effects with other CNS depressants e.g. benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), opioids, alcohol

**Dosing:**
- terminal agitation
  - oral: 60 to 180mg per day
  - sc: 600 to 1,200mg/ 24 hours
- rectal: not available

**Syringe driver:** give alone and watch for irritation at injection site

**Mechanism of Action:** depresses activity of all excitable tissue perhaps via GABA

**Availability:**
- Tab 15mg, 30mg fully funded
- Inj 20mg/0.5mL, 200mg/mL, 1mL not funded (200mg section 29)

**Cost:** Approx $0.05 per tab, $8.34 per 200mg inj

**Notes:**
- Risk of respiratory depression in overdose.
- Oral liquid can be made and is funded.

**PHENYTOIN**
(Dilantin™, phenytoin (DBL), (Hospira), (Mayne))

**Class:** anticonvulsant - hydantoin

**Indication:** epilepsy, prophylaxis in neurosurgery, arrhythmias

**Contraindications/cautions:** low albumin

**Adverse reactions:** common gingival hyperplasia less common slurred speech, confusion, dizziness, blood disorders, skin reactions, hepatitis

**Metabolism/clearance:** metabolised by metabolising enzymes CYP2C9 and 2C19 mainly in the liver

**Interactions:**
- increased clinical effect/toxicity of phenytoin (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. fluconazole, fluoxetine, ketoconazole, omeprazole, valproate
- decreased clinical effect/toxicity of phenytoin (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. phenobarbitone, rifampicin
- decreased clinical effect/toxicity of some drugs (due to decreased blood concentrations of them) may occur with phenytoin due to metabolising enzyme induction by phenytoin e.g. aprepitant, busiprone, amitriptyline, carbamazepine, clonazepam, dexamethasone, diazepam, domperidone, fentanyl, itraconazole, ketoconazole, methadone, midazolam, NSAIEds (e.g. diclofenac), olanzapine, ondansetron, phenytoin, prednisone, quetiapine, triazolam, warfarin
- additive CNS effects with other CNS depressants e.g. benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), opioids, alcohol

**Dosing:**
- oral: 100 to 300mg/24 hours (titrate to plasma concentrations)
- sc: inj available but not given sc
- rectal: not available

**Syringe driver:** not applicable

**Mechanism of Action:** inhibits spread of seizure through the motor cortex possibly via sodium channels

**Peak response:** 7 to 10 days (if loaded 8 to 12 hours)

**Availability:**
- Tab 50mg fully funded (Dilantin™)
- Cap 30mg, 100mg fully funded (Dilantin™)
- Oral liq 30mg/5mL fully funded (Dilantin™)
- Inj 50mg/mL, 2mL and 5mL fully funded (Mayne)

**Cost:** Approx $0.21 per tab, $0.09 to $0.10 per cap, $0.04 per mL liq, $13.85 to $15.45 per inj

**Notes:**
- Monitor plasma concentrations.
- Small dose increases may result in large plasma concentration increases.
- If the patient has NG feeds these will affect phenytoin concentrations.
Alteration in mood not usually seen below 40mg prednisone (6mg dexamethasone) per day.

Corticosteroid induced insomnia responds to benzodiazepines (e.g. temazepam) but not to zopiclone.

Corticosteroid induced mood disorder is usually depression and rarely mania.

Metabolised to prednisolone. Prednisolone liquid 5mg/mL (Redipred™) is available but is only funded for children.
**RANITIDINE**  
(Apo-Ranitidine™, Arrow-Ranitidine™, Zantac™, Peptisoothe™)  
Class: ulcer healing/prophylactic - H₂ antagonist  
Indication: duodenal/gastric ulcer, reflux oesophagitis, dyspepsia  
Unlicensed indications: subcutaneous injection/infusion, itch, sweating  
Contraindications/cautions: renal impairment  
Adverse reactions: common diarrhoea, tiredness; less common blurred vision, gynaecomastia, bradycardia, tachycardia, hypotension, agitation, hallucinations, blood disorders, dizziness, headache, confusion  
Metabolism/clearance: metabolised by the liver to 3 inactive metabolites which are excreted by the kidney together with 30% of the parent drug.  
Interactions:  
• increased anticoagulation effect of warfarin may occur  
• decreased absorption of itraconazole, ketoconazole may occur  
• increased clinical effect/toxicity of metformin, oral midazolam may occur  
Dosing:  
oral: 150mg twice a day or 300mg at night (reduce dose in elderly and renal impairment)  
si: 100 to 200mg/24 hours  
rectal: not available  
Syringe driver: not available  
Mechanism of Action: inhibits gastric acid secretion via histamine receptor blockade  
Onset (acid suppression): oral 10 to 20 minutes  
Availability:  
Tab 150mg, 300mg fully funded (Arrow-Ranitidine™)  
Oral Liq 150mg/10mL fully funded (Peptisoothe™)  
Inj 25mg/mL, 2mL fully funded (Zantac™)  
Cost: Approx $0.03 to $0.04 per tab, $0.20 per 10mL liq, $1.75 per inj  
Notes:  
• Omeprazole is considered the drug of choice for prophylaxis or treatment of NSAID-induced gastrointestinal damage.  
• If gastrointestinal reflux is uncontrolled by omeprazole, adding in a night time dose of ranitidine may help.

**QUETIAPINE**  
(Quetapell™, Seroquel™, Dr Reddy’s Quetiapine™)  
Class: antipsychotic - atypical  
Indication: acute and chronic psychoses including schizophrenia, manic episodes associated with bipolar disorder  
Unlicensed indications: nausea and vomiting, delirium  
Contraindications/cautions: liver dysfunction, cardiovascular and cerebrovascular disease, hypotension, seizures  
Adverse reactions: common drowsiness, dry mouth, GI effects, tachycardia, dizziness, headache, agitation, insomnia, weight gain, dyspepsia; less common neuroleptic malignant syndrome, tardive dyskinesia, cholesterol changes, thyroid hormone changes, peripheral oedema, diabetes, extrapyramidal adverse effects, hepatotoxicity, blood disorders, postural hypotension, seizures, dyspnoea, sweating, rash  
Metabolism/clearance: metabolised almost completely mainly in the liver by the metabolising enzyme CYP3A4/5/7  
Interactions:  
• increased clinical effect/toxicity of quetiapine (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. aripiprazole, clarithromycin, fluconazole, fluoxetine, grapefruit juice, itraconazole, ketoconazole, valproate  
• decreased clinical effect/toxicity of quetiapine (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampicin, St John’s wort  
• possible increase risk of extrapyramidal effects with dopamine antagonists e.g. metoclopramide  
• additive hypotension with antihypertensives e.g. propranolol may occur  
• additive CNS effects with other CNS depressants e.g. benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), opioids, alcohol  
Dosing:  
oral: psychosis – initially 50mg/day increasing daily to 150 to 750mg per day in 2 divided doses mania – initially 100mg/day increasing daily to 200 to 800mg per day in 2 divided doses tranquillisation, sedation, antiemetic 25 to 100mg at night  
si: not available  
rectal: not available  
Syringe driver: not available  
Mechanism of action: antagonises serotonin and dopamine receptors in the CNS  
Availability: Tab 25mg, 100mg, 200mg, 300mg fully funded  
Cost: Approx $0.12 to $0.67 per tab  
Notes:  
• Lower potential for neurological adverse effects (e.g. extrapyramidal effects) than conventional antipsychotics.  
• Increasingly used in acute delirium and behavioural disturbances associated with brain tumours.
RISPERIDONE
(Apo-risperidone™, Ridal™, Risperdal™, Dr Reddy’s Risperidone™, Risperon™)

Class: antipsychotic - atypical

Indication: schizophrenia, psychosis, behavioural/psychological symptoms of dementia, conduct/behavioural disorders in mentally retarded, autism, mania in bipolar disorder

Unlicensed indications: delirium

Contraindications/cautions: Parkinson’s disease, epilepsy, cardiovascular/cerebrovascular disease, diabetes

Adverse reactions: common insomnia, anxiety, headache, extrapyramidal symptoms
less common drowsiness, dizziness, GI upset, sexual dysfunction, constipation, dry mouth, postural hypotension

Metabolism/clearance: metabolised by metabolising enzymes CYP3A/4/5/7 and 2D6 mainly in the liver

Interactions:
- increased clinical effect/toxicity of risperidone (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. aprepitant, bupropion, clarithromycin, fluconazole, fluoxetine, grapefruit juice, itraconazole, ketoconazole, paroxetine, valproate
- decreased clinical effect/toxicity of prednisone (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. carbamazepine, dexamethasone, phenobarbitone, phenytoin, rifampicin, St John’s wort
- possible increased risk of extrapyramidal effects with dopamine antagonists e.g. metoclopramide
- additive hypotension may occur with antihypertensives e.g. enalapril
- additive CNS effects with other CNS depressants e.g. benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), opioids, alcohol

Dosing:
opticate:
- schizophrenia initially 2mg/day increasing to 4 to 6mg/day (max 16mg/day)
- bipolar mania initially 2mg/day increasing to 2 to 6mg/day
- dementia initially 0.25mg twice a day increasing to a max. of 1mg twice a day
- psychosis 0.5 to 4mg twice a day

oral:
- schizophrenia initially 2mg/day increasing to 4 to 6mg/day (max 16mg/day)
- bipolar mania initially 2mg/day increasing to 2 to 6mg/day
- dementia initially 0.25mg twice a day increasing to a max. of 1mg twice a day
- psychosis 0.5 to 4mg twice a day

Mechanism of Action: antagonises serotonin and dopamine receptors in the CNS

Onset: psychosis 1 to 2 weeks

Availability:
- Tab 0.5mg, 1mg, 2mg, 3mg, 4mg  fully funded
- Oral disintegrating tabs 0.5mg, 1mg, 2mg  fully funded as below
- Oral liquid 1mg/mL  fully funded
- Inj long acting 25mg, 37.5mg, 50mg (not usually used in palliative care) fully funded as below

Special Authority required for oral disintegrating tabs and long acting injections.

Cost: Approx $0.06 to $0.32 per tab, $0.76 to $3.06 per oral disintegrating tab, $0.61 per mL liq, $175 to $280 per inj.

Notes:
- Lower potential for neurological adverse effects e.g. extrapyramidal effects than conventional antipsychotics.
- Increasingly used in acute delirium and behavioural disturbances associated with brain tumours.
- At high dose (> 6 to 8mg a day) or in the cerebrally compromised patient extrapyramidal side-effects may occur.
**SPIRONOLACTONE**  
(Spiritone™, spironolactone (Biomed))  
**Class:** diuretic - aldosterone antagonist, potassium sparing  
**Indication:** oedema, hypertension, congestive heart failure, hirsutism, hyperaldosteronism  
**Unlicensed indications:** malignant ascites  
**Contraindications/cautions:** moderate/severe renal dysfunction, hyperkalaemia, hyponatraemia  
**Adverse reactions:** common GI upset, drowsiness, hyperkalaemia, rash, headache, confusion, impotence, gynaecomastia, hyponatraemia  
**Metabolism/clearance:** metabolised in liver to active metabolites which are excreted partially by the kidneys  
**Interactions:**  
- increased risk of hyperkalaemia with NSAIDs (e.g. diclofenac), ACE inhibitors (e.g. cilazapril, quinapril), potassium supplements  
- increased clinical effect/toxicity of digoxin may occur via increased digoxin concentrations  
**Dosing:**  
- oral: 100 to 200mg once a day (max. 400mg daily)  
- rectal: not available  
**Syringe driver:** not available  
**Mechanism of Action:** inhibits aldosterone causing naturesis and potassium retention  
**Peak response:** aldosterone antagonism 6 to 8 hours, reduced ascites 10 to 25 days  
**Availability:**  
- Tab 25mg, 100mg fully funded  
- Oral susp 5mg/mL fully funded  
- Specialist endorsement for liquid  
**Cost:** Approx $0.05 to $0.15 per tab, $1.07 per mL liq  
**Notes:**  
- Paracentesis may be necessary in malignant ascites.  
- Monitor body weight and renal function.

**SENN**  
(Senokot™)  
(in combination Coloxyl with Senna™, Laxsol™)  
**Class:** laxative - stimulant  
**Indication:** constipation  
**Contraindications/cautions:** acute abdominal pain, intestinal obstruction  
**Adverse reactions:** common abdominal cramps, diarrhoea, perianal irritation less common atonic colon (with prolonged use), hypokalaemia, discolouration of urine (brown or pink)  
**Metabolism/clearance:** not absorbed to a great extent  
**Interactions:**  
- decreased antispasmodic effects of antispasmodics e.g. hyoscine butylbromide may occur  
**Dosing:**  
- oral: 2 to 4 tabs (14 to 28mg) at night with docusate 1 to 2 tabs at night (max. 4 tabs)  
- rectal: not available  
**Syringe driver:** not available  
**Mechanism of Action:** stimulates colonic activity via nerves in the intestinal mucosa. May also have stool softening properties.  
**Onset:** 6 to 12 hours  
**Availability:**  
- Tab 7.5mg not fully funded  
- Tab 8mg with 50mg docusate fully funded (Laxsol™)  
**Cost:** Approx $0.02 per tab, $0.03 per combination tab  
**Notes:**  
- May be useful in opioid induced constipation.
TRAMADOL
(Tramal™, tramadol (AFT, Arrow))
Class: analgesic - opioid (with extra effect on inhibitory pain pathways)
Indication: step 2 on the WHO analgesic ladder
Unlicensed use: subcutaneous injection/infusion
Contraindications/cautions: epilepsy, drug abuse, respiratory depression
Adverse reactions: common nausea, vomiting, diarrhoea, sweating (dose related) less common dry mouth, sedation, headache, hypertension, confusion
Metabolism/clearance: metabolised by metabolising enzyme CYP2D6 mainly in the liver to an active metabolite
Interactions:
  • increased clinical effect/toxicity of tramadol (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. bupropion, fluoxetine, paroxetine, quinine
  • additive CNS effects with other CNS depressants e.g. benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), other opioids, alcohol
  • additive risk of serotonin syndrome (potentially fatal syndrome - symptoms include sweating, diarrhoea, confusion) with other serotonergic drugs e.g. amitriptyline, carbamazepine, citalopram, fluoxetine, lithium, paroxetine
  • decreases seizure threshold so may interact with anticonvulsants e.g. carbamazepine
Dosing:
oral: normal release 50 to 100mg 4 hourly (max. 400mg/24 hours)
slow release 100 to 200mg twice a day
sc: up to 600mg/24 hours
rectal: not available
Syringe driver: give separately as compatibility as yet unknown
Mechanism of Action: stimulates mu opioid receptors in CNS and gastrointestinal tract and also affects noradrenaline and serotonin in descending spinal inhibitory pain pathways
Peak effect: oral normal release 0.5 to 1 hour
Duration: oral normal release 3 to 7 hours
Availability: Caps (normal release) 50mg funded (Arrow)
Oral drops 100mg/mL not funded
SR tab 50mg, 100mg, 150mg, 200mg not funded
Inj 50mg/mL, 1mL, 2mL not funded
Cost: Approx $0.05 per cap, $0.66 per mL oral drops, $0.31 to $1.66 per SR tab, $1.22 to $1.41 per inj
Notes:
  • Place in palliative therapy still to be established.
  • May be useful in patients who are constipated on codeine as it is less constipating generally.
  • Start with low dose to minimise adverse effects.
  • It is not a controlled drug.

TRANEXAMIC ACID
(Cyclokapron™)
Class: antifibrinolytic, haemostatic
Indication: haemorrhage - surface bleeding from tumours, nose and other organs
Unlicensed indications: subcutaneous injection/infusion
Contraindications/cautions: active clotting, urinary tract bleeds, renal dysfunction, subarachnoid haemorrhage, acquired defective colour vision
Adverse reactions: common GI upset less common dizziness (iv), thrombocytopenia, headache, restlessness, impaired colour vision
Interactions:
  • decreased clinical effect of anticoagulants e.g. warfarin may occur with tranexamic acid
Dosing: haemorrhage
oral: 1 to 1.5g three to four times a day
sc: not used
rectal: the injection has been used rectally for rectal bleeding
topical: the injection has been used topically on bleeding wounds
iv: 0.5 to 1g two to three times a day
Syringe driver: not applicable
Mechanism of Action: interacts with plasminogen to cause antifibrinolysis
Peak effect: 3 hours
Availability:
Tab 500mg fully funded
Inj 500mg/5mL not funded
Cost: Approx $0.33 per tab, $12.47 per inj.
Notes:
  • Tablets are large and many patients may have difficulty swallowing them.
**VALPROATE (SODIUM)**
(Epilim™)

**Class:** anticonvulsant, antipsychotic

**Indication:** epilepsy, bipolar disease

**Unlicensed indications:** neuropathic pain

**Contraindications/cautions:** liver dysfunction

**Adverse reactions:** common GI upset, tremor less common thrombocytopenia, sedation, transient hair loss, hepatotoxicity

**Metabolism/clearance:** may be metabolised by CYP metabolising enzymes family mainly in the liver

**Interactions:**
- **increased clinical effect/toxicity of some drugs** (due to increased blood concentrations of them) may occur with valproate due to metabolising enzyme inhibition by valproate e.g. amitriptyline, carbamazepine, citalopram, NSAIDs (e.g. diclofenac), omeprazole, phenobarbitone, phenytoin
- **decreased clinical effect/toxicity of valproate** (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers e.g. carbamazepine

**Dosing:** neuropathic pain
- oral: 200 to 1,000mg twice a day (max. 2,500mg per day, start low)
- sc: available in injectable form, not usually used
- rectal: not available

**Syringe driver:** not applicable

**Mechanism of Action:** pain - as for carbamazepine

**Peak effect:** not known but peak concentrations reached in 4 to 8 hours

**Availability:**
- Tab crushable 100mg fully funded
- Tab ec 200mg, 500mg fully funded
- Liq 200mg/5mL fully funded
- Inj 100mg/mL, 4mL fully funded

**Costs:** Approx $0.14 to $0.52 per tab, $0.07 per mL liq, $41.50 per inj

**Notes:**
- Co-analgesic often used with opioids in the treatment of neuropathic pain although gabapentin has become a common alternative.
- May be used in neuropathic pain when tricyclic antidepressants have failed or in combination with tricyclic antidepressants.
- When switching from carbamazepine to sodium valproate watch for toxicity from other drugs as carbamazepine induces the metabolism of several drugs while sodium valproate inhibits the metabolism of several drugs.
- Don’t discontinue abruptly as risk of rebound seizures.
- Therapeutic drug monitoring is usually available but is of limited value.
- Monitor LFTs.

**VENLAFAXINE**
(Efexor™, Arrow-venlafaxine XR™)

**Class:** antidepressant - bicyclic, SNRI

**Indication:** depression, anxiety disorders

**Unlicensed indications:** neuropathic pain, hot flushes

**Contraindications/cautions:** renal/hepatic failure, volume depletion, epilepsy, mania, heart disease

**Adverse reactions:**
- common nervousness, headache, fatigue, blood pressure changes, dizziness, dry mouth, insomnia, drowsiness, weight gain or loss, GI effects, sexual dysfunction, sweating, weakness, prolongation of the QT interval
- less common tremor, mania, anxiety, palpitations, heart failure, loss of consciousness, seizures, blood disorders, hepatitis, arrhythmias, neuroleptic malignant syndrome, pancreatitis, extrapyramidal adverse effects, hypercholesterolaemia

**Metabolism/clearance:** metabolised by metabolising enzyme CYP2D6 mainly in the liver to active metabolites. Some venlafaxine and some of its metabolites are excreted by the kidneys.

**Interactions:**
- **increased clinical effect/toxicity of venlafaxine** (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. bupropion, fluoxetine, paroxetine, quinine
- **increased clinical effect/toxicity of some drugs** (due to increased blood concentrations of them) may occur with venlafaxine due to metabolising enzyme inhibition e.g. codeine (effect may be decreased due to lack of metabolism to morphine), nortriptyline
- **increased risk of serotonin syndrome with MAOIs** e.g. phenelzine so avoid venlafaxine within 2 weeks of MAOI therapy
- **increased risk of prolonged QT interval with other drugs** which prolong the interval e.g. haloperidol

**Dosing:** neuropathic pain
- oral: modified release 37.5 to 375mg once a day
- sc: not available
- rectal: not available

**Syringe driver:** not applicable

**Mechanism of Action:** inhibits reuptake of serotonin (at high dose), noradrenaline and dopamine in the CNS

**Availability:**
- modified release tab 37.5mg, 75mg, 150mg fully funded as below
- modified release cap 37.5mg, 75mg, 150mg fully funded as below

Special authority for patients with treatment resistant depression and after 2 antidepressants have failed or, if hospitalised for depression, 1 other antidepressant. Applications from specialist or vocational registered general practitioner. Valid for 2 years.

**Costs:** Approx $0.67 to $1.63 per tab/cap

**Notes:**
- Effectiveness in neuropathic pain is yet to be evaluated.
**WARFARIN**

(Coumadin™, Marevan™)

**Class:** anticoagulant

**Indication:** thrombotic disorders prophylaxis

**Contraindications/cautions:** potential haemorrhagic conditions

**Adverse reactions:** common bleeding less common hair loss, rare - purple toe syndrome

**Metabolism/clearance:** metabolised by the metabolising enzymes CYP 1A2, 2C9 mainly in the liver

**Interactions:**
- increased clinical effect/toxicity of warfarin (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. ciprofloxacin, fluconazole, fluoxetine, ketoconazole, omeprazole, valproate
- decreased clinical effect/toxicity of warfarin (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. broccoli like vegetables, carbamazepine, phenobarbital, phenytoin, rifampicin, smoking
- increased risk of bleeding with aspirin, SSRIs (e.g. fluoxetine), NSAIDs (e.g. diclofenac)
- increased clinical effect of warfarin may occur with paracetamol
- decreased clinical effect of warfarin may occur with phytomenadione (vitamin K) and foods rich in vitamin K

NB Any changes in drug therapy should be accompanied by an INR check.

**Dosing:** oral: adjusted to INR (see below)

<table>
<thead>
<tr>
<th>Strength</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tab 1mg, 3mg, 5mg</td>
<td>(Marevan™) fully funded</td>
</tr>
<tr>
<td>Tab 1mg, 2mg, 5mg</td>
<td>(Coumadin™) fully funded</td>
</tr>
</tbody>
</table>

**Cost:** $0.07 to $0.09 per tab

**Notes:**
- A low molecular weight heparin e.g. enoxaparin may be better tolerated.
- Different brands are not proven to be equivalent.

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**ZOLEDRONIC ACID**

(Aclasta™, Zometa™)

**Class:** bisphosphonate - calcium regulator

**Indications:** Aclasta™: osteoporosis treatment and prevention, Paget’s disease, prevention of further fracture after hip fracture, Zometa™: hypercalcaemia of malignancy, bone metastases

**Contraindications/cautions:** renal or hepatic impairment, cardiac impairment, hypo-, hypocalcaemic, phosphataemic or magnesaemic patients, administration with diuretics and other nephrotoxic drugs

**Adverse reactions:**
- common hypotension, fatigue, fever and other flu-like symptoms, GI upset (nausea), rash, chest pain, renal toxicity
- less common anxiety, insomnia, hypocalcaemia, hypophosphataemia and hypomagnesaemia, sore mouth/throat, eye irritation, conjunctivitis

**Metabolism/clearance:** excreted unchanged by the kidneys and not metabolised

**Interactions:**
- additive risk of renal toxicity with other nephrotoxic drugs e.g. frusemide, thalidomide

**Dosing:**
- oral: not available
- sc: not usual but has been tried
- rectal: not available
- iv infusion: hypercalcaemia 4mg iv infused over 15 mins
  - bone met pain 4mg iv as above every 3 to 4 weeks

**Syringe driver:** not applicable

**Mechanism of Action:** inhibits bone resorption

**Availability:**
- Tab 1mg, 3mg, 5mg (Marevan™) fully funded
- Tab 1mg, 2mg, 5mg (Coumadin™) fully funded

**Cost:** Approx $550 to $600 per inj/inf

**Notes:**
- Advantage over pamidronate is the shorter infusion time but zoledronic acid is a lot more expensive.
- Routinely check serum creatinine concentrations pre-administration and cease zoledronic acid if creatinine is rising.
SYRINGE DRIVERS
A syringe driver is a battery-operated pump which administers drugs subcutaneously—consult a specialist for information on the pump used in your area and how to use it.
Many of the drugs administered via the syringe driver are not licensed for subcutaneous use and the responsibility for their use lies with the prescriber.

Indications
- severe nausea and/or vomiting
- dysphagia
- severe oral lesions
- non-absorption of oral medication
- unconscious or sedated patient

Diluent
- most drugs and drug combinations used in a syringe driver need to be made up to a certain number of millimeters or volume with a diluent
- generally water for injection is currently used
- some drugs, however, must be diluted with a specified diluent e.g. levomepromazine (methotrimeprazine) in normal saline
- both water for injection and normal saline have advantages and disadvantages:
  - water for injection
    - has few ions present and therefore is less likely to cause precipitation of drugs out of solution
    - BUT may be more irritant to subcutaneous tissue
  - normal saline
    - contains ions and so is more likely to cause precipitation of drugs
    - BUT may be more like interstitial fluid and therefore less irritant to subcutaneous tissue

Compatibility
- often several drugs are combined in one syringe
- little work has been done on the compatibility of drugs in syringe drivers (see chart)
- examination of the drugs in the syringe may reveal visual incompatibility, e.g. precipitation BUT non-visual chemical reactions may be occurring leading to the inactivation of one or more of the drugs or the production of potentially toxic compounds
- only combine drugs that are absolutely essential - if there is any doubt, consultation with a drug information pharmacist will guide practice
- avoid combining more than three drugs in one syringe
- consider the use of more than one syringe driver when more than three drugs need to be given via this route or if there are concerns about compatibility

The following drugs should never be given subcutaneously
DIAZEPAM, PROCHLORPERAZINE, CHLORPROMAZINE
**SYRINGE DRIVER COMPATIBILITY TABLE**

| Compatibility of drugs for use in syringe drivers over 24 hours of subcutaneous infusions | clonazepam | cyclizine | dexamethasone | fentanyl | glycopyrrolate | haloperidol | hyoscine butyl bromide | hyoscine hydrobromide | ketamine | methotrimeprazine/levomepromazine | methadone | metoclopramide | midazolam | morphine tartrate (high strengths) | ondansetron | oxycodone | phenobarbitone |
| clonazepam | - | SI | Y | ? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | ? | Y | ? |
| glycopyrrolate | Y | Y | ? | Y | - | Y | NA | Y | Y | Y | Y | Y | ? | Y | Y | ? |
| haloperidol | Y | Y | SI | Y | Y | Y | Y | Y | Y | Y | SI | Y | Y | SI | Y | SI | ? |
| hyoscine butyl bromide (Buscopan™) | Y | SI | Y | Y | ? | - | NA | Y | Y | ? | Y | Y | ? | Y | SI | Y | ? |
| hyoscine hydrobromide | Y | Y | Y | NA | Y | NA | - | Y | Y | Y | Y | Y | Y | Y | SI | Y | SI | ? |
| ketamine | Y | ? | Y | Y | Y | Y | Y | Y | Y | - | Y | Y | Y | SI | Y | Y | Y | ? |
| methotrimeprazine/levomepromazine (Nozinan™) | Y | Y | SI | Y | Y | Y | Y | Y | Y | - | Y | Y | Y | SI | Y | SI | Y | Y | ? |
| metoclopramide | Y | Y | Y | Y | Y | Y | Y | Y | Y | - | Y | Y | Y | Y | Y | Y | Y | Y | ? |
| midazolam | Y | SI | SI | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | ? |
| morphine sulphate (normal strengths) | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | NA | ? | ? | N |
| morphine tartrate (high strengths) | Y | Y | Y | ? | ? | SI | ? | Y | Y | Y | NA | Y | SI | Y | Y | NA | Y | N |
| ondansetron | ? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | NA | Y | Y | Y | Y | Y | - | Y | ? |

**Combinations that have been used:**

- **Y** = compatible
- **N** = incompatible
- **SI** = sometimes incompatible (usually at higher concentrations)
- **NA** = not usually used together
- **?** = unknown

Y = compatible
- morphine+clonazepam+cyclizine (morphine sulphate and tartrate)
- morphine+cyclizine+dexamethasone (morphine sulphate and tartrate)
- morphine+dexamethasone+haloperidol (morphine sulphate and tartrate)

N = incompatible
- morphine+clonazepam+dexamethasone (morphine sulphate and tartrate)
- morphine+cyclizine+haloperidol (morphine sulphate and tartrate)
- morphine+dexamethasone+hyoscine hydrobromide (morphine sulphate and tartrate)

SI = sometimes incompatible (usually at higher concentrations)
- morphine+clonazepam+haloperidol (morphine sulphate and tartrate)
- morphine+cyclizine+hyoscine butyl bromide (morphine sulphate, tartrate SI)
- morphine+cyclizine+metoclopramide (morphine sulphate and tartrate)

NA = not usually used together
- morphine+clonazepam+ketamine (morphine sulphate and tartrate)
- morphine+cyclizine+metoclopramide (morphine sulphate and tartrate)
- morphine+cyclizine+midazolam (morphine sulphate and tartrate)

? = unknown
- morphine+clonazepam +metoclopramide (morphine sulphate Y, tartrate SI)
- morphine+cyclizine+midazolam (morphine sulphate and tartrate)
- morphine+dexamethasone+haloperidol (morphine sulphate and tartrate)

Diluent: water is recommended for all infusions except ketamine, octreotide, ondansetron and levomepromazine where sodium chloride 0.9% should be used although in combinations consider water.

Info from:
3) Compatibility of syringe driver admixtures for continuous subcutaneous infusions, Department of Pharmacy, Auckland District Health Board 2002
4) Palliative Care Formulary on line at www.palliativedrugs.co.uk
5) Gardiner P R Compatibility of an injectable oxycodone formulation with typical diluents, syringes, tubings, infusion bags and drugs for potential co-administration. Hospital Pharmacist 2003; 10: 354-61
USEFUL RESOURCES

International Association for the Study of Pain (IASP)
http://www.iasp-pain.org/
Palliativedrugs.com
http://www.palliativedrugs.com/
Palliative Care Matters
http://www.pallcare.info/
National Cancer Institute
http://www.cancer.gov/
Macmillan Cancer Support
http://www.macmillan.org.uk/
Quality of life
http://www.dyingwell.org/landmarks.htm
Spirituality
http://www.facit.org
Dying matters
http://www.dyingmatters.org
Hospice New Zealand
http://www.hospice.org.nz

FURTHER READING

BOOKS
disease. Oxford University Press, Oxford
Oxford; Oxford University Press
disorder.3rd Edition. Oxford; Blackwell
Oxford University Press
Cambridge University Press
mind. Oxford; Radcliffe Publishing
Books.
Sandler J, Dare C, Holder A. (1972) The Patient and the Analyst: The basis of the
psychoanalytic process. New York; International Universities Press
Oxford University Press
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