Nurse Maude

The Palliative Care Handbook

Incorporating the

Nurse Maude Palliative Care Formulary

Guidelines for clinical management and symptom control

4th EDITION

2009

Prof Rod MacLeod, Jane Vella-Brincat, Dr A.D. (Sandy) Macleod

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Acknowledgements to:
The organ failure at the end of life section and much of the drug interaction data is based on part of the Canterbury District Health Board's Preferred Medicines List, Antibiotic Guidelines and Pharmacology Guidelines 12th Ed. 2008
Thanks to Helen Lunt for the diabetes section.

2009

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.

Printed by The Caxton Press

Cover: Image courtesy of MODIS Rapid Response Project at NASA/GSFC

ISBN:0-473-08172-5

FOREWORD

A message of hope to those in painful expectation of death:

"a testimonial to the wonder of morphine, and a personal tribute to that most marvellous product of twentieth century medicine, PALLIATIVE CARE"

Dr Paul Egermayer (1946-2001) New Zealand Medical Journal, Aug 2001 page 367

This moving tribute to palliative care written by a colleague just before his death from cancer highlights the importance of this often unheralded field of medicine. This handbook itself assists the process. Its mere presence gives strength to the growing credibility of the field. Its contents assist the practitioners within the field to do it better.

This handbook will be an invaluable ready reference for doctors and nurses involved in the field but also for those in need of palliative care, and their whanau.

Somehow, by addressing all the topics in a brief, easily accessible and non-judgemental way, the subject becomes just another part of life, which is how it should be.

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CONTENTS

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 is information about drugs:
    - 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 which 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

- The third section is a list of medicines used in palliative care. The medicines are by symptom and in order of preference where appropriate. Most of the medicines listed are included in the main body of the book some, however, are not.

- The fourth section contains further reading.

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 problems
- to be applicable from early on in the course of the illness

The World Health Organisation defined Palliative Care as[1]:

"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

1) Sepulveda C. Marlin A, Yoshida T, Urlich A. Palliative Care: The World Health Organisation's Global Perspective. Journal of Pain and Symptom Management 2002; 24(2): 91-96

PAIN

The assessment and management of pain are seen by many as 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 griping (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

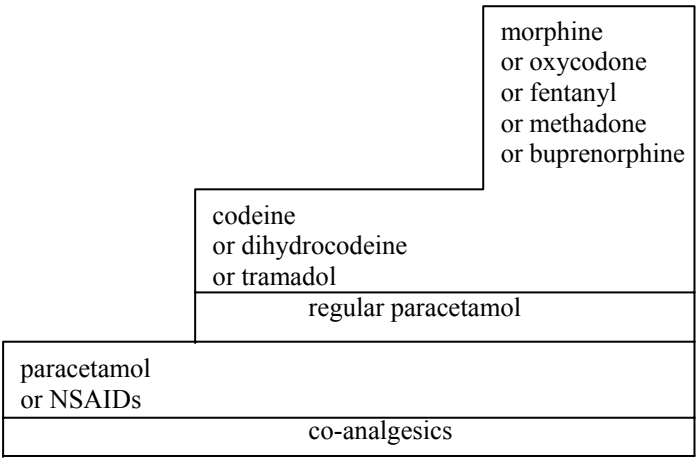
Other assessment factors

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

- some pains may not respond completely to opioids
- co-analgesics are useful when response to opioids is poor
- in prescribing analgesics use a step-wise approach:



- there is some debate over the second step in this ladder
    - many 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 is unclear

Initiating morphine (first line opioid) in opioid naïve patients

- start with small regular oral (if possible) doses
- prescribe morphine elixir (2.5-5mg) 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 liquid 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 elixir 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 over 24 hours
    - '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)

Initiating oxycodone in opioid naïve patients

- start with small regular oral (if possible) doses
- use oxycodone immediate release capsules or liquid (OxyNorm^{TM}) every 4 hours and titrate
- prescribe 'when required' doses of 1/10th to 1/12th initially (although many practioners 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^{TM})
    - 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 practioners 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)

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 doseage and consideration should be given to dose reduction once at steady state (minimum 5 days)

Adverse effects of opioids

- all opioids are associated with the following adverse effects but the incidence (incidences below 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) - 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 haloperidol
    - **hallucinations** - 1% of patients - give haloperidol or change to a different opioid

Opioid Rotation

- tolerance to the analgesic effects of opioids can occur over time and may involve stimulation of NMDA receptors
- severe adverse effects can occur
- opioid rotation (or changing from one opioid to another) is often used when either of the above occurs
- opioid rotation works because of the difference in the mix of opioid receptors stimulated by each individual opioid
- in practice rotation is 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 over - 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	60 mg oral	=	6 mg oral morphine
tramadol	100 mg oral	=	10 mg oral morphine
oxycodone	5mg oral	=	10mg oral morphine
	5mg sc	=	5mg sc morphine
pethidine	75 mg im/sc	=	10 mg im/sc morphine
	300 mg oral	=	35 mg oral 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
- **bone pain** - due to tumour or metastatic involvement
    - NSAIDs e.g. diclofenac - inhibit prostaglandins
    - bisphosphonates e.g. pamidronate
- **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/antimuscurinic 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
    - steroids e.g. dexamethasone - decrease inflammation around tumour
    - NSAIDs e.g. diclofenac - inhibit prostaglandins
- **liver capsule stretch pain** - from an enlarged liver
    - steroids e.g. dexamethasone

NEUROPATHIC PAIN

- often the most severe and difficult to manage of all persisting pains
- caused by damage to the nervous system
- 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

Characterisation

- characterised by description and by cause
    - BUT the pain is not always within the distribution of a dermatome or a peripheral nerve
- includes allodynia (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 used may help to differentiate between superficial and deep neuropathic pain:

"Superficial"	**"Deep"**
burning	cramping
cutting	aching
stabbing	throbbing
sharp/shooting	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 (now 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
        - tricyclic antidepressants e.g. nortriptyline
        - SSRIs e.g. citalopram, paroxetine
        - anticonvulsants e.g. valproate, gabapentin
        - benzodiazepines e.g. clonazepam
        - antiarrhythmics e.g. mexiletine
        - muscle relaxants e.g. baclofen
        - NMDA antagonists e.g. ketamine
        - alpha-adrenergic agents e.g. clonidine
        - calcium channel blockers e.g. nifedipine
        - steroids e.g. dexamethasone for nerve pressure pain

  Although the above drugs do not appear to have differing analgesic 'strengths', the following approach is usually used:

  antidepressant → (if ineffective/intolerable) anticonvulsant (+/- antidepressant)

    - if the above are ineffective consider intrathecal/epidural opioids, local anaesthetics and clonidine
- other analgesic modalities
    - nerve blocks
        - availablility is dependent on the skills of the team
        - access to a specialist anaesthetist is not always possible
        - consultation with an anaesthetist can guide practice
        - useful for pain which breaks through analgesia, pain which is controlled at rest but not on movement, pain which is not responding - may be analgesic sparing

- others - often used in conjunction with analgesics
  - mobilisation e.g. structured stretching, strengthening and aerobics
  - 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 stimulation or dorsal column nerve stimulation

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, 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)
- 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
    - 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
- 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
    - **intestinal obstruction**
        - cyclizine
        - levomepromazine
        - avoid prokinetics e.g. metoclopramide in complete obstruction although use in partial obstruction may help - see intestinal obstruction protocol
- chemoreceptor trigger zone stimulation (uraemia, hypercalcaemia, drugs e.g. morphine)
    - haloperidol
    - levomepromazine
- vestibular nerve stimulation (motion)
    - cyclizine
    - hyoscine patch (scopolamine)
- other drugs which may be useful where others have failed
    - atypical antipsychotics e.g. olanzapine
    - ondansetron
    - 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.

BOWEL MANAGEMENT

- alteration in bowel function is common in the terminally ill
- 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
- 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)
- 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
- excercise 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^{TM})
    - if constipation is already present give a bisacodyl 10mg and a glycerin suppository or a sodium lauryl sulphoacetate enema (Microlax^{TM})
    - avoid stimulant laxatives in people with signs or symptoms of gastrointestinal obstruction
    - if the patient has a partial small bowel obstruction an osmotic/softener laxative such as docusate should be used and stimulant laxatives should be avoided
    - if the patient has a spinal cord compression where evacuation is difficult the bowel motion should be kept firm so a stimulant without softener such as senna should be used
    - 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 Microlax™ 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
- faeces consist of 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
- antibiotics
- bowel surgery or inflammation
- anxiety

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
- 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
- secretory diarrhoea (associated with carcinoid syndrome or AIDS) may respond to octreotide

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
- 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 sc fluids may have a role
- 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

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

Assessment/causes

- appropriate and effective oral assessment should be carried out on each patient daily using a pen torch and spatula
- assess mental state, nutritional state, physical state, pain, concurrent medications, tongue assessment, state of teeth/dentures, state of mucous membranes, type of saliva, and state of 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 mouthcare 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
    - 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

- chlorhexidine mouthwash is a useful cleansing agent
- benzydamine is an analgesic mouthwash for painful mouths
- nystatin suspension is useful in the treatment of oral thrush but may take up to two weeks to clear an infection
- miconazole oral gel is also useful in the treatment of oral thrush, 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 infections
- aciclovir may be useful for herpetic infections

- topical corticosteroids e.g. triamcinolone in orabase may be useful for aphthous ulcers
- frequency of care is dependent on the patient
- there is little point in cleaning the mouth if dentures are worn unless those dentures are also meticulously cleaned (including soaking overnight)
- 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)
- pilocarpine solution (1mg/mL, 5mL rinse three times a day) may be useful for dry mouths
- 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 or radiotherpay

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

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

Causes

- peritoneal fluid build up in the abdomen due to a failure of the lymph system to adequately drain
- tumour in peritoneal cavity
- low serum albumin
- excess fluid production

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)
- 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
- **Drug treatment of symptoms**
    - if the patient is fit for diuretics, give spironolactone 100mg (or more) with or without frusemide 40mg once daily
    - if there is evidence of gastric stasis give a prokinetic agent e.g. metoclopramide
    - if evidence of liver capsule stretch pain use a steroid e.g. dexamethasone - see co-analgesics protocol

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 figures of a median of 15% (compared with 5 to 10% in the general population) are quoted, most commonly in the early cancer stages
- reaching a diagnosis of depression in terminal patients is difficult as many of the usual physical symptoms of depression in the otherwise well such as anorexia, weight loss and 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 sensitive 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
- 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 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
- ruminative negative thoughts
- nihilistic and depressive delusions
- feeling of unreality

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 50-70% of cases
        - a therapeutic trial is usually appropriate
        - if in doubt, refer to a specialist psychiatrist
        - SSRI e.g. citalopram, fluoxetine
            - if no response in 4 to 6 weeks try a tricylic antidepressant e.g. nortriptyline
    - psychostimulants e.g. methylphenidate
        - not as effective as SSRIs but may help retarded or withdrawn, physically frail patients who may only require short courses (a few weeks)
        - 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

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 (difficulty in expressing thoughts in 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

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)
    - major tranquillisers or neuroleptics (calm or pacify rather than sedate)
        - haloperidol is the drug of choice (see haloperidol in second section) BUT not in AIDS delirium (HIV makes the CNS sensitive to dopamine antagonists), hepatic encephalopathy or alcohol withdrawal where benzodiazepines only should be used
        - levomepromazine
        - 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 a tranquilliser)
        - 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 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 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. notriptyline 10 to 20mg
    - major tranquillisers or neuroleptics e.g. quetiapine 25 to 50mg at night may be considered if insomnia is resistant to above

DROWSINESS/HYPERSOMNIA
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

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
    - major tranquillisers or neuroleptics 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 27)
- 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
  - BUT benzodiazepines e.g. midazolam in inadequate doses can aggravate (by disinhibition) rather than relieve restlessness in some patients

TERMINAL SEDATION

This is considered when all other symptom-relieving measures have failed and the patient is clearly distressed.

Reasons for terminal sedation

- terminal restlessness (see terminal restlessness)
- uncontrolled delirium (see delirium)
- severe breathlessness (see dyspnoea)
- massive haemorrhage (see haemorrhage)
- neurogenic or cardiogenic pulmonary oedema

How terminal sedation is achieved

- the level of sedation should be titrated to removal of distress
- drugs
    - benzodiazepines e.g. midazolam, clonazepam
    - major tranquillisers or neuroleptics e.g. levomepromazine
    - barbiturates e.g. phenobarbitone
    - opioids
        - BUT increasing doses may not result in increased sedation (opioids tend only to be sedating in the opioid naïve or transiently after dose increases) 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. Terminal 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
- failing to complete life goals or obligations
- uncontrolled pain or other symptoms
- abandonment
- not knowing how death will occur
- 'death anxiety' (the fear of non-being)
- spirituality

Management

- careful listening and attention to detail
- support to maintain independence and autonomy
- honest and open discussion about the future with the patient and family at a pace that they can accommodate
- support realistic hope for the future
- provide distractions to avoid boredom and excessive self-reflection
- attend to social and financial problems
- use desensitisation techniques for phobias
- provide focussed spiritual care if appropriate
- psychotropic drugs - may be a useful adjunct
  - benzodiazepines e.g. lorazepam can be very effective in the short term (days to weeks) but this may fade and there is a risk of tolerance and dependency
  - beta-blockers e.g. propranolol may block the peripheral symptoms and thus ease the unease
  - antidepressants e.g. citalopram, fluoxetine may be more effective longer term than benzodiazepines

RESPIRATORY SYSTEM

Respiratory symptoms are amongst the commonest at the end of life. Studies have shown that dyspnoea (breathlessness), for example, occurs in 29% to 74% of dying patients. In addition cough, haemoptysis, hiccup and pleural pain are present in a considerable number of dying people.

DYSPNOEA (breathlessness)

Breathlessness is one of the commonest and most distressing symptoms for both patients and relatives as the end of life approaches.

- it has an incidence of 29-74% of people near the end of life
- the distress caused by breathlessness should not be underestimated
- a careful evaluation of the nature of the breathlessness is important
- listening to the descriptors (the language that the patient uses to describe the sensation) of the quality and quantity of breathlessness is important in choosing management
- breathlessness will only rarely be expressed in purely physical terms
- the assessment of breathlessness should use a multidimensional approach, as with the assessment of pain
- identifying the cause(s) is an essential step in effective management

Causes

- often multifactorial
- it is not always possible to identify one treatable cause
- impaired performance (can be broken down further into a number of separate entities)
    - airflow obstruction
        - this can be related to **large** airways (tumour producing either extrinsic or intrinsic obstruction, laryngeal palsy, radiation stricture)
        - or **smaller** airways (asthma, emphysema, chronic bronchitis, lymphangitis carcinomatosis)
    - decreased effective lung volume (effusions, ascites, pneumothorax, tumour, lung collapse, infection)
    - increased lung stiffness (pulmonary oedema, lymphangitis carcinomatosis, pulmonary fibrosis, mesothelioma)
    - decreased gas exchange (as above plus pulmonary emboli, thrombotic tumour, tumour effect on pulmonary circulation)
    - pain (pleurisy, infiltration of the chest wall, rib or vertebral fractures)
    - neuromuscular failure (paraplegia, motor neurone disease, phrenic nerve palsy, cachexia, paraneoplastic syndromes)
    - left ventricular failure (congestive heart failure)

    - ascites/pleural effusion
- increased ventilatory demand (related to anxiety, anaemia or metabolic acidosis)

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 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 physio - therapists 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
- drugs
    - opioids (usually morphine)
        - oral/parenteral (inhaled opioids are not effective)
        - doses should be titrated to response
    - oxygen
        - a draught of fresh air may be as effective as oxygen so only use in hypoxic patients
    - nebulised normal saline
    - bronchodilators (nebulised/inhaled) e.g. salbutamol
        - for patients with reversible airway obstruction
    - corticosteroids e.g. dexamethasone
        - for patients with lymphangitis carcinomatosis, bronchial obstruction or radiation pneumonitis
    - benzodiazepines (short acting) e.g. midazolam
        - in anxious or fearful patients where other methods have failed
    - antibiotics e.g. amoxicillin
        - if infection is suspected
    - diuretics
        - if congestive heart failure or pulmonary oedema are present
    - anticholinergics e.g. hyoscine, glycopyrrolate
        - if secretions are bothersome - see excessive (retained) secretions

COUGH

Cough is often associated with other symptoms such as dyspnoea, wheezing or chest tightness.

- a defensive mechanism, like pain
- 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, 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

- nebulised local anaesthetics e.g. lignocaine (lidocaine)
  - may be useful in intractable cough
  - patients should be warned not 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 the cough associated with endobronchial tumour, 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.

- the phrenic and vagal nerve and the brain stem are involved
- a most distressing symptom and should be attended to with urgency

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 pCO_2 using paper bag rebreathing or breath holding
- drugs
    - neuroleptics e.g. haloperidol, chlorpromazine, levomepromazine
    - muscle relaxants e.g. baclofen
    - benztropine
    - anticonvulsants e.g. phenytoin, valproate, carbamazepine, gabapentin
        - may be useful if a CNS cause is present
    - corticosteroids e.g. prednisone, dexamethasone

  Several of the above may have to be tried.

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

Causes

- inability to swallow or clear secretions
    - salivary secretions
    - bronchial secretions

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 may cause delirium while glycopyrrolate does not
- 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/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. cetirizine, promethazine
    - bile sequestrant e.g. cholestyramine 4-8g 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 150-300mg per day (chronic cholestasis)
    - 5HT3 antagonists e.g. ondansetron
    - doxepin capsules or cream
    - thalidomide
    - paroxetine (paraneoplastic itch)
    - gabapentin

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
    - tricyclic anti-depressants
    - opioids

Management

- treat/remove causes
- drugs
    - NSAIDs e.g. diclofenac
        - acts via prostaglandins in the hypothalamus
    - cimetidine 400mg to 800mg at night
        - acts on histamine receptors in skin
    - steroids e.g. dexamethasone
    - paracetamol (for night sweats)

PRESSURE AREA CARE

Pressure areas 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 by nursing staff
- 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 sores 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
- honey dressings may be of value as antibacterials

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 – see the bulletin board at www.palliativedrugs.com

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 idoform paraffin paste (BIPP) paste may help in drying up the wound and reducing odour
- many fungating wounds are painful - use systemic analgesics
- morphine injection added to KY jelly in a clean environment and used topically may help
- radiotherapy, chemotherapy and hormone manipulation should be considered for some tumours

MISCELLANEOUS

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 BUT 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
    - negative energy balance (negative calorie and nitrogen balance), increased calorific requirements, decreased efficiency, cachetin/tumour necrosis factor increase
- 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
- carcinomatous neuropathy and myopathy

- paraneoplastic syndromes e.g. Lambert-Eaton myasthenic syndrome, motor neuropathy
- radiotherapy and chemotherapy
- insomnia

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, SBE, 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
        - BUT effect on fatigue is thought to be minimal
    - prokinetic antiemetics e.g. metoclopramide
        - decrease nausea and vomiting, increase food intake and appetite
        - BUT no evidence of weight gain reported

- steroids e.g. dexamethasone
    - weight gain and fat deposition has been documented but with no increase in lean body mass
    - benefit may be transient

Although the above drugs may be effective in some patients potential benefit should be weighed against adverse effects e.g. long term steroids causing muscle weakness.

ANAEMIA

A significant proportion of people with advanced disease are anaemic.

- symptomatic anaemia usually presents when the haemoglobin is below 80g/L

Symptoms

- fatigue
- delirium
- dyspnoea
- 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 taking a calcium concentration blood sample
- 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
- emotional disturbance

Causes

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

Management

- make the diagnosis
- decide about the most appropriate course of action together with the patient, family and team
- the aim is to provide symptom relief and reduce serum calcium to an acceptable level using minimal intervention
    - mild-moderate (serum calcium 2.6 to 3.0 mmol/L)
        - initially oral then, if necessary, iv rehydration
        - consider steroids
    - moderate-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
            - pamidronate 90mg iv infusion (can be given as a subcutaneous infusion)
            - zoledronic acid 4mg iv infusion can be used but is significantly more expensive

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 patient and family

Management

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 above
- other drug therapy
  - tranexamic acid 1-1.5g po two to four times daily (inhibits plasminogen activation and fibrinolysis)

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 (5 g twice daily)
  - 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

Symptoms

- pain
- weakness especially of lower limbs
- sensory disturbance
- loss of sphincter control

Management

- urgent assessment
    - history and clinical findings
    - MRI or CT 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.

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 is 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
- 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))

- 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 convert to insulin to avoid the adverse effects of metformin e.g. nausea, weight loss and lactic acidosis,
- 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
- 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
    - 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 as it may be difficult to reverse without systemic therapy especially if the patient is vomiting or not eating

- give a fast acting insulin analogue e.g. aspart insulin (NovoRapid™) 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, once or twice daily injections at 75% of the 24 hour short acting dose. Chart a fast acting insulin analogue e.g. aspart insulin (NovoRapid™) 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.

- 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 daily and chart a fast acting insulin analogue e.g. aspart insulin (NovoRapid™) 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

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
  - 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 terminal patients
  - 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
- drug related monitoring of blood glucose
    - corticosteroids e.g. dexamethasone, prednisone
        - often cause hyperglycaemia
        - any patient who has taken them for longer than three weeks should have intermittent blood glucose concentration monitoring
        - diabetic patients taking them should have more intense blood glucose monitoring depending on the prognosis
            - monitor fasting blood glucose concentrations daily for a week then three times a week for three weeks or until stable then weekly
            - in terminal patients take a fasting blood glucose concentration every two days for one week and then according to clinical status

HYPOGLYCAEMIA

Symptoms - CNS

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

Symptoms - peripheral

- palpitations
- tremor
- sweating

- hunger
- paraesthesia
- pallor
- increased heart rate

Causes

- diseases
  - insulomas (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. tolbutamide
  - alcohol
  - quinine
  - pentamidine

Management

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

ORGAN FAILURE at the END of LIFE

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)
- 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 that if urea is raised risk of GI bleed increases

Drug dosing

- as the kidneys fail creatinine plasma concentrations will rise
- many labs around New Zealand now report an estimated glomerular filtration rate (eGFR) using the MDRD equation - 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:

Creatinine clearance (CrCl)

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

(lean 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:

$$\textbf{Adjusted dose} = \frac{\text{calculated creatinine clearance}}{100\text{mL/min}} \times \frac{\text{normal dose}}{1}$$

LIVER FAILURE

End stage liver failure is usually seen with liver metastases or past alcohol abuse.

Symptoms

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

Drug dosing

- albumin concentrations and INR are a measure of how well the liver can clear drugs (its metabolic capacity)
- doses of metabolised drugs should be adjusted only in severe liver failure as the liver has a large functional reserve
- doses of drugs with low therapeutic index may need to be reduced in moderate (reduce by 25%) and severe liver failure
- severe liver failure
    - albumin of < 30g/L and an INR of > 1.2
    - affects the metabolism of drugs that are mainly cleared from the body by the liver rather than the kidneys (metabolised drugs)
    - most metabolised drugs - 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.

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 icthyosis (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 hyponatremia which is common near the end of life
    - symptoms appear at plasma sodium concentrations <125 mmol/L and include stupor, coma and seizures

Neurological syndromes

- Lambert-Eaton myasthenic syndrome (LEMS)
    - associated with small-cell lung cancer
    - manifests as muscle weakness and fatigue
    - may respond to immunosuppression, plasmaphoresis 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

Management

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

AMITRIPTYLINE

(Amitrip™, Amirol™)

Class: tricyclic antidepressant - co-analgesic in neuropathic pain

Indication: depression

Unlicensed indications: co-analgesic in neuropathic pain

Contraindications/cautions: arrhythmias, recent MI, epilepsy (lowers seizure threshold), urinary retention, severe hepatic dysfunction (reduce dose), hyponatraemia

Adverse reactions:

common anticholinergic - dry mouth, blurred vision, urinary retention, drowsiness (tolerance may develop), constipation

less common sweating, confusion, arrhythmias (and QT interval prolongation), tachycardia, postural hypotension (may double incidence of femoral fractures), serotonin syndrome, lowered seizure threshold

Metabolism/clearance extensively metabolised by the metabolising enzymes CYP3A4, 2D6, 2C19, 2C9 and 1A2 mainly in the liver - active metabolite is nortriptyline

Interactions:

- *increased clinical effect/toxicity of amitriptyline* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. **fluconazole, fluoxetine, grapefruit juice, haloperidol, itraconazole, ketoconazole, metronidazole, miconazole, omeprazole, paroxetine, valproate**
- *decreased clinical effect/toxicity of amitriptyline* (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. **broccoli-like vegetables, cannabis, carbamazepine, cigarette smoke, dexamethasone, phenobarbitone, phenytoin, prednisone, rifampicin**
- *additive risk of serotonin syndrome* (potentially fatal syndrome - symptoms include sweating, diarrhoea, confusion) with other serotonergic drugs e.g. **carbamazepine, citalopram, fluoxetine, lithium**, **paroxetine, tramadol**
- *additive drowsiness* with **alcohol, benzodiazepines (e.g. clonazepam), opioids**
- *additive increased risk of QT interval prolongation* (cardiac adverse effect which may lead to arrhythmias) with CYP metabolising enzyme inhibitors (see above) and others e.g. **lignocaine, lithium, haloperidol**
- *additive analgesia* with **opioids**

Dosing: pain (neuropathic): 10 to 50mg at night (start at 10mg)
depression: 50 to 200mg per 24 hours

Syringe driver: not available

Mechanism of action: pain - unclear but may be related to effects on serotonin and noradrenaline in descending pain pathways

Onset: pain: 3 to 7 days depression: 3 to 4 weeks

Availability: Tab 10mg, 25mg, 50mg fully funded (Amitrip™, (Amirol™10mg))

Cost: Approx $0.03-$0.05 per tab

Notes:

- May enhance opioid effects.
- Doses of > 50mg a day may be ineffective for nerve pain as there may be an analgesic 'therapeutic window'.
- Metabolised to nortriptyline which is more tolerable.

BISACODYL

(Bisacodyl (AFT), (Baxter), Dulcolax™, Fleet Laxative Supp™, Lax-Tabs™)

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 twice a day	
sc:	not available	
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-Tabs™)
Supp 5mg	not fully funded (Dulcolax™)
Supp 10mg	fully funded (Fleet™)

Cost: Approx $0.02 per tab, $0.33-$0.39 per supp

Notes:

- May be useful in opioid induced constipation especially in combination with a softener.

BUPRENORPHINE

(Temgesic™, Norspan™)

(in combination: Suboxone™)

Class: analgesic – opioid, partial mu agonist/kappa antagonist

Indication: step 3 on the WHO ladder for 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 metabolising enzyme CYP3A4 mainly in the liver.

Interactions:

- *increased clinical effect/toxicity of buprenorphine* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. **fluconazole, fluoxetine, grapefruit juice, itraconazole, ketoconazole, metronidazole, valproate**
- *decreased clinical effect/toxicity of buprenorphine* (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. **carbamazepine, dexamethasone, phenobarbitone, phenytoin, prednisone**
- *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:

sl:	up to 32mg/day
sc:	? 300-900mcg in 24 hours
patch:	5-20mcg/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 11-21 hours

Duration: patch: 7 days

Availability:

Patches: 5mcg, 10mcg, 20mcg/hour	not funded
Injection: 300mcg/mL	not fully funded
SL Tabs with naloxone: 2mg/0.5mg, 8mg/2mg	not funded

Controlled drug form required.

Cost: Approx $1.48 per inj, approx $8.55-$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.
- Use within 24hours of other opioids may lead to severe opioid withdrawal.
- A ceiling of 32mg per 24 hours is thought to exist for buprenorphine above which no added analgesia is seen.
- 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 use more than two 20mcg patches at once.
- Do not cut patches.
- Equivalence to other opioids data are sparse.

CARBAMAZEPINE

(Tegretol™)

Class: anticonvulsant - co-analgesic in neuropathic pain

Indication: epilepsy, neuropathies, mood stabiliser

Contraindications/cautions: bone marrow depression, severe hepatic dysfunction (reduce dose)

Adverse reactions:

common dry mouth, diarrhoea, constipation, dizziness, nausea, ataxia (dose related), blurred vision, rash

less common vomiting, confusion (dose related), blood dyscrasias, increased LFTs

Metabolism/clearance: metabolised by metabolising enzymes CYP3A4 (major) and 2C8 mainly in the liver

Interactions:

- *increased clinical effect/toxicity of carbamazepine* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. **fluconazole, fluoxetine, grapefruit juice, itraconazole, ketoconazole, metronidazole, miconazole, valproate**
- *decreased clinical effect/toxicity of carbamazepine* (due to decreased blood concentrations) may occur with some CYP metabolising enzyme inducers (see above) e.g. **dexamethasone, phenobarbitone, phenytoin, prednisone, rifampicin**
- *decreased clinical effect/toxicity of carbamazepine and other drugs metabolised by CYP enzymes (*due to induction of their metabolism by carbamazepine) may occur e.g. **amitriptyline, dexamethasone, itraconazole, ketoconazole, midazolam, prednisone, triazolam**
- *additive risk of serotonin syndrome* (potentially fatal syndrome - symptoms include sweating, diarrhoea, confusion) with other serotonergic drugs e.g. **amitriptyline, citalopram, fluoxetine, paroxetine, tramadol, lithium**

Dosing: pain (neuropathic)

oral:	100 to 600mg twice a day (withdraw slowly) Start with 100 to 200mg once or twice daily and titrate to pain, increasing by 100 to 200mg every 2 weeks to a maximum of 800 to 1200mg per 24 hours in divided doses.
sc and rectal:	not available

Syringe driver: not available

Mechanism of action in pain still unknown but may be related to reduction in nerve cell excitability

Peak concentrations: normal release: 4 to 5 hours syrup: 1.5 hours CR: 3 to 12 hours

Onset (pain): 3 to 7 days

Availability:	Tab 200mg, 400mg	fully funded (Tegretol™)
	Tab CR 200mg, 400mg	fully funded (Tegretol CR™)
	Syrup 100mg/5mL	fully funded (Tegretol™)

Cost: Approx $0.15 - $0.39 per tab, approx $0.55 per 5mL syrup

Notes:

- Monitor plasma concentrations.
- Co-analgesic often used with opioids in the treatment of neuropathic pain.
- May be used in neuropathic pain where tricyclic antidepressants have failed or in combination with tricyclic antidepressants - see neuropathic pain section.
- Valproate is a more often used anticonvulsant in neuropathic pain.

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 (decreases platelet aggregation), 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

Metabolism/clearance: metabolised by metabolising enzymes CYP2C19 and 3A4 (minor) 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, tamoxifen, valproate**
- *decreased clinical effect/toxicity of citalopram* (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. **dexamethasone, 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 **warfarin**

Dosing: oral: 10-40mg 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 (except Cipramil™)

Cost: Approx $0.04-$0.12 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.

CLONAZEPAM

(Rivotril™, Paxam™)

Class: anticonvulsant - benzodiazepine

Indication: epilepsy, convulsions

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

Contraindications/cautions: avoid sudden withdrawal, respiratory depression

Adverse reactions:

common fatigue, drowsiness (at higher doses)

less common respiratory depression, incontinence, co-ordination problems, disinhibition, increase in salivation, confusion

Metabolism/clearance: metabolised by metabolising enzyme CYP3A4 (minor) mainly in the liver

Interactions:

- *increased clinical effect/toxicity of clonazepam* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. **fluconazole, fluoxetine, grapefruit juice, itraconazole, ketoconazole, metronidazole, 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**
- *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: sedation, anxiety, agitation, restless leg syndrome, neuropathic pain, dyspnoea, hiccups, convulsions

oral:	0.5 to 8mg a day (1 to 2mg a day usually adequate)
sc:	1 to 8mg/24 hours
rectal:	not available

Syringe driver: see syringe driver compatibility table

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

Onset: oral (seizure control) 20 to 40 minutes

Half life: > 30 hours (18 to 45 hours)

Availability:	Tab 0.5, 2mg	fully funded (Paxam™)
	Oral drops 2.5mg/mL	fully funded (Rivotril™)
	Inj 1mg/mL 1mL	fully funded (Rivotril™)

Cost: Approx $0.06 to $0.11 per tab, $0.74 per mL oral drops, $1.87 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

Drug	Anxiolytic	Night sedation	Muscle relaxant	Anticonvulsant
Diazepam	+++	+	+++	++
Lorazepam	+++	++	+	+
Clonazepam	++	+	+	+++
Temazepam	+	+++	+	+
Midazolam	+	+++	+	+++
Zopiclone	-	+++	-	-

CODEINE PHOSPHATE

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

(in combination Codalgin™, Codral™, Panadeine™, Mersyndol™, Neurofen Plus™, Paracotene™)

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

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. **fluoxetine, paroxetine (not citalopram)**
- *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)
	Combination tabs	fully funded (Codalgin™)
	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.

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)
sc:	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 (Valoid (AFT)™)

Cost: Approx $0.19 per tab and $3.00 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.

DEXAMETHASONE

(Dexamethasone (Biomed), (Douglas), dexamethasone sodium phos (DBL))

Class: corticosteroid - glucocorticoid

Indication: cerebral oedema (raised intracranial pressure), allergy/anaphylaxis, replacement, shock

Unlicensed indications: nausea/vomiting, inflammation in gastrointestinal obstruction, sweating, itch, hypercalcaemia, hiccup, pain, dyspnoea (lymphangitis), 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 (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. **fluconazole, fluoxetine, grapefruit juice, itraconazole, ketoconazole, metronidazole, 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**
- *decreased clinical effect/toxicity of other drugs metabolised by CYP enzymes (*due to induction of their metabolism by dexamethasone) may occur e.g. **amitriptyline, carbamazepine, citalopram, diazepam, itraconazole, ketoconazole, midazolam, omeprazole, phenobarbitone, phenytoin, prednisone, triazolam, warfarin**
- *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

Mechanism of action: decreases inflammatory response via induction of lipocortin.

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
Inj 120mg/5mL(iv only)	not funded

Tablets must be endorsed by a specialist. 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 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™, Voltaren™, Voltfast™)

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, ketoconazole, metronidazole, miconazole, 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 (sometime 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 EC 25mg, 50mg (normal release)	some fully funded (Apo-Diclo EC™)
Tab dispersible 50mg (normal release)	not fully funded (Voltaren D Disp™)
Tab sustained release 75mg,100mg	some fully funded (ApoDiclo SR™)
Supp 12.5mg, 25mg, 50mg, 100mg	fully funded (Voltaren™)
Inj 25mg/mL	fully funded (Voltaren™)

Special Authorities may apply.

Cost: Approx $0.04 per tab, $0.18-$0.22 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.

DOCUSATE

(Coloxyl™)

(in combination Coloxyl with Senna™, Laxsol™)

Class: laxative - faecal softener

Indication: constipation

Contraindications/cautions: acute abdominal pain

Adverse reactions:

less common abdominal cramps, atonic colon (on prolonged use), bitter taste

Metabolism/clearance: absorbed from the gastrointestinal tract and excreted mainly in the bile

Interactions:

- *decreased clinical effect of* **antispasmodics (e.g. hyoscine butylbromide)** may occur with concomitant docusate

Dosing:

oral:	100 to 480mg daily (with senna 1 to 2 tabs at night - Max 4 tabs)	
sc:	not available	
rectal:	1 as required	

Syringe driver: not available

Mechanism of action: thought to increase intestinal secretions and facilitate their movement into faeces producing softer stools

Onset: oral 1 to 3 days

Availability:

Tab 50mg, 120mg	fully funded (Coloxyl™)
Tab 50mg (with 8mg senna)	fully funded (Laxsol™)
Enema 18%	fully funded (Coloxyl™)

Cost: Approx $0.05 to $0.07 per tab, $0.03 per combination tab, $5.40 per enema

Notes:

- As docusate has some stimulant action it should be avoided in complete intestinal obstruction, as should all stimulant laxatives.
- Not laxative of choice in opioid induced constipation as a single agent but useful in combination with a stimulant. (e.g. Laxsol™) although giving a softener and a stimulant as separate tablets may be more effective.

DOMPERIDONE

(Motilium™)

Class: antiemetic - prokinetic, dopamine antagonist

Indication: nausea, vomiting, flatulence, gastro-oesophageal reflux

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 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. **fluconazole, fluoxetine, grapefruit juice, itraconazole, ketoconazole, metronidazole, 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**
- *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
sc:	not available
rectal:	10mg supp 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	not fully funded
Supp 10mg	not funded, not licensed

Special Authority available for full funding for nausea and vomiting in terminally ill patients. Valid for 6 months.

Costs: Approx $0.04 per tab

Notes:

- Main advantage over metoclopramide is lack of extrapyramidal side-effects but not available in injectable form.
- Useful in nausea and vomiting associated with gastric stasis.

ENOXAPARIN

(Clexane™)

Class: anticoagulant - low molecular weight heparin

Indication: prophylaxis and treatment of venous thromboembolism, unstable angina, MI

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
- *decreased effect* of enoxaparin may occur with **haemostats e.g. tranexamic acid and phytomenadione (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)

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,	not funded
	60mg/0.6mL, 80mg/0.8mL	not funded
	100mg/1mL, 120mg/0.8mL,	not funded
	150mg/mL	not funded

Costs: Approx $4.90 to $24.00 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 warfarin.

FENTANYL

(Sublimaze™, Durogesic™, Fentanyl (AstraZeneca), (DBL), Fensic™)

Class: analgesic - opioid

Indication: step 3 on the WHO ladder for severe pain

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 (minor) 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. **fluconazole, fluoxetine, grapefruit juice, itraconazole, ketoconazole, metronidazole, 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, dexamethasone, phenobarbitone, phenytoin, prednisone**
- *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: sc: 50 to 300mcg in 24 hours
patch: 25 to 300mcg/hour (each patch lasts for 3 days)

Syringe driver: compatibility unknown so best to infuse on its own

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

Peak effect: patch: 12 to 24 hours after initial application

Duration: patch: 72 hours (plus depot effect see later)

Availability: Patches: 12.5mcg, 25mcg, 50mcg, 75mcg, 100mcg/hour - fully funded
Injection: 100mcg/2mL, 500mcg/10mL, 1mg/20mL- not funded

Controlled drug form required. Special Authority is available for patches for patients who are terminally ill, who are opioid responsive and are unable to take oral medication or are intolerant to morphine or in whom morphine is contraindicated. Restrictions to be removed when Fensic™ are registered.

Cost: Approx $11.00 to $34.24 per patch, $0.92 to $2.19 per inj

Notes:

- Unsuitable for opioid naïve patients.
- If patient is hot, or there is a heat pad near the patch, rate of absorption may increase.
- If patch comes unstuck use Micropore™ round edges to reattach.
- For acute toxicity give naloxone 2mg and repeat as required (max 10mg) over a prolonged time (depot in skin - see below).
- Patches leave a depot in the skin which will carry on releasing fentanyl after removal (at least 17 hours for concentrations to drop by 50%).
- Dose adjustments should usually be done every 3 days.
- Use another opioid or sc fentanyl for rescue or the injection may be used between cheek and gum - dose is usually the same as the patch strength e.g. if 50mcg/hour patch use 50mcg.
- Approximate conversion is morphine (po) :fentanyl(sc/patch) = 150:1 i.e. 10mg morphine po = 66 mcg fentanyl sc but in chronic use this can only be used as an estimate.

Oral morphine (mg/ 24 hours)	Fentanyl patch (mcg/hour)	Oral morphine (mg/ 24 hours)	Fentanyl patch (mcg/hour)
<135	25	585-674	175
135-224	50	675-764	200
225-314	75	765-854	225
315-404	100	855-944	250
405-494	125	945-1,034	275
495-584	150	1,035-1,124	300

FLUCONAZOLE

(Diflucan™, Flucazole™, fluconazole (Pacific), Canesten Fluconazole™, m-Fluconazole™)

Class: antifungal - triazole

Indication: fungal infections

Contraindications/cautions: renal impairment, hepatic impairment

Adverse reactions:

common gastrointestinal upset, headache

less common rash (discontinue), 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, carbamazepine, citalopram, dexamethasone, diazepam, itraconazole, ketoconazole, NSAIDs (e.g. diclofenac), phenobarbitone, phenytoin, midazolam, omeprazole, prednisone, 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

sc: 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) (Diflucan™ 200mg)
	Susp 50mg/5mL	not funded
	Inj 2mg/ml 50ml	not funded

Cost: Approx $0.24 to $0.68 per cap, $0.99 per mL of suspension, $7.10 per 100mg inj

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.

FLUOXETINE

(Prozac™, Fluox™)

Class: antidepressant - SSRI (Selective Serotonin Re-uptake Inhibitor)

Indication: depression, bulimia nervosa, obsessive-compulsive disorder, premenstrual dysphoric disorder

Unlicensed indications: neuropathic pain, anxiety (chronic)

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, amnesia, visual disturbances, pruritus, hyponatraemia

Metabolism/clearance: metabolised by metabolising enzyme CYP2D6 (minor) 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. **terbinafine**
- *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. **amitriptyline, carbamazepine, codeine** (decreased morphine concentrations so decreased clinical efficacy of codeine), **dexamethasone, haloperidol, itraconazole, ketoconazole, midazolam, nortriptyline, NSAIDs (e.g. diclofenac), phenobarbitone, phenytoin prednisone, promethazine, tamoxifen, 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 $0.05 per cap and $0.18 per tab

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.

GABAPENTIN

(Neurontin™, Nupentin™)

Class: anticonvulsant

Indication: epilepsy - partial seizures with or without secondarily generalised tonic-clonic seizures not adequately controlled by other anticonvulsants, 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

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 P™** 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	

Syringe driver: 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

Special Authority available.

Cost: Approx $0.13 to $0.80 per cap

GLYCOPYRROLATE

(Robinul™)

Class: anticholinergic - antisecretory/antispasmodic
Indication: antisecretory premedication, reversal of neuromuscular blockade
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

Syringe driver: best given alone
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 $3.00 per 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.

HALOPERIDOL

(Serenace™, Haldol™)

Class: antipsychotic - butyrophenone

Indication: nausea and vomiting, mania, schizophrenia, anxiety

Unlicensed indications: delirium, hiccup, subcutaneous injection/infusion

Contraindications/cautions: hepatic encephalopathy, epilepsy, Parkinsons

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

Metabolism/clearance: metabolised by metabolising enzyme CYP2D6 and perhaps 3A4 (minor) 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. **fluconazole, fluoxetine, grapefruit juice, itraconazole, ketoconazole, metronidazole, 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, phenytoin, prednisone, rifampicin**
- *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 *de*creased clinical efficacy of codeine), **nortriptyline, 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/vomiting		delirium (see notes)	
oral:	1.5 to 3 mg once a day	oral:	1.5-20mg per 24 hours
sc:	1 to 2mg/24 hours	sc:	1-15mg/24 hours
		iv:	2-5mg (at1mg/minute)

Syringe driver: see syringe driver compatibility table

Mechanism of Action: nausea/vomiting - blocks dopamine receptors in the chemo-receptor 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

Availability:		
	Tab 0.5mg, 1.5mg, 5mg	fully funded
	Oral liq 2mg/mL	fully funded
	Inj 5mg/mL	fully funded

Cost: Approx $0.05 to $0.23 per tab, $0.18 per mL liq and $1.70 per inj

Notes:

- Useful as an antiemetic where causes of nausea and vomiting are biochemical imbalance or toxins.
- Particularly useful in opioid induced nausea and vomiting. It may be given as a single oral dose at night. Doses greater than 3mg daily add no benefit.
- Delirium: The primary pharmacological intervention for delirium is to tranquillise (to control psychotic features). Occasionally sedation (to induce sleep) is an additional requirement.

- **Haloperidol regime 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. benztropine 2mg only if extrapyramidal symptoms appear
  - extrapyramidal side-effects are less pronounced with the parenteral route

HYOSCINE BUTYLBROMIDE

(Buscopan™, Gastro-Soothe™)

Class: antispasmodic - gastrointestinal tract

Indication: GI spasm/colic

Unlicensed indications: some action as anti-emetic and antisecretory, useful in intestinal obstruction, 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	fully funded
Inj 20mg/mL	fully funded

Cost: Approx $0.08 per 10mg tab and $1.61 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, hyoscine- Scopaderm™)

Class: anticholinergic - antisecretory

Indication: antisecretory premedication, nausea/vomiting, 'death rattle'

Contraindications/cautions: elderly, urinary retention, cardiac disease, glaucoma

Adverse reactions:

common dry mouth, tachycardia, hypotension (especially with morphine)

less common urinary retention, 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 (1mg)/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): 1-2 hours (antisecretory)

Duration: im: 8 hours

Availability:

Inj 0.4mg/mL (hydrobromide)	fully funded
Patch 1mg	not fully funded

Special Authority required for patches and available only from 'hospital only' pharmacies. Only for control of nausea in the treatment of malignant or chronic disease.

Cost: Approx $1.33 per inj and $4.78 per patch

Notes:

- Thought to cross the blood brain barrier more easily than hyoscine butylbromide.
- Risk of confusion in the elderly is high.
- May be particularly useful in nausea and vomiting related to motion.

IBUPROFEN

(ACT-3™, Apo-Ibuprofen™, Brufen™, Ethics Ibuprofen™, Fenpaed™, I-Profen™, Ibucare™, Nurofen™, Panafen™)

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

Indication: pain associated with inflammation (including bone pain), antipyretic

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

NB Inhibits platelet aggregation so may prolong bleeding time

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

Interactions:

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

Dosing:			
	oral:	normal release	600 to 2,400mg per day in 3 to 4 divided doses
		sustained release	1,600mg once a day to 2,400mg in 2 divided doses
	sc:	not available	
	rectal:	not available	

Syringe driver: not available

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

Peak effect: 0.5 to 1.5 hours

Availability:		
	Tab 200mg, 400mg, 600mg	200mg only fully funded (I-Profen™)
	Tab sustained release 800mg	not fully funded
	Oral liquid 100mg/5mL	fully funded (Fenpaed™)

Non funded preparations may be subsidised for certain patients on Special Authority.

Cost: Approx $0.02 to $0.50 per tab and $0.01 per mL

Notes:

- Co-analgesic often used with opioids in the treatment of bone and soft tissue pain.
- Patients at risk of gastro-intestinal bleeds should be prescribed prophylactic gastric protection e.g. omeprazole.

KETAMINE
(Ketalar™)

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: not available (diluted injection has been given orally)
sc: 60 to 300mg in 24 hours (initially 0.1 to 0.5mg/kg/hr). Give a test dose of 10mg before starting infusion.
rectal: not available

Syringe driver: best infused alone
Mechanism of action: in pain thought to act at NMDA receptors in the dorsal horn
Peak effect: iv: 10 to 15 minutes
Duration: iv: 15 to 30minutes
Availability: Inj: 200mg/2mL not funded
Cost: Approx $15.51 per inj
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.
- 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.
- Burst 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 then consider discontinuation.

KETOCONAZOLE
(Nizoral™)

Class: antifungal - imidazole
Indication: fungal infections where other treatment has failed or is contraindicated
Contraindications/cautions: hepatic impairment
Adverse reactions:
common gastrointestinal upset, pruritus
less common raised liver enzymes/hepatitis/liver damage (usually if given for more than 14 days), gynaecomastia, blood disorders, headache, dizziness, hypertension, adrenal suppression.
Metabolism/clearance: metabolised by metabolising enzyme CYP3A4 mainly in the liver
Interactions:

- *increased clinical effect/toxicity of ketoconazole* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. **fluconazole, fluoxetine, grapefruit juice, itraconazole, metronidazole, valproate**
- *decreased clinical effect/toxicity of ketoconazole* (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. **carbamazepine, dexamethasone, phenobarbitone, phenytoin, prednisone, rifampicin**
- *increased clinical effect/toxicity of some drugs* (due to increased blood concentrations of them) may occur with ketoconazole due to metabolising enzyme inhibition by ketoconazole e.g. **amitriptyline, carbamazepine, dexamethasone, itraconazole, midazolam, NSAIDs (e.g. diclofenac), phenobarbitone, phenytoin, prednisone, tamoxifen, triazolam, warfarin**
- *disulfiram-like reaction* may occur with **alcohol**
- *decreased absorption* of ketoconazole may occur with **antacids, ranitidine, omeprazole**
- *decreased clinical effect* of **amphotericin** may occur with ketoconazole

Dosing: oral: 200mg to 400mg once a day
sc: not available
rectal: not available
Syringe driver: not available
Mechanism of action: increases fungal cell membrane permeability
Availability: Tab 200mg fully funded
On specialist endorsement.
Cost: Approx $1.27 per tab
Notes:

- More hepatotoxic than fluconazole or itraconazole.

LEVOMEPROMAZINE
(METHOTRIMEPRAZINE)
(Nozinan™)

Class: antipsychotic/neuroleptic - phenothiazine
Indication: psychosis, severe 'terminal' pain with anxiety/distress/restlessness, schizophrenia
Unlicensed indications: nausea/vomiting, delirium
Contraindications/cautions: hepatic dysfunction, encephalopathy, Parkinsons
Adverse reactions:
common somnolence, postural hypotension, sedation
less common dry mouth, hypotension, extrapyramidal side-effects (long term high dose usually)
Metabolism/clearance: metabolised by sulphonation then glucuronidation. Metabolites may be active and are excreted by the kidneys so care in renal dysfunction
Interactions:

- *additive CNS effects* with other CNS depressants e.g. **benzodiazepines (e.g. lorazepam), other phenothiazines (e.g. chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), opioids, alcohol**
- *additive increased risk of QT interval prolongation* (cardiac adverse effect which may lead to arrhythmias) with **tricyclic antidepressants (e.g. amitriptyline), flecainide, erythromycin, theophylline**.

Dosing:	pain, restlessness, distress, delirium	nausea/vomiting
oral:	6.25 to 50mg every 4 to 8 hours	6.25 to 12.5mg daily
sc:	5 to 200mg/24 hours	6.25 to 12.5mg/24 hours
rectal:	not available	

Syringe driver: dilute with 0.9% sodium chloride - see syringe driver compatibility table
Mechanism of Action: suppresses sensory impulses in the CNS via various neuro-transmitters.
Onset: im/?sc inj (analgesia) 20-40 minutes

Duration:	im/?sc 12 to 24 hours	**Half life:** 15 to 30 hours
Availability:	Tab 25mg, 100mg	fully funded
	Inj 25mg/mL 1mL	fully funded

Cost: Approx $0.17 to $0.44 per tab and $7.37 per inj
Notes:

- Only phenothiazine with analgesic properties.
- Doses of less than 25mg are associated with minimal sedation.
- Benztropine may be useful in alleviating extrapyramidal side-effects.
- May be a useful option in patients with multiple symptoms.

LOPERAMIDE

(Apo-Loperamide™, Diamide™, Dicap™, Imodium™, Nodia™)

Class: antidiarrhoeal - opioid

Indication: diarrhoea, harden/reduce number of stools in ileostomy 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 - 3 hours

Availability:

Tab 2mg	fully funded (Nodia™)
Caplets, chewable tablets 2mg	not funded

Cost: Approx $0.03 per tab/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.

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:	anxiety	insomnia
		1 to 3mg/day in 2 to 3 doses (max. 10mg/24 hours)	1 to 2mg at bedtime
	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 $0.03 to $0.04 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.

METHADONE

(Biodone™, Methatabs™, Methadone inj BP (AFT))

Class: analgesic - opioid

Indications: step 3 in the WHO analgesic ladder, opioid dependence

Contraindications/cautions: may accumulate as long half life

Adverse reactions:

see morphine but less drowsiness, nausea and constipation. Has a long and variable half life so watch for signs of accumulation e.g. decreased respiratory rate or mental status (particularly in the elderly).

Metabolism/clearance: metabolised by metabolising enzyme CYP3A4 (minor) mainly in the liver. Demethylation is the major route of metabolism and metabolites are excreted by the kidney.

Interactions:

- *increased clinical effect/toxicity of methadone* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. **fluconazole, fluoxetine, grapefruit juice, itraconazole, ketoconazole, metronidazole, valproate**
- *decreased clinical effect/toxicity of methadone* (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. **carbamazepine, dexamethasone, phenobarbitone, phenytoin, prednisone, rifampicin**
- *additive CNS effects* (including respiratory depression) with **other CNS depressants** e.g. **benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), other opioids, alcohol**

Dosing: (and see notes)		
	oral:	5 to 10mg 4 to 6 hourly initially then twice daily
	sc:	50 to 75% of oral dose
	rectal:	not available in NZ

Syringe driver: compatibility unknown so don't mix

Mechanism of Action: stimulates opioid receptors in the CNS and gastrointestinal tract and also thought to act at the NMDA receptor

Onset: 0.5 to 1 hour initially

Duration: 6 to 8 hours initially then 22 to 48 hours on repeat dosing

Availability:		
	Tab 5mg	fully funded (Methatabs™)
	Liquid 2mg/mL, 5mg/mL, 10mg/mL	fully funded (Biodone™)
	Inj 10mg/mL 1mL	fully funded (AFT)

Controlled drug form required.

Costs: Approx $0.21 per tab, $0.03 to $0.05 per mL liq and $5.20 per inj

Notes:

- May be useful in opioid rotation.
- Dose conversion (see below) from morphine is variable as individuals have differing methadone half lives.
- 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 may be irritant.
- When converting from oral morphine to oral methadone stop the oral morphine and calculate the dose of methadone as follows:
    - Give 3 hourly as required doses of oral methadone which are 1/10 of the previous 24 hour oral morphine dose, up to a maximum of 30mg.
    - On day 6, the amount of methadone taken over the previous 2 days is noted and divided by 4 to give a regular 12 hourly dose, with 1/4 of the regular 12 hourly dose given 3 hourly if required
    - If 2 doses or more per day of as required methadone continue to be needed, the dose of regular methadone should be increased by 1/3-1/2 once a week. (Morley JS, Makin MK. The use of methadone in cancer pain. poorly responsive to other opioids. Pain Rev. 1998;5:51-8.)
- 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.

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 and perhaps partially by the metabolising enzyme CYP3A4. 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. terazocin)** may occur with concomitant methylphenidate
- *hypertension* with **tricyclic antidepressants (e.g. amitriptyline)** may occur

Dosing: depression (max. adult dose of 1mg/kg/24 hours)

oral:	normal release	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 (Rubifen™)
	Tab SR 20mg	fully funded for below (Rubifen SR™)
	Tab extended release 18mg, 27mg, 36mg, 54mg	fully funded for below (Concerta™)

Special authority for full funding for narcolepsy or ADHD. Controlled drug form required.

Cost: Approx $0.14 to $0.36 per tab

Notes:

- Patients may respond to short courses of 2 to 3 weeks then withdraw.
- Methylphenidate is occasionally used to treat opioid-induced drowsiness.

METOCLOPRAMIDE

(Maxolon™, Metamide™, metoclopramide (AstraZeneca), (Pifizer))
(in combination Paramax™)

Class: antiemetic - prokinetic
Indication: nausea and/or vomiting, restoration of tone in upper GI tract
Unlicensed use: hiccups, subcutaneous injection/infusion
Contraindications/cautions: complete intestinal obstruction. Young persons (< 20 years old) are more prone to extrapyramidal side-effects so use lower doses
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 doesn't enter the CNS), diarrhoea, restlessness
Interactions:

- *increased clinical effect/toxicity of metoclopramide* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. **fluoxetine, paroxetine, terbinafine**
- *faster onset of action of* **SR morphine** may occur with concomitant metoclopramide
- *prokinetic activity* of metoclopramide may be affected by concomitant **opioids**, **anticholinergics** e.g. **hyoscine**
- *increased risk of extrapyramidal effects and neurotoxicity with* **lithium**

Dosing: oral: 10mg three times a day (max. 0.5mg/kg)
sc: 30 to 60mg over 24 hours (watch for extrapyramidal effects at > 30mg/24 hours)
rectal: 10mg up to three times a day
Syringe driver: see syringe driver compatibility table
Mechanism of Action: blocks dopamine receptors in the gastro-intestinal tract (increasing peristalsis), CNS and chemoreceptor-trigger zone (CTZ)

Peak effect:	oral/ rectal	1 to 3 hours	
Availability:	Tabs 10mg		some fully funded (Metamide™)
	Inj 10mg/2mL		some fully funded (Pfizer)

Cost: Approx $0.05 per tab and $0.45 per inj
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.
- Benztropine may be used as an antidote.

METRONIDAZOLE

(Flagyl™, Rozex ™, Trichozole™, metronidazole (AFT), (DBL), (Orion))

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 to some active and some inactive metabolites which are excreted with some parent drug by the kidneys

Interactions:

- *increased clinical effect/toxicity of some drugs* (due to increased blood concentrations of them) may occur with metronidazole due to metabolising enzyme inhibition by metronidazole e.g. **amitriptyline, carbamazepine, dexamethasone, itraconazole, ketoconazole, midazolam, NSAIDs (e.g. diclofenac), phenobarbitone, phenytoin, prednisone, tamoxifen, triazolam, warfarin**
- *disulfiram-like reaction* 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, 1g	fully funded (Flagyl™)
	Inj 500mg	not funded
	Topical Gel 0.5%	not funded (Orion)
	Topical Gel 7.5mg/g	not funded (Rozex™)
	Topical Cream 7.5mg/g	not funded (Rozex™)

Cost: Approx $0.09 to $0.17 per tab and $2.40 to $3.33 per supp, $0.25 per mL liq, $5.76 per inf, $8.69 per 10g tube of gel, $16.67 to $21.80 per 30 to 50g gel

MICONAZOLE

(Daktarin™, Resolve™, Tinasolve™, miconazole (Multichem))

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)

- *increased clinical effect/toxicity of some drugs* (due to increased blood concentrations of them) may occur with miconazole due to metabolising enzyme inhibition by miconazole e.g. **amitriptyline, carbamazepine, NSAIDs (e.g. diclofenac), phenobarbitone, phenytoin, tamoxifen, warfarin**
- *decreased clinical effect* of **amphotericin** may occur with miconazole

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 fully funded
Powder 2% 20g	not funded
Spray 2% 100g	not funded
Tincture 2% 30mL	not fully funded
Solution 2% 25mL	not funded
Vaginal cream 2%	not fully funded

Cost: Approx $8.95 per 40g oral gel, $0.42 per 20g cream, $4.36 per 30g lotion, $4.36 per 30mL Tinct, $2.75 per 40g vaginal cream

MICROLAX™

(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

Cost: Approx $0.61 per enema

MIDAZOLAM

(Hypnovel™, midazolam (Pfizer))

Class: sedative - benzodiazepine

Indication: insomnia, sedation, anaesthetic induction agent

Unlicensed indications: subcutaneous injection/infusion, hiccups, epilepsy, muscle spasm, dyspnoea

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 (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. **fluconazole, fluoxetine, grapefruit juice, itraconazole, ketoconazole, metronidazole, 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, phenobarbitone, phenytoin, prednisone**, **rifampicin**
- *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: 7.5 to 15mg at bed-time
sc: 5 to 60mg/24 hours (up to 150mg in terminal sedation)
rectal: not available

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, iv 2 to 3 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 $1.26 to $2.80 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) at doses of 1 to 2mg as required.

MORPHINE

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

Class: analgesic - opioid

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

Unlicensed indications: 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* **SR 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 1/5 to 1/6 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

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/sc 4 to 5 hours
oral: slow release 8 to 12 hours

Availability:

Oral liq 1mg, 2mg, 5mg, 10mg/mL (RA Morph™)	fully funded
Tab normal release 10mg, 20mg (Sevredol™)	fully funded
Cap long acting 10mg, 30mg, 60mg, 100mg, 200mg (m-Eslon™)	fully funded
Tab long acting 10mg, 30mg, 60mg, 100mg (LA Morph™)	fully funded
Inj 5mg/mL, 10mg/mL, 15mg/mL, 30mg/mL as sulphate	fully funded
Inj 120mg/1.5mL, 400mg/5mL as tartrate	fully funded
Suppositories 30mg	fully funded

Controlled drug form required.

Cost: Approx $0.04 per mL to $0.06 per mL liq, $0.26 to $0.51 per normal release tab, $0.18 to $0.72 per slow release cap (m-Eslon™), $0.90 to $13.47 per inj and $2.62 per supp.

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 in Intrasite™ gel, metronidazole gel or KY Jelly™.

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/day
		faecal impaction	8 sachets/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™, $0.33 per sachet of Movicol Half™
Notes:

- Effective laxative in palliative care.
- More acceptable than lactulose.

NALOXONE

(Narcan™, naloxone (DBL), (CSL), (Mayne))

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 respiratory depression 0.4 to 2mg every 2 to 3 minutes up to 10mg for overdose by opioid-dependent patients
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.

NAPROXEN

(Naprosyn™, Naxen™, Noflam™, Naprogesic™, Sonaflam™, Synflex™)

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

Indication: pain associated with inflammation (including bone pain)

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 naproxen* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g **fluconazole, fluoxetine, ketoconazole, metronidazole, miconazole, valproate**
- *decreased clinical effect/toxicity of naproxen* (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. **phenobarbitone, phenytoin, rifampicin**
- *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 **heparins** 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, 550mg	fully funded (Sonaflam™, Synflex™)
	Tab long-acting 750mg, 1g	fully funded (Naprosyn™)

Special Authority may be required for full funding.

Cost: Approx $0.04 to $0.12 per 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. **fluoxetine, paroxetine, terbinafine**.
- *additive 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:

	depression	pain
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 (Norpress™)
Cost: Approx $0.06 to $0.07 per tab
Notes:

- Metabolite of amitriptyline, less adverse reactions (including sedation) than amitriptyline.
- 25mg nortriptyline = 75mg amitriptyline (approx).

NYSTATIN
(Nilstat™)

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)

oral candidiasis:	100,000 units (1mL or 1 pastille) four times a day
gastrointestinal candidiasis:	500,000 to 1,000,000 units three times a day
sc:	not available
rectal:	not available
topical:	apply two to three times a day
vaginal:	1 pessary or 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, $0.19 per tab/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 (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:

oral:	not available
sc:	0.2 to 0.6mg/24 hours (max. 1mg/24 hours)
	LAR - not usually used in palliative care
rectal:	not available
iv:	not available

Syringe driver: compatibilities unknown so give alone

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 only and from 'hospital only' pharmacy for acromegaly, VIPomas, glucagonomas, gastrinomas, insulinomas, pre-op hypoglycaemia, carcinoid.

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.
- Use in the unlicensed indications above is more prevalent in countries other than New Zealand.

OLANZAPINE

(Zyprexa™)

Class: antipsychotic, antimanic, mood stabiliser

Indication: acute and chronic psychoses including schizophrenia, acute mania, 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, hypercholesteraemia, Parkinson's disease

Adverse reactions:

common drowsiness, weight gain, dizziness, hallucinations, akathisia and other extrapyramidal side effects, oedema, elevated blood glucose and triglycerides, chest pain, oedema, constipation, dry mouth

less common angioedema, urticaria, diabetic coma, hepatitis, pancreatitis, priapism, tardive dyskinesia, neuroleptic malignant syndrome, blood disorders, hypotension, mania, seizures

Metabolism/clearance: metabolised mainly in the liver by the metabolising enzymes CYP1A2 and 3A4 (minor) to inactive metabolites which are partially excreted by the kidneys

Interactions:

- *increased clinical effect/toxicity of olanzapine* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. **ketoconazole, ciprofloxacin, propranolol**
- *decreased clinical effect/toxicity of olanzapine* (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. **broccoli-like vegetables, cannabis, carbamazepine, cigarette smoke, omeprazole, phenobarbitone, 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 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

Syringe driver: not available

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

Availability:		
	Tab 2.5mg, 5mg, 10mg	fully funded as below
	Oral wafers 5mg, 10mg	fully funded as below
	Inj 10mg	not funded

Special Authority available for full funding of tablets and wafers - initial application from a psychiatrist.

Cost: Approx $1.82 to $7.30 per tablet, $3.65 to $7.30 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 Reddys™, Omezole™)

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 CYP3A4 (minor) and 2C19 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. **fluconazole, fluoxetine, ketoconazole, tamoxifen, valproate**
- *decreased clinical effect/toxicity of omeprazole* (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. **dexamethasone, phenytoin, rifampicin**
- *decreased clinical effect/toxicity of some drugs* (due to decreased blood concentrations of them) may occur with omeprazole due to metabolising enzyme induction by omeprazole e.g **amitriptyline, olanzapine, ondansetron, warfarin**
- *increased clinical effect/toxicity of some drugs* (due to increased blood concentrations of them) may occur with omeprazole due to metabolising enzyme inhibition by omeprazole e.g **amitriptyline, citalopram, phenobarbitone, phenytoin, warfarin**
- *decreased absorption* of **ketoconazole, itraconazole** may occur with omeprazole

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: not applicable

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 $0.07 to $0.12 per cap, $12.50 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.

ONDANSETRON
(Zofran™)

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 enzyme CYP3A4 (minor) 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 **ciprofloxacin, ketoconazole, metronidazole, propranolol**
- *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, cannabis, carbamazepine, cigarette smoke, omeprazole, phenobarbitone, phenytoin, rifampicin**

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 only as below
	Oral wafers 4mg, 8mg	fully funded only as below
	Inj 4mg/2ml, 8mg/4mL	not funded

Tabs/wafers - specialist endorsement. Only available from 'hospital only' pharmacies. SA for longer use for highly emetogenic chemo- or radio- therapy
Cost: Approx $1.71 per tab, $1.71 to $2.04 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. Expensive.

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 enzymes CYP2D6 and 3A4 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. **fluoxetine, haloperidol, paroxetine, terbinafine, valproate**
- *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**
- *additive respiratory depression* with **benzodiazepines (e.g. midazolam), other respiratory depressants**

Dosing: (and see notes)

oral:	immediate release	initially in opioid naïve 5mg 4 to 6 hourly
	slow release	initially 10mg every 12 hours
sc:	oral:sc 2:1	
rectal:	no longer available in New Zealand	

Syringe driver: see syringe driver compatibility table
Mechanism of Action: stimulates opioid receptors in the CNS and gastrointestinal tract
Onset: 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™)

Controlled drug form required.
Costs: Approx $0.14 to $0.49 per immediate release cap, $0.38 to $2.90 per slow release tab, $0.04 per mL oral liq and $2.88 to $5.76 per inj.
Notes:

- May be useful in opioid rotation.
- Dose conversion from oral morphine to oral oxycodone in 2:1 i.e. 10mg oral morphine = 5mg oral oxycodone.
- The slow release tablets have a coating of immediate release so that the last dose of immediate release does not have to be given with the first dose of slow release.
- The slow release tabs and the immediate release caps should not be opened or crushed/chewed.
- Renal and hepatic impairment are rarely a problem.
- sc use may be limited by low concentration availability.

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:	long sc infusions have been used in palliative care	
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	fully funded as below (Pamisol™)
	Inj 90mg	not funded

Hospital pharmacy only. Special Authority for hypercalcaemia and osteolysis under hospice care, specialist must apply.

Cost: Approx $18.75 to $75.00 per inj

Notes:

- 50% of patients with metastatic bone pain may be responsive.

PANTOPRAZOLE

(Dr Reddys™)

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, tamoxifen, valproate**
- *decreased clinical effect/toxicity of pantoprazole* (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. **dexamethasone, phenytoin, rifampicin**
- *decreased absorption* of **ketoconazole, itraconazole** may occur with pantoprazole

Dosing:

oral:	20 to 80mg once a day
sc:	not available
rectal:	not available

Syringe driver: not applicable

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™)

Cost: Approx $0.08 to $0.12 per cap

PARACETAMOL

(Disprol™, Ethics Paracetamol™, Lemsip Liquid Caps™, Pamol™, Panadol™, Paracare™, Perfalgan™, Parapaed™)

(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)	
sc:	inf available but large volume	
rectal:	as for oral	

Syringe driver: not available in New Zealand

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	some fully funded (Panadol™)
Supp 125mg, 250mg, 500mg	some fully funded (Paracare™)
Liq 120mg/5mL, 250mg/5mL	some fully funded (Paracare™)
Sol tab 500mg	not funded
Inf 1g/100mL	not funded

Cost: Approx $0.01 per tab, $0.32 per supp, $0.01 per mL liq, $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.

PHENOBARBITONE
(phenobarbitone (PSM), (Mayne))

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 CYP2C9 and 2C19 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, metronidazole, miconazole, omeprazole, tamoxifen, valproate**
- *decreased clinical effect/toxicity of phenobarbitone* (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. **dexamethasone, 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. **amitriptyline, carbamazepine, dexamethasone, itraconazole, ketoconazole, midazolam, NSAIDs (e.g. diclofenac), olanzapine, ondansetron, phenytoin, prednisone, tamoxifen, 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 200mg/mL, 1mL	not funded

Cost: Approx $0.05 per tab, $8.00 per inj
Notes:

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

PHENYTOIN

(Dilantin™, phenytoin (DBL), (Hospira))

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 enzyme 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, metronidazole, miconazole, omeprazole, tamoxifen, valproate**
- *decreased clinical effect/toxicity of phenytoin* (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. **dexamethasone, 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 **amitriptyline, carbamazepine, citalopram, dexamethasone, itraconazole, ketoconazole, midazolam, NSAIDs (e.g. diclofenac), olanzapine, omeprazole, ondansetron, pantoprazole, phenobarbitone, prednisone, tamoxifen, triazolam, warfarin.**

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 (DBL)

Cost: Approx $0.07 per tab, $0.07 per cap, $0.02 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.

PREDNISONE

(Apo-Prednisone™)

Class: corticosteroid - glucocorticoid

Indication: allergy, asthma, rheumatic disease, inflammatory conditions

Unlicensed indications: nausea/vomiting, inflammation in gastrointestinal obstruction, sweating, itch, hypercalcaemia, hiccup, pain, dyspnoea (lymphangitis), liver capsule pain, tenesmus

Contraindications/cautions: infections, gastrointestinal bleeding, diabetes, congestive heart failure, mood disorders

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), proximal muscle weakness, Cushing's syndrome, weight gain, depression, mania, delirium

Metabolism/clearance: metabolised by the metabolising enzyme CYP3A4 mainly in the liver

Interactions:

- *increased clinical effect/toxicity of prednisone* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. **fluconazole, fluoxetine, grapefruit juice, itraconazole, ketoconazole, metronidazole, 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**
- *decreased clinical effect/toxicity of some drugs* (due to decreased blood concentrations of them) may occur with prednisone due to metabolising enzyme induction by prednisone e.g **carbamazepine, dexamethasone, itraconazole, ketoconazole, midazolam, triazolam**
- *increased risk of GI bleed/ulceration* when given with **NSAIDs (e.g. diclofenac)**

Dosing:

oral:	10 to 100mg usually once a day (max. 250mg/day)
sc:	not available
rectal:	not available

Syringe driver: not available

Mechanism of Action: decreases inflammatory response thought to be via induction of lipocortin, an anti-inflammatory protein

Availability: Tab1mg, 2.5mg, 5mg, 20mg fully funded (Apo-Prednisone™)

Cost: Approx $0.02 to $0.06 per tab

Notes:

- 0.75mg dexamethasone has an equivalent anti-inflammatory effect to 5mg prednisone or 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 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.

QUETIAPINE

(Quetapel™, Seroquel™)

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 (minor)

Interactions:

- *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
	sc:		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 $0.23 to $1.32 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.

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)

sc: 100 to 200mg/24 hours

rectal: not available

Syringe driver: ? infuse alone

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, $0.30 per 10mL liq, $1.75 per inj

Notes:

- Omeprazole is considered the drug of choice for prophylaxis or treatment of NSAID-induced gastrointestinal damage.

RISPERIDONE
(Ridal™, Risperdal™)

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 enzyme CYP2D6 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. **fluoxetine, haloperidol, paroxetine, terbinafine, valproate**
- *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:	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
	sc/rectal:		not available

Syringe driver: not available
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	fully funded as below

Special Authority required for oral disintegrating tabs and long acting injections.
Cost: Approx $0.26 to $2.05 per tab, $0.76 to $3.06 per oral disintegrating tab, $1.53 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.

SENNA

(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)	
sc:	not available	
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	fully funded (Laxsol™)
with 50mg docusate	

Cost: Approx $0.02 per tab, $0.04 per combination tab

Notes:

- May be useful in opioid induced constipation.

SPIRONOLACTONE

(Spirotone™, 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

less common rashes, 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:	malignant ascites	100 to 200mg once a day (max. 400mg daily)
	sc/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 $0.08 to $0.21 per tab, $1.07 per mL liq

Notes:

- Paracentesis may be necessary in malignant ascites.
- Monitor body weight and renal function.

TRAMADOL

(Tramal™, Tramedo™, tramadol (AFT))

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 and 3A4 (minor) 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. **fluoxetine, haloperidol, paroxetine, terbinafine**
- *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		not funded
	Oral drops		not funded
	SR tab 100mg, 150mg, 200mg		not funded
	MR tab 75mg, 100mg, 150mg, 200mg		not funded
	Inj 50mg/mL, 1mL,100mg/2mL, 2mL		not funded

Cost: Approx $0.37 per cap, $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 - 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 $0.49 per tab, $12.47 per inj.

Notes:

- Tablets are large and many patients may have difficulty with swallowing them.

VALPROATE (SODIUM)
(Epilim™)

Class: anticonvulsant, antipsychotic
Indication: epilepsy, bipolar disorder
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 metabolising enzymes of the CYP 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, tamoxifen**
- *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)
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.
- 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™)

Class: antidepressant - bicyclic, SNRI
Indication: depression, anxiety disorders
Unlicensed indications: ? neuropathic pain, hot flushes
Contraindications/cautions: renal/hepatic failure, volume depleted patients, 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, hypercholesteraemia
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. **fluoxetine, haloperidol, paroxetine, terbinafine**
- *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 that prolong the interval e.g**. haloperidol**

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

Syringe driver: not available
Mechanism of Action: inhibits reuptake of serotonin (at high dose), noradrenaline and dopamine in the CNS
Availability: 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 psychiatrists only and first prescription to be written by consultant or registrar psychiatrist. Valid for 2 years.
Costs: Approx $0.67 to $1.63 per modified release cap
Notes:

- Effectiveness in neuropathic pain is yet to be elucidated.

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 CYP3A4 (minor), 1A2 (minor), 2C19, 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. **fluconazole, fluoxetine, ketoconazole, metronidazole, miconazole, omeprazole, tamoxifen, valproate**
- *decreased clinical effect/toxicity of warfarin* (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g**. dexamethasone, phenobarbitone, phenytoin, rifampicin**
- *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)
sc: not available
rectal: not available

Syringe driver: not available

Mechanism of Action: interferes with vitamin K synthesis

Availability: Tab 1mg, 2mg, 3mg, 5mg fully funded

Cost: $0.05 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.

Treatment in DVT and PE	**INR**	**Duration**
Pre and perioperative anticoag.	1.5 to 2.0	days
Treatment of DVT	2.0 to 3.0	12-26weeks
Treatment of PE or massive DVT	2.0 to 3.0	26-52 weeks
Treatment of recurrent DVT or PE*	3.0 to 4.0	?life long
Atrial Fibrillation	2.0 to 3.0	life long
Prosthetic heart valves	2.0 to 4.0	life long
Arterial disease	3.0 to 4.0	life long

*recurrence despite prothrombin ratio between 2 and 3

Table from Management Guidelines for Common Medical Conditions, 11th Edition 2005, Canterbury District Health Board

ZOLEDRONIC ACID
(Aclasta™, Zometa™)

Class: bisphosphonate - calcium regulator
Indication: hypercalcaemia of malignancy, bone metastases
Unlicensed indications: bone pain, osteoporosis
Contraindications/cautions: renal or hepatic impairment, cardiac impairment, hypo- calcaemic, 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

Onset:	hypercalcaemia	2 to 3 days
Duration:	hypercalcaemia	32 to 39 days
	bone pain	4 to 6 weeks

Availability:	4mg inj	not funded
	5mg inf	not funded

Cost: Approx $550 to $680 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
- 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
- always consider the rectal route as an alternative first

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 with a diluent
- generally water for injection is currently used
- some drugs, however must be diluted with a specified diluent e.g. levomepromazine 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 human 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
- 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
- never combine 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

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

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.

Y = compatible

N = incompatible

SI = sometimes incompatible (usually at higher concentrations)

NA = not usually used together

? = unknown

Combinations that have been used

morphine+clonazepam+cyclizine (morphine sulphate and tartrate)

morphine+clonazepam+dexamethasone (morphine sulphate and tartrate)

morphine+clonazepam+haloperidol (morphine sulphate and tartrate)

morphine+clonazepam+ketamine (morphine sulphate and tartrate)

morphine+clonazepam+metoclopramide (morphine sulphate Y, tartrate SI)

morphine+cyclizine+dexamethasone (morphine sulphate and tartrate)

morphine+cyclizine+haloperidol (morphine sulphate and tartrate)

morphine+cyclizine+hyoscine butyl bromide (morphine sulphate, tartrate SI)

morphine+cyclizine+metoclopramide (morphine sulphate and tartrate)

morphine+cyclizine+midazolam (morphine sulphate and tartrate)

morphine+dexamethasone+haloperidol (morphine sulphate and tartrate)

morphine+dexamethasone+hyoscine hydrobromide (morphine sulphate and tartrate)

morphine+dexamethasone+metoclopramide (morphine sulphate and tartrate)

morphine+dexamethasone+midazolam (morphine sulphate SI, tartrate SI)

morphine+dexamethasone+haloperidol (morphine sulphate and tartrate)

Info from:
1) The Palliative Care Handbook 2nd Edition 2004 – 24 hour syringe driver compatibility for subcutaneous administration table. 2) Palliative Medicine Handbook on line at http://book.pallcare.info/index.php 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

DRUGS BY SYMPTOM

Anxiety

- **acute**
  lorazepam
  clonazepam
- **chronic**
  citalopram
  fluoxetine

Ascites (malignant)

spironolactone
frusemide

Bleeding (haemorrhage)

tranexamic acid

Confusion (see delirium)

Constipation

- **softeners**
  docusate
- **stimulants**
  bisacodyl
  senna
- **combination - softener & stimulant**
  Movicol™
  docusate with senna
- **rectal**
  Microlax™
  glycerine
  mineral oil enema

Convulsions (seizures)

diazepam
valproate
carbamazepine
phenytoin
clonazepam
midazolam

Cough

codeine phosphate
morphine

Death Rattle (retained secretions)

hyoscine hydrobromide
hyoscine butylbromide
glycopyrrolate

Delirium (confusion)

haloperidol
levomepromazine
olanzapine
risperidone

Depression (Major Depressive Episode)

- citalopram
- fluoxetine
- nortriptyline
- methylphenidate

Diarrhoea

- codeine phosphate
- loperamide
- morphine
- octreotide (secretory)

Dyspnoea (breathlessness)

- morphine
- midazolam
- clonazepam
- dexamethasone
- prednisone

Hiccup

- dexamethasone
- prednisone
- haloperidol
- levomepromazine
- metoclopramide
- benzodiazepines
- nifedipine
- baclofen
- valproate
- antacids

Hypercalcaemia

- pamidronate
- dexamethasone
- prednisone

Insomnia

- temazepam
- zopiclone

Intestinal obstruction

- morphine
- hyoscine butylbromide
- haloperidol
- cyclizine
- dexamethasone
- prednisone
- octreotide

Itch (pruritus)

- promethazine
- cetirizine
- cholestyramine (bile salt chelator)
- ranitidine, cimetidine
- diclofenac
- benzodiazepines
- dexamethasone

prednisone
rifampicin (chronic cholestasis)
ondansetron
paroxetine
naltrexone
doxepin

Mouth Care

- **mouth washes**
  chlorhexidine mouthwash (cleanser)
  benzydamine (analgesic)
- **saliva stimulants**
  iced pineapple chunks, lime juice
  chewing gum
  pilocarpine (1mg/mL, 5mL rinse three times a day)
- **saliva substitutes**
- **anti-fungal agents**
  nystatin
  miconazole
  ketoconazole
  fluconazole
- **aphthous ulceration**
  triamcinolone in orabase
  choline salicylate gel
  thalidomide
- **herpetic infection**
  aciclovir

Nausea/Vomiting

- **higher centre stimulation** (emotion - anxiety /fear)
  lorazepam
  midazolam
- **vomiting centre stimulation** (radiotherapy to the head, raised intracranial pressure)
  cyclizine
  dexamethasone
- **vagal and sympathetic afferent stimulation**
  hepatomegaly
    dexamethasone
    cyclizine
  gastric stasis
    metoclopramide
    domperidone
  intestinal obstruction
    cyclizine
    levomepromazine
- **chemoreceptor trigger zone stimulation** (uraemia, hypercalcaemia, drugs e.g. morphine)
  haloperidol
  levomepromazine
- **vestibular nerve stimulation** (motion)
  cyclizine
  hyoscine patch
- **complicated/ resistant**
  ondansetron

Pain

- **nociceptive** (soft tissue)
  paracetamol
  codeine phosphate
  diclofenac
  naproxen
  ibuprofen
  tramadol
  morphine
  oxycodone
  methadone
  fentanyl
  ketamine
- **bone pain** (with radiotherapy)
  paracetamol
  diclofenac
  naproxen
  ibuprofen
  morphine
  oxycodone
  methadone
  fentanyl
  pamidronate
- **neuropathic pain** (usually with opioids)
  antidepressants
    nortriptyline
    fluoxetine
    citalopram
  anticonvulsants
    valproate
    carbamazepine
    gabapentin
  others
    dexamethasone
    prednisone
    clonidine
    ketamine
- **raised intracranial pressure pain**
    diclofenac
    morphine
    dexamethasone
    prednisone
- **liver capsule pain**
    dexamethasone
    prednisone
- **tenesmus** (see constipation)
    dexamethasone
    prednisone
- **intestinal spasm**
    hyoscine butylbromide
- **bladder spasm**
    oxybutynin
    hyoscine butylbromide (high dose)

Restlessness (Terminal) (See pain, delirium, sedation)

Sedation
- midazolam
- clonazepam
- levomepromazine
- phenobarbitone

Sweating
- diclofenac
- ranitidine
- dexamethasone
- prednisone

Thrombosis
- heparin (low molecular weight)
- warfarin

Twitching (myoclonic jerks)
- midazolam
- clonazepam
- phenobarbitone

Ulcer prophylaxis (GI)
- omeprazole
- ranitidine

Wound Care
- metronidazole

FURTHER READING

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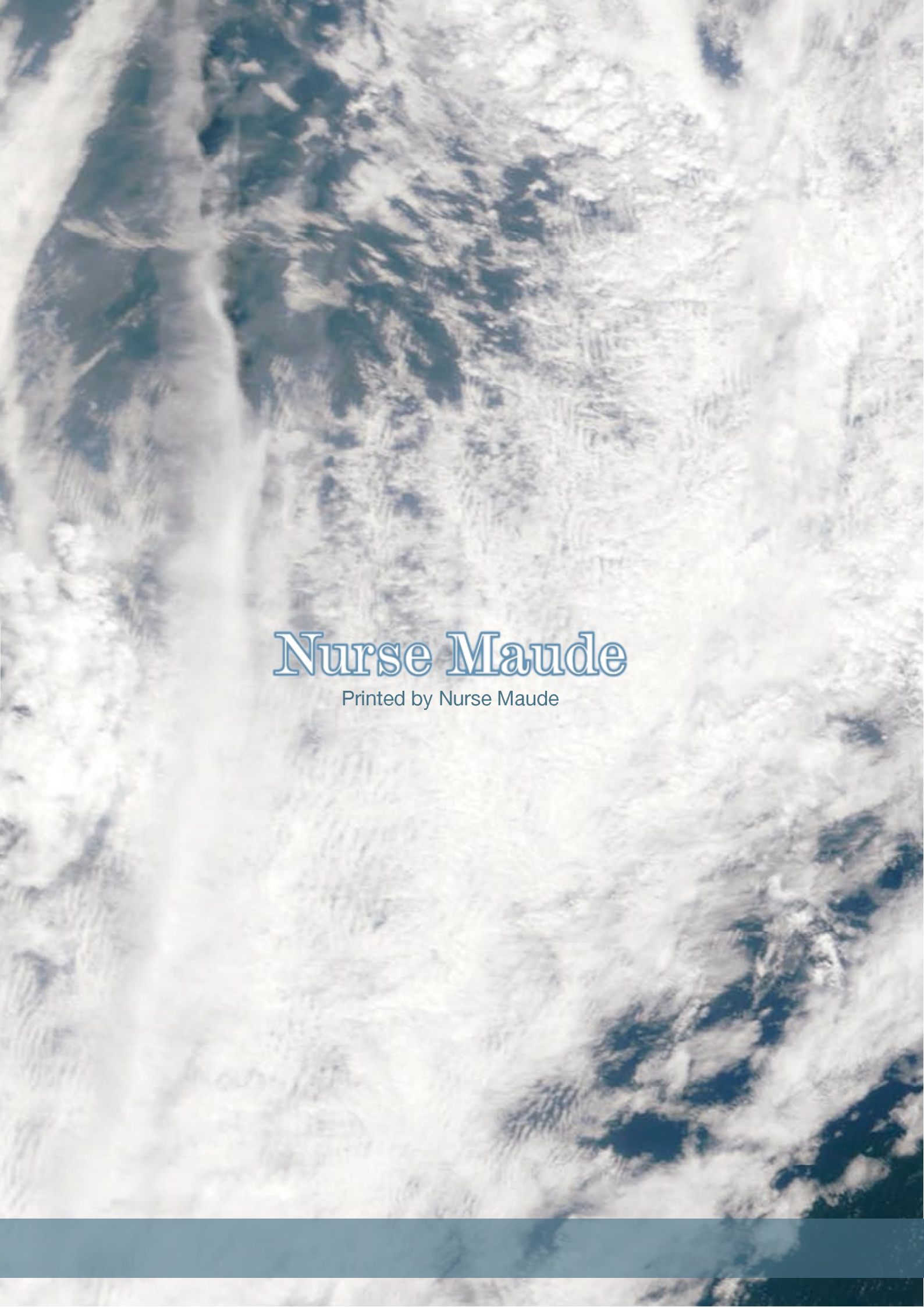

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