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The Palliative Care Handbook

Guidelines for clinical management and symptom control, featuring extensive support for advanced dementia

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Pharmacopoeia

Drugs listed are preferred choices in palliative care.

Baclofen

Class: GABA derivative musculoskeletal muscle relaxant

Indications: relief of musculoskeletal spasm

Contraindications/cautions: epilepsy, subcut injection, psychosis, schizophrenia, depression, mania, GI ulceration, cerebrovascular disease, alcoholism, diabetes (may increase blood glucose concentrations), hypertension

Adverse reactions: *common* nausea, sedation, somnolence; *less common* decreased cardiac output, hypotension, GI disturbance, respiratory depression, light-headedness, personality changes, headache, insomnia, euphoria, depression, weakness, tremor, hallucinations, dry mouth, tinnitus

Metabolism/clearance: mainly excreted in urine unchanged (80%) so dose adjust in renal impairment

Interactions:

- *additive drowsiness and CNS depression* with other **CNS depressant drugs e.g. alcohol, benzodiazepines (e.g. clonazepam), opioids**
- *increased muscle relaxation* with **tricyclic antidepressants e.g. nortriptyline**

Dosing:

oral:	5 to 20 mg 3 to 4 times a day (start at 5 mg 3 times a day)
subcut:	not available

Syringe driver: only intrathecal inj available - not for subcut use

Mechanism of action: works in the spinal cord where it stimulates GABA-receptors which inhibit the release of glutamate and aspartate (excitatory). Also has CNS depressant actions.

Onset: variable - hours to weeks

Notes:

- Stopping abruptly may result in a withdrawal reaction (confusion, psychosis, tachycardia, hyperthermia and rebound spasticity).

Bisacodyl

Class: laxative - stimulant

Indications: 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 10 mg at night or 5 mg twice a day
subcut:	not available
rectal:	10 mg 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

Notes:

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

Buprenorphine*

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

Indications: moderate to severe pain

Contraindications/cautions: buprenorphine hypersensitivity/allergy, use with other opioids, adverse effects such as respiratory depression may not completely respond to naloxone, COPD, use with benzodiazepines

Adverse reactions: *see morphine*

Metabolism/clearance: metabolised by unclear pathway

Interactions:

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

Dosing:

sublingual combo:	not used
subcut:	not used
patch:	5 to 20 micrograms/hour (each patch lasts for 7 days)

Syringe driver: compatibility unknown so best to infuse on its own. Irritancy potential is unknown.

Mechanism of action: partially stimulates mu- and blocks kappa opioid receptors in the CNS and gastrointestinal tract

Peak effect: patch: 60 hours after initial application

Onset: 11 to 21 hours

Duration: patch: 7 days

Notes:

- As buprenorphine is only a partial agonist of mu receptors and an antagonist of kappa receptors it should not be used with other opioids or within 24 hours of them as it may lead to severe opioid withdrawal.
- As patches last for 7 days and peak concentrations occur at 60 hours do not use in rapidly escalating pain.
- For acute toxicity give naloxone 2 mg and repeat as required (max 10 mg) over a prolonged time but be aware that full reversal of toxicity may not occur as buprenorphine binding to opioid receptors is high.
- Do not cut patches.
- Equivalence to other opioid data are sparse but 20 micrograms/hour patch may be equivalent to 90 mg oral morphine per day.
- It is recommended that no more than two patches be applied at the same time regardless of the patch strength
- A new patch should not be applied to the same skin site for the subsequent 3 to 4 weeks

*** Drugs that are either not available or not funded in New Zealand**

Cholestyramine

Class: anion exchange resin

Indications: hypercholesterolaemia, pruritis due to partial biliary obstruction, diarrhoea associated with ileal resection or cholerrhoeic enteropathy

Contraindications/cautions: complete biliary obstruction, diabetes, nephrotic syndrome, phenylketonuria, prolonged use, constipation

Adverse reactions: *common* constipation, faecal impaction, hyperchloraemic acidosis, perianal irritation, intestinal obstruction; *less common* nausea, bloating

Metabolism/clearance: combines with bile acids and is excreted in the faeces - not absorbed

Interactions:

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

Dosing:

oral: 4 to 16 g per day

Syringe driver: not available

Mechanism of action: binds bile acids which reduces plasma bile acid concentrations

Onset: pruritus: 4 to 7 days

Notes:

- As absorption of other drugs will be affected take all other drugs 1 hour before or 4 to 6 hours after cholestyramine. Sachet contents must be mixed with 100 to 150 mL of fluid before administering.

Citalopram

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

Indications: depression, anxiety (chronic)

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

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

Metabolism/clearance: metabolism unknown

Interactions:

- *additive risk of serotonin syndrome* (potentially fatal syndrome - symptoms include sweating, diarrhoea, confusion) with other serotonergic drugs **e.g. amitriptyline, carbamazepine, fluoxetine, paroxetine, tramadol, lithium**
- *increased risk of bleeding* (antiplatelet effect) with **anticoagulants**

Dosing:

oral:	10 to 40 mg once a day
subcut/rectal:	not available

Syringe driver: not available

Mechanism of action: blocks the reuptake of serotonin

Onset: depression: 2 to 4 weeks anxiety or pain: 3 to 7 days

Peak response: 5 to 6 weeks

Notes:

- **Escitalopram** is available. Doses used are approximately half.
- Doses of greater than 40 mg per day have been associated with QT interval prolongation.

Clonazepam

Class: anticonvulsant - benzodiazepine

Indications (NB some may be unlicensed): epilepsy, convulsions, sedation, anxiety, agitation, restless leg syndrome, neuropathic pain, dyspnoea, hiccups, myoclonic jerks

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 CYP3A 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. clarithromycin, fluconazole, grapefruit juice, itraconazole, ketoconazole**
- *decreased clinical effect/toxicity of clonazepam* (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) **e.g. carbamazepine, phenobarbitone, phenytoin, rifampicin, St John's wort**
- *additive CNS effects* with other **CNS depressants e.g. opioids (e.g. morphine), phenothiazines (e.g. chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), alcohol may occur with concomitant clonazepam**

Dosing: sedation, anxiety, agitation, restless leg syndrome, neuropathic pain, dyspnoea, hiccups, convulsions

oral:	0.5 to 8 mg a day (1 to 2 mg a day usually adequate)
subcut:	1 to 8 mg/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)

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	5 mg
lorazepam	0.5 to 1 mg
clonazepam	0.5 mg
temazepam	10 mg
midazolam	7.5 mg
triazolam	0.25 mg

Pharmacological properties of benzodiazepines

Drug	Anxiolytic	Night sedation	Muscle relaxant	Anticonvulsant
diazepam	+++	+	+++	++
lorazepam	+++	++	+	+
clonazepam	++	+	+	+++
temazepam	+	+++	+	+
midazolam	+	+++	+	+++

Codeine phosphate

Class: analgesic - opioid (metabolised to morphine)

Indications (NB some may be unlicensed): step 2 in the WHO analgesic ladder, cough, diarrhoea

Contraindications/cautions: avoid use with other opioid analgesics

Adverse reactions: as for morphine - very constipating

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

Interactions:

- *decreased clinical effect/toxicity of codeine* (due to decreased blood concentrations of morphine - an active metabolite) may occur with some CYP metabolising enzyme inhibitors (see above) **e.g. bupropion, fluoxetine, paroxetine (not citalopram), quinine**
- *additive CNS effects with other* **CNS depressants e.g. benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), other opioids, alcoho**l 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 60 mg 4 to 6 hourly (max. 240 mg in 24 hours)
subcut:	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

Notes:

- Combination products are not recommended.
- 10% of dose is converted to morphine in “normal” metabolisers i.e. 60 mg codeine = 6 mg morphine.
- 5 to 10% of the Caucasian population may be unable to metabolise codeine to morphine.
- Combination with other opioids is illogical.
- Dihydrocodeine slow release is available although it is not often used in palliative care.

Cyclizine

Class: antiemetic - antihistaminic

Indications: nausea/vomiting (including motion sickness)

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), cardiac 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 50 mg 3 times a day (cyclizine hydrochloride)
subcut:	75 to 150 mg/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

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

Class: corticosteroid - glucocorticoid

Indications (NB some may be unlicensed): cerebral oedema (raised intracranial pressure), allergy/anaphylaxis, replacement, shock, collagen diseases, asthma, respiratory insufficiency, leukaemia, lymphoma, rheumatic disease, psoriasis, colitis, enteritis, hypercalcaemia of malignancy, nausea/vomiting, sweating, itch, hiccup, pain, liver capsule pain, tenesmus, increased energy, weight gain

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 CYP3A (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. aprepitant, clarithromycin, grapefruit juice, indinavir, itraconazole, ketoconazole, nelfinavir, ritonavir, telapravir, voriconazole**
- *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, rifampicin, St John's wort**
- *decreased clinical effect/toxicity of other drugs metabolised by CYP enzymes* (due to induction of their metabolism by dexamethasone) may occur **e.g. aprepitant, carbamazepine, clonazepam, diazepam, domperidone, fentanyl, itraconazole, ketoconazole, methadone, midazolam, prednisone, quetiapine, triazolam**
- *increased ris***k of GI bleed/ulceration** when given with NSAIDs (e.g. diclofenac)

Dosing:

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

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

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

Onset: 8 to 24 hours

Notes:

- Anti-inflammatory effect: 3 mg dexamethasone = 20 mg prednisone = 80 mg hydrocortisone.
- On discontinuation decrease dose slowly (taper) unless the patient has been taking it for less than 5 days in which case dose tapering is not necessary.
- Alteration in mood is not usually seen below 6 mg dexamethasone (40 mg prednisone) per day.

- Corticosteroid-induced insomnia responds to benzodiazepines (e.g. temazepam)
- Corticosteroid induced mood disorder is usually depression and rarely mania.
- The use of steroids in palliative care is common and sometimes, particularly at high dose, consideration should be given to the appropriateness of their use.
- The use of 0.5 to 1 mg 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

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

Indications (NB some may be unlicensed): pain associated with inflammation, 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**
- *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. furosemide), antihypertensives (e.g. propranolol)** may occur with concomitant diclofenac

Dosing:

oral:	50 to 150 mg per day in 3 divided doses for normal release and 2 divided doses (sometimes just 1) for long acting preparations.
subcut:	inj available but not for subcut 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

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. pantoprazole) prophylactically.

Docusate

Class: laxative - faecal softener

Indications: 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 480 mg daily (with senna 1 to 2 tabs at night - max 4 tabs)
subcut:	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

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

Class: antiemetic - prokinetic, dopamine antagonist

Indications: dyspeptic symptom complex including gastro-oesophageal reflux oesophagitis, epigastric sense of fullness, feeling of abdominal distension, upper abdominal pain, eructation, flatulence and heartburn, nausea, vomiting

Contraindications/cautions: complete intestinal obstruction

Adverse reactions: *common* hyperprolactinaemia, breast tenderness, QT prolongation; *less common* abdominal cramps, diarrhoea, dry mouth, headache, dizziness

Metabolism/clearance: metabolised by metabolising enzyme CYP3A 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. aprepitant, clarithromycin, grapefruit juice, indinavir, itraconazole, ketoconazole, nelfinavir, ritonavir, telapravir, voriconazole**
- *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, rifampicin, St John's wort**
- *decreased prokinetic effect of domperidone* may occur with **anticholinergic drugs (e.g. amitriptyline, hyoscine)**
- *additive increased risk of QT interval prolongation* (cardiac adverse effect which may lead to arrhythmias) with **tricyclic antidepressants (e.g. amitriptyline), flecainide, erythromycin, theophylline, methotrimeprazine (levomepromazine)**

Dosing:

oral:	10 mg 3 times a day
subcut:	not available
rectal:	10 mg 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

Notes:

- Main advantage over metoclopramide is less extrapyramidal side effects but not available in injectable form.
- Useful in nausea and vomiting associated with gastric stasis.
- The United States Federal Drug Agency has warned of domperidone induced QT interval prolongation and recommend a maximum of 30 mg in 24 hours. A risk benefit assessment should be carried out when higher doses are considered along with a baseline QT interval assessment.

Duloxetine*

Class: serotonin and noradrenaline reuptake inhibitor antidepressant

Indications (NB some may be unlicensed): depression, anxiety, neuropathic pain

Contraindications/cautions: concurrent MAOI, hepatic failure, raised ocular pressure, severe renal impairment

Adverse reactions: *common* insomnia, sweating, fatigue, nausea, dry mouth, diarrhoea, palpitations, blurred vision, hypotension, syncope; *less common* mydriasis, suicidal ideation, hepatotoxicity, hyponatraemia, serotonin syndrome, tachycardia, dizziness, tinnitus

Metabolism/clearance: Metabolised by CYP1A2 and 2D6

Interactions:

- *increased clinical effect/toxicity of duloxetine** (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) **e.g. bupropion, paroxetine (not citalopram), quinine, ciprofloxacin, ketoconazole**
- *decreased clinical effect/toxicity of duloxetine** (due to decreased blood concentrations) may occur with some CYP metabolising enzyme inducers (see above) **e.g. phenobarbitone, phenytoin, rifampicin, cruciferous vegetables, smoking, barbecued food**
- *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** interacts with excessive **alcohol** *to cause hepatic injury*

Dosing:

depression	oral:	60 mg/day
anxiety	oral:	30 mg to 120 mg/day
neuropathic pain	oral:	60 mg to 120 mg/day
subcut:	not available	
rectal:	not available	

Syringe driver: not available

Mechanism of action: increases available noradrenaline and serotonin in the CNS

*** Drugs that are either not available or not funded in New Zealand**

Enoxaparin

Class: anticoagulant - low molecular weight heparin

Indications: prophylaxis of venous thromboembolic disease post-op and bedridden patients.
Treatment of venous thromboembolic disease, unstable angina and myocardial infarction.
Prevention of thrombus during haemodialysis, duration of more than 30 days treatment

Contraindications/cautions: heparin allergy, active bleeding, recent haemorrhagic stroke, low platelets, renal impairment (adjust dose), spinal/epidural medication, prosthetic heart valve, history of gastrointestinal ulceration/bleed

Adverse reactions: *common* haemorrhage, haematoma, elevated LFTs; *less common* allergic reactions, skin necrosis, thrombocytopenia

Metabolism/clearance: metabolised but cleared mainly by the kidneys so adjust dose in renal failure

Interactions:

- *increased effect of enoxaparin* may occur with **other drugs that decrease blood clotting e.g. aspirin, clopidogrel, warfarin, heparin**
- *increased risk of bleeding* when combined with **NSAIDs e.g. diclofenac**
- *decreased effect of enoxaparin* may occur with **haemostats e.g. tranexamic acid, phytomenadione (vitamin K)**

Dosing:

oral:	not available
subcut:	treatment (of DVT etc): 1.5 mg/kg once a day or 1 mg/kg twice a day (lower in the obese and renal failure patients)
prophylaxis:	20 to 40 mg 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

Notes:

- As the coagulation ability of cancer patients is altered it may be that low molecular weight heparins are a better choice in these patients than oral anticoagulants.

Fentanyl

Class: analgesic - opioid

Indications: step 3 on the WHO ladder for severe pain, anaesthetic premed

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 CYP3A 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. aprepitant, clarithromycin, grapefruit juice, indinavir, itraconazole, ketoconazole, nelfinavir, ritonavir, telapravir, voriconazole**
- *decreased clinical effect/toxicity of fentanyl* (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) **e.g. carbamazepine, phenobarbitone, phenytoin, rifampicin, St John's wort**
- *additive CNS depression* with other CNS depressants **e.g. benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), other opioids, alcohol**

Dosing:

subcut: 50 to 300 micrograms in 24 hours initially
patch: 12.5 to 300 micrograms/hour (each patch lasts for 3 days)

Syringe driver: see syringe driver compatibility table

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)

Notes:

- Patches are 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 2 mg and repeat as required (max 10 mg) 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 the fentanyl injection subcut/sublingual/intranasal for breakthrough - for fentanyl the dose may not relate to background so start at 25 micrograms fentanyl and titrate to effect.

continued

- Approximate conversion is morphine (po): fentanyl (subcut/patch) = 150:1 i.e. 10 mg morphine po = 66 micrograms fentanyl subcut but in chronic use this can only be used as an estimate.

Conversion Chart:

Oral morphine (mg/24 hours)	fentanyl patch (mcg/hour)
<60	12.5
60-134	25
135-224	50
225-314	75
315-404	100
405-494	125
495-584	150
585-674	175
675-764	200
765-854	225
855-944	250
945-1,034	275
1,035-1,124	300

Fluconazole

Class: antifungal - triazole

Indications: fungal infections – cryptococcosis, candidiasis, prophylaxis, dermatomycoses

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. diazepam, diclofenac, gliclazide, ibuprofen, indomethacin, lansoprazole, naproxen, omeprazole, pantoprazole, phenytoin, warfarin**
- *decreased clinical effect* of **amphotericin** may occur with concomitant fluconazole

Dosing:

oral:

vaginal candidiasis	150 mg as a single dose
cryptococcal infections/systemic candidiasis	200 to 400 mg once a day for 7 days
oropharyngeal candidiasis	50 to 100 mg once a day for 7 days
prophylaxis in malignancy	50 mg once a day

subcut: not usually used subcut, iv: refer to package insert

rectal: not available

Syringe driver: not applicable

Mechanism of action: inhibits fungal cell membrane formation

Notes:

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

Fluoxetine

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

Indications (NB some may be unlicensed): depression and associated anxiety, bulimia nervosa, obsessive-compulsive disorder, premenstrual dysphoric disorder, neuropathic pain

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

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

Metabolism/clearance: metabolised by metabolising enzyme CYP2D6 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. bupropion, paroxetine (not citalopram), quinine**
- *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, codeine** (decreased morphine concentrations so decreased clinical efficacy of codeine), **haloperidol, metoclopramide, nortriptyline, promethazine, tamoxifen** (decreased endoxifen (active metabolite) concentrations so decreased clinical effects)
- *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 80 mg in the morning
subcut:	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: 2 to 4 weeks pain: 3 to 7 days

Peak response: 5 to 6 weeks

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 < 20 mg. Capsule contents are also dispersible in water.

Gabapentin

Class: anticonvulsant

Indications (NB some may be unlicensed): partial seizures, including secondarily generalised tonic-clonic seizures, initially as add-on therapy in patients who have not achieved adequate control with standard antiepileptic drugs, neuropathic pain, insomnia

Contraindications/cautions: renal disease (reduce dose), absence seizures, encephalopathy

Adverse reactions: *common* easy bruising (purpura), increased blood pressure, dizziness, ataxia, somnolence, blurred vision; *less common* fatigue, headache, anxiety, GI effects, sexual dysfunction, oedema, twitching, tremor, confusion, suicidal thoughts

Metabolism/clearance: not metabolised, mainly excreted unchanged by the kidneys (fraction excreted unchanged by the kidney = 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 1,800 mg/day in divided doses max 2,400 mg
	neuropathic pain	900 to 3,600 mg/day in divided doses
subcut:	not available	
rectal:	not available	

Syringe driver: not available

Mechanism of action: may act through effects on the synthesis of GABA in the CNS

Glycopyrrolate

Class: anticholinergic - antisecretory/antispasmodic

Indications (NB some may be unlicensed): antisecretory premedication, adjunctive peptic ulceration treatment, excess/retained secretions ('death rattle')

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)
subcut:	200 to 600 micrograms/24 hours
rectal:	not available

Syringe driver: see compatibility chart

Mechanism of action: blocks cholinergic receptors

Initial response: (im): 30 to 45 minutes

Duration: (im): 7 hours

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

Class: antipsychotic - butyrophenone

Indications (NB some may be unlicensed): psychotic disorders, acute alcoholism, intractable nausea and vomiting, neuroleptanalgesia, hiccup

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

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

Metabolism/clearance: metabolised by metabolising enzyme CYP2D6 and 3A mainly in the liver

Interactions:

- *increased clinical effect/toxicity of haloperidol* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) **e.g. aprepitant, bupropion, clarithromycin, fluoxetine, grapefruit juice, itraconazole, ketoconazole, paroxetine, valproate, voriconazole**
- *decreased clinical effect/toxicity of haloperidol* (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) **e.g. carbamazepine, phenobarbitone, phenytoin, rifampicin, St John's wort**
- *increased clinical effect/toxicity of some drugs* (due to increased blood concentrations of them) may occur with haloperidol due to metabolising enzyme inhibition by haloperidol e.g. **amitriptyline, codeine** (decreased morphine concentrations so decreased clinical efficacy of codeine), **haloperidol, metoclopramide, nortriptyline, promethazine, tamoxifen** (decreased endoxifen (active metabolite) concentrations so decreased clinical effects)
- *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 to 20 mg per 24 hours
subcut:	1 to 2 mg/24 hours	subcut:	1 to 15 mg/24 hours
		iv:	2 to 5 mg (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

continued

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

Duration: up to 24 hours

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 3 mg 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. (See delirium page)

Hydromorphone*

Class: analgesic - opioid

Indication (NB some may be unlicensed): step 3 on the WHO ladder for severe pain, more effective in nociceptive than in neuropathic/visceral pains, severe breathlessness, cough, diarrhoea

Contraindications/cautions: hydromorphone hypersensitivity/allergy (this doesn't mean 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, MAO inhibitors**

Dosing:

pain

oral: initially 0.25 to 1 mg 4 hourly and prn

- prescribe rescue doses of 1/5th to 1/6th of the total 24 hour dose 4 to 6 hourly
- there is no real maximum dose but it is usually less than 200 mg/24 hours. If it is
- > 40 mg/24 hours consider the aetiology of the pain and the use of co-analgesia
- review doses regularly

subcut:	oral: subcut	=	2:1
rectal:	oral: rectal	=	1:1
epidural:	subcut:epidural	=	10:1
intrathecal	subcut:intrathecal	=	100:1

breathlessness, cough

oral: 0. 5 to 1 mg 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: 1 hour

Duration: oral: 4 to 5 hours

*** Drugs that are either not available or not funded in New Zealand**

continued

Notes:

- Tolerance to effect does occur but progressive disease is also a cause of dose fade.
- Toxicity: decrease in respiratory rate, mental status and blood pressure - give naloxone (see naloxone page).
- For conversion to morphine, oxycodone, fentanyl or methadone, see relevant pages.
- Hydromorphone can affect the ability to drive. Some patients may need to be told not to drive while taking hydromorphone. Always advise patients not to drive for several days after a dose increase.

Hyoscine butylbromide

Class: antispasmodic - gastrointestinal tract

Indications (NB some may be unlicensed): GI spasm/colic, some action as anti-emetic and antisecretory, sialorrhoea, 'death rattle'

Contraindications/cautions: megacolon, stenosis, glaucoma, tachycardia, urinary retention

Adverse reactions: *common* dry mouth; *less common* urinary retention, tachycardia, visual problems, dizziness, constipation

Metabolism/clearance: metabolised but also some excreted unchanged by the kidneys so care in renal dysfunction

Interactions:

- *additive anticholinergic effects* (e.g. dry mouth, urinary retention) may occur with other drugs which have anticholinergic effects **e.g. cyclizine, amitriptyline, phenothiazines (e.g. chlorpromazine)**
- *decreased clinical effect (prokinetic effects)* of **metoclopramide/domperidone** may occur with concomitant hyoscine butylbromide

Dosing:

oral: 20 mg 4 times a day

subcut: 40 to 100 mg/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 subcut: 5 to 10 minutes

Duration: oral: 2 hours or less

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

Class: anticholinergic - antisecretory

Indications (NB some may be unlicensed): premedication for sedation/amnesia, nausea/vomiting from motion sickness, '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
subcut (as the hydrobromide): 0.4 to 2.4 mg/24 hours (usually 0.8 to 1.2 mg stat)
rectal: not available
patch: 1 patch (1.5 mg)/72 hours (behind the ear)

Syringe driver: see syringe driver compatibility table

Mechanism of action: blocks cholinergic receptors in CNS and the gastrointestinal tract

Peak response: im: 1 to 2 hours (antisecretory)

Duration: im: 8 hours

Notes:

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

Ketamine

Class: anaesthetic

Indications (NB some may be unlicensed): general anaesthesia (400-700 mg im), severe pain (at sub-anaesthetic doses), opioid tolerance reversal, neuropathic pain

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

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

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

Interactions:

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

Dosing:

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

Syringe driver: see syringe driver compatibility table

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

Notes:

- May be useful in opioid tolerance/intolerance, in 'wind-up' (or rapidly escalating doses) and may allow a reduction in opioid dose.
- May be useful in neuropathic pain although 'pulse' therapy has been shown to be no better than placebo in one study.
- If hallucinations occur reduce the dose of ketamine and give a benzodiazepine (e.g. diazepam 5 mg orally, midazolam 5 mg subcutaneously) or haloperidol 2 to 5 mg orally or subcutaneously.
- Has been effective when used topically.
- 'Pulse' therapy (increasing subcutaneous doses over 3 to 5 days) may be sufficient to 'reset' the NMDA/opioid receptors. Give 100 mg/24 hours then 200 mg/24hrs then 300 mg/24hrs for 3 days then consider discontinuation.
- Oral administration usually involves lower doses e.g. 25 to 50 mg 3 times a day as more norketamine is produced due to first pass metabolism. Norketamine is active and may be more potent than the parent ketamine.
- Oral formulations include the injection given orally either straight or made up into a syrup (see www.palliativedrugs.com for formula), oral lozenges and oral capsules.
- Sublingual use of the injection may also be effective.
- May have a role treating severe depressive disorders.

Levetiracetam

Class: anticonvulsant

Indications: seizure control

Contraindications/cautions: monitor for behavioural changes, hepatic and renal impairment

Adverse reactions: *common* somnolence, asthenia, infection, GI disturbance, blurred vision, hostility, pruritis

Metabolism/clearance: metabolised by hydrolysis. Fraction excreted unchanged in the urine is 0.7

Interactions:

- *increased clinical effect/toxicity of levetiracetam* may occur with other drugs that are excreted by active tubular secretion **e.g. probenecid**
- *increased clinical effect/toxicity of levetiracetam* (due to increased blood concentrations) may occur with **valproate**
- *decreased clinical effect/toxicity of levetiracetam* (due to decreased blood concentrations) may occur with **carbamazepine, phenobarbitone, phenytoin**

Dosing:

oral:	500 mg twice daily initially (reduce in renal impairment)
subcut:	not available
rectal:	not available

Syringe driver: not available

Mechanism of action: inhibits Ca2+ currents and reduces the release of Ca2+ from intraneuronal stores. Reverses the reductions in GABA- and glycine-gated currents induced by zinc and βcarbolines.

Onset: peak concentrations at 1.5 hours

Levomepromazine (Methotrimeprazine)

Class: antipsychotic/neuroleptic - phenothiazine

Indications (NB some may be unlicensed): psychosis, severe 'terminal' pain with anxiety/distress/restlessness, schizophrenia, with other analgesics for pain, anxiety and distress, nausea/vomiting

Contraindications/cautions: hepatic dysfunction, encephalopathy, Parkinson's disease, DLB

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. May inhibit CYP2D6.

Interactions:

- *increased clinical effect/toxicity of some drugs* (due to increased blood concentrations of them) may occur with levomepromazine (methotrimeprazine) due to metabolising enzyme inhibition by levomepromazine (methotrimeprazine) **e.g. amitriptyline, codeine** (decreased morphine concentrations so decreased clinical efficacy of codeine), **fluoxetine, nortriptyline, oxycodone, paroxetine, promethazine**
- *additive CNS effects* with other CNS depressants **e.g. benzodiazepines (e.g. lorazepam), 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, domperidone**

Dosing:

	pain, restlessness, distress, delirium	*nausea/vomiting*
oral:	6.25 to 50 mg every 4 to 8 hours	6.25 to 12.5 mg daily
subcut:	6.25 to 200 mg/24 hours	6.25 to 12.5 mg/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/?subcut (analgesia): 20 to 40 minutes

Duration: im/?subcut: 12 to 24 hours Half life: 15 to 30 hours

Notes:

- Only phenothiazine with analgesic properties.
- Doses of less than 25 mg/24 hours are associated with minimal sedation.
- Benztropine 2 mg may be useful in alleviating extrapyramidal side effects.
- May be a useful option in patients with multiple symptoms.
- For smaller doses disperse tablets in water and give a fraction of it.

Loperamide

Class: antidiarrhoeal - peripheral opioid receptor agonist

Indications: diarrhoea, reduce number of stools in ileostomy and colostomy patients

Contraindications/cautions: diarrhoea due to infection or antibiotics

Adverse reactions: *common* flatulence, constipation, abdominal distension, abdominal pain, bloating; *less common* giddiness, dry mouth

Metabolism/clearance: transported out of cells by P-glycoprotein which stops it crossing the blood-brain barrier. Metabolised by oxidation but 50% excreted unchanged in faeces.

Interactions:

- *decreased clinical effect of loperamide* with *prokinetics* **e.g. metoclopramide/ domperidone**
- *CNS adverse effects may occur with* P-glycoprotein inhibitors **e.g. grapefruit juice, itraconazole, ketoconazole, tamoxifen**

Dosing:

oral:	2 mg after each loose stool (max. of 16 mg/24 hours)
subcut:	not available
rectal:	not available

Syringe driver: not available

Mechanism of action: binds to opioid receptors in gastrointestinal tract. May also affect cholinergic receptors.

Onset: 1 to 3 hours

Notes:

- May not be of benefit if patient is already taking morphine.
- Absorbed but doesn't normally cross the blood-brain barrier BUT may become active in the CNS as an opioid if given with P-glycoprotein inhibitors e.g. itraconazole.

Lorazepam

Class: anxiolytic - short acting benzodiazepine

Indications (NB some may be unlicensed): anxiety, insomnia, premedication, 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 1 to 3 mg/day in 2 to 3 doses (max. 10 mg/24 hours)	insomnia 1 to 2 mg at bedtime
subcut:	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

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 see clonazepam page.

Methadone

Class: analgesic - opioid

Indications (NB some may be unlicensed): step 3 in the WHO analgesic ladder, cough, 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 CYP3A 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. aprepitant, clarithromycin, grapefruit juice, indinavir, itraconazole, ketoconazole, nelfinavir, ritonavir, telapravir, voriconazole**
- *decreased clinical effect/toxicity of methadone* (due to decreased blood concentrations) may occur with some CYP metabolising enzyme inducers (see above) **e.g. carbamazepine, phenobarbitone, phenytoin, rifampicin, St John's wort**
- *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**
- *additive increased risk of QT interval prolongation* (cardiac adverse effect which may lead to arrhythmias) with other drugs that prolong it.

Dosing: (and see notes)

oral:	2.5 to 5 mg twice daily initially
subcut:	50 to 75% of oral dose
rectal:	not available in NZ

Syringe driver: see syringe driver compatibility table

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

Notes:

- May be useful in opioid rotation.
- Dose conversion ratios from other opioids is variable as individuals have differing methadone half lives and the ratio varies with dose (see next page).
- As affects NMDA receptors may prevent 'wind up' (rapidly escalating doses) on long term use and is useful in neuropathic pain.
- Renal and hepatic impairment are rarely a problem.
- Subcutaneous injection/infusion may be irritant.
- Some centres use low dose methadone alongside other opioids.
- In opioid naïve patients starting doses are usually 2.5 to 5 mg twice a day with 3 hourly prn breakthrough doses. Titrate dose weekly.

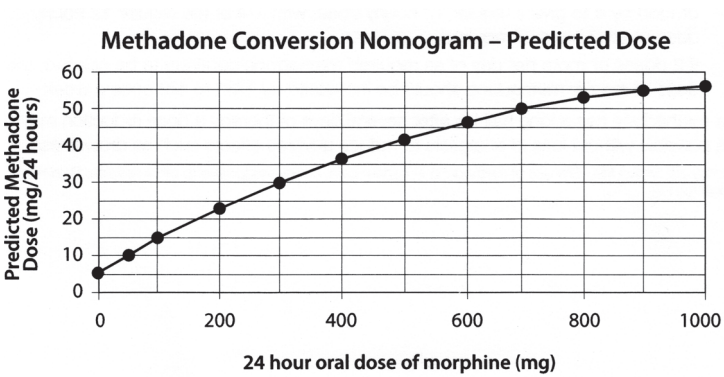
Conversion to methadone

Toombs/Ayonide method

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

Based on ratios by Ayonide, 2000:

mg oral morphine	ratio of morphine:methadone
<100	3:1
101-300	5:1
301-600	10:1
601-800	12:1
801-1000	15:1
>1001	20:1



Toombs J Oral methadone dosing for chronic pain. A practioner's guide. 2008 Pain Treatment Topics, Ayonide OT et al The rediscovery of methadone for cancer pain management. Med J Aust. 2000 173:536-540

Methylphenidate

Class: central stimulant - amphetamine related

Indications (NB some may be unlicensed): attention deficit hyperactivity disorder (possible restrictions), narcolepsy, depression, neurobehavioural symptoms in brain tumours/injuries

Contraindications/cautions: anxiety, glaucoma, agitation, hyperthyroidism, cardiac problems, hypertension, epilepsy

Adverse reactions: *common* nervousness, insomnia, tachycardia, urticarial; *less common* blurred vision, hallucinations, blood disorders, psychosis (very high doses), arrhythmias

Metabolism/clearance: metabolised by hydrolysis. Inactive metabolite is excreted by the kidneys.

Interactions:

- *increased analgesia and decreased sedation* may occur with some **opioids**
- *hypertensive crisis may occur with concomitant* **MAOIs (e.g. tranylcypromine)**
- *decreased hypotensive effect* of **adrenergic blockers (e.g. terazosin) may occur with concomitant methylphenidate**
- *hypertension with* **tricyclic antidepressants (e.g. amitriptyline)** may occur

Dosing:

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

oral:	normal release	10 to 30 mg a day (morning and mid-day)
subcut:	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

Notes:

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

Metoclopramide

Class: antiemetic - prokinetic

Indications: nausea and/or vomiting, restoration of tone in upper GI tract, hiccups

Contraindications/cautions: complete intestinal obstruction. Young persons (< 20 years old) are more prone to extrapyramidal side effects so use lower doses

Adverse reactions: *less common* tardive dyskinesia - usually on prolonged use, extrapyramidal reactions e.g. Parkinsonism, akathisia (usually at doses > 30 mg/24 hours - switch to domperidone which enters the CNS to a lesser extent), diarrhoea, restlessness

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

Interactions:

- *increased clinical effect/toxicity of metoclopramide* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) **e.g. bupropion, fluoxetine, paroxetine, quinine**
- *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:	10 mg 3 times a day (max. 0.5 mg/kg)
subcut:	30 to 60 mg over 24 hours (watch for extrapyramidal effects at > 30 mg/24 hours)
rectal:	10 mg up to 3 times a day

Syringe driver: see syringe driver compatibility table

Mechanism of action: blocks dopamine receptors and perhaps affects 5HT receptors in the gastro-intestinal tract (increasing peristalsis), CNS and chemoreceptor-trigger zone (CTZ)

Peak effect: oral/rectal: 1 to 3 hours

Notes:

- 'High dose' metoclopramide may work via 5HT3 antagonism (like ondansetron) but is associated with severe extrapyramidal effects.
- Most effective for nausea/vomiting due to gastric stasis. Some clinicians believe that metoclopramide is no better than placebo as an antiemetic but is useful as a prokinetic.
- Benztropine 2 mg may be used as an antidote.
- The European Medicines Agency's Committee recommends that metoclopramide should only be prescribed for short-term use (up to five days) and that it should only be used as a second-line.

Metronidazole

Class: antibiotic - anti-anaerobe

Indications (NB some may be unlicensed): 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:

- *disulfiram-like reaction* (nausea, vomiting, sweating) may occur with concomitant alcohol
- *increased toxicity of* **lithium** may occur with metronidazole

Dosing:

oral:	800 mg stat then 400 mg 3 times a day
subcut:	injection available but not usually used subcut
iv:	500mg 3 times a day (infusion)
rectal:	1 g 3 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

*** Drugs that are either not available or not funded in New Zealand**

Miconazole

Class: antifungal - imidazole

Indications: fungal infection - topical, oral, GI, vaginal

Contraindications/cautions: hepatic impairment

Adverse reactions: *common* oral gel - GI upset; *less common* oral gel - hepatitis, topical/vaginal- burning, itching

Metabolism/clearance: metabolised by the liver

Interactions: Oral gel/vaginal preparations (absorption is likely)

- *decreased clinical effect* of **amphotericin** may occur with miconazole
- *may affect INR* of patients taking **warfarin**. Monitor even if only using oral gel.

Dosing:

mouth (topical):50 mg 4 times a day for 7 days
subcut: 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

Microlax™/Micolette™

(Sodium citrate 450 mg, sodium lauryl sulphoacetate 45 mg, sorbitol 3.125 g, sorbic acid 5 mg, water to 5 mL)

Class: rectal laxative - stimulant, faecal softener and osmotic

Indications: constipation, bowel evacuation

Dosing:

oral:	not available
subcut:	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

Midazolam

Class: sedative - benzodiazepine

Indications (NB some may be unlicensed): sedation, anaesthetic induction agent, hiccups, epilepsy, muscle spasm, dyspnoea, insomnia

Contraindications/cautions: avoid sudden withdrawal, respiratory depression

Adverse reactions: *common* fatigue, drowsiness, amnesia; *less common* respiratory depression (high dose), aggression, confusion, hypotension

Metabolism/clearance: metabolised by metabolising enzyme CYP3A (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. clarithromycin, fluconazole, grapefruit juice, itraconazole, ketoconazole**
- *decreased clinical effect/toxicity of midazolam* (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) **e.g. carbamazepine, phenobarbitone, phenytoin, rifampicin, St John's wort**
- *additive CNS effects* with other CNS depressants **e.g. other benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), opioids, alcohol**

Dosing:

oral:	7.5 to 15 mg at bed-time
subcut:	5 to 60 mg/24 hours (up to 150 mg in sedation at the end-of-life)
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 subcut: 5 to 10 min iv: 2 to 3 mins

Duration: 15 minutes to several hours

Half life: 2 to 5 hours

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 bucally.

Mirtazapine

Class: antidepressant – central presynaptic alpha 2 and 5HT antagonist

Indications (NB some may be unlicensed): major depression, nausea

Contraindications/cautions: bipolar depression, epilepsy, cardiac disease, prostatic hypertrophy, diabetes, abrupt withdrawal

Adverse reactions: *common* increased appetite, dizziness, headache, dry mouth; *less common* convulsions, tremor, nightmares, mania, syncope, hyponatraemia, nausea

Metabolism/clearance: metabolised by metabolising enzyme CYP2D6, 1A2 and 3A mainly in the liver to at least one active metabolite (by CYP3A)

Interactions:

- *increased clinical effect/toxicity of mirtazapine* (due to increased blood concentrations of parent) may occur with some CYP metabolising enzyme inhibitors (see above) **e.g. bupropion, aprepitant, ciprofloxacin, clarithromycin, fluconazole, fluoxetine, grapefruit juice, itraconazole, ketoconazole, paroxetine, quinine**
- *decreased clinical effect/toxicity of mirtazapine* (due to decreased blood concentrations of parent) may occur with some CYP metabolism enzyme inducers (see above) **e.g. broccoli, carbamazepine, dexamethasone, phenobarbitone, phenytoin, prednisone, rifampicin, smoking, St John's wort**
- *additive risk of serotonin syndrome* (potentially fatal syndrome - symptoms include sweating, diarrhoea, confusion) with other serotonergic drugs **e.g. amitriptyline, carbamazepine, fluoxetine, paroxetine, tramadol, lithium**

Dosing:

oral:	15 to 45 mg at bed-time
subcut:	not available

Syringe driver: not available

Mechanism of action: blocks presynaptic alpha 2 and 5HT2 and 3 receptors increasing central noradrenaline and serotonin (blocking 5HT2 and 5HT3 receptors allowing stimulation of 5HT1 receptors)

Peak concentrations: oral: 2 hours

Half life: 20 to 40 hours

Morphine

Class: analgesic - opioid

Indications (NB some may be unlicensed): step 3 on the WHO ladder for severe pain, more effective in nociceptive than in neuropathic/visceral pains, severe breathlessness, cough, diarrhoea

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

Adverse reactions: *common* nausea/vomiting in 10 to 30% of patients (usually transient for 1 to 5 days) - give haloperidol, constipation in 90% of patients - give a stimulant & softener laxative prophylactically, dry mouth, dizziness, sedation (usually transient and on initiation or dose increase); *less common* respiratory depression (high doses) - pain is an antidote - give naloxone if severe, visual problems - may see things upside down/flipping, myoclonic jerking - sign of toxicity - try a different opioid, delirium in 2% of patients - give haloperidol rare hallucinations, hyperalgesia, raised intracranial pressure, biliary/urinary tract spasm, muscle rigidity, pruritus, pulmonary oedema, physical dependence (irrelevant in dying)

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

Interactions:

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

Dosing:

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

oral: normal release initially 5 to 10 mg 4 hourly and prn
slow release initially 10 to 30 mg 12 hourly

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

subcut:	oral: subcut	=	2:1
rectal:	oral: rectal	=	1:1
epidural:	subcut:epidural	=	10:1
intrathecal	subcut:intrathecal	=	100:1

breathlessness, cough

oral: normal release 5 to 10 mg 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

continued

Peak effect:	oral:	normal release	1 hour
Duration:	oral:	normal release	4 to 5 hours
	oral:	slow release	8 to 12 hours

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).
- For conversion to oxycodone, hydromorphone*, fentanyl or methadone, see relevant pages.
- Morphine can affect the ability to drive. Some patients may need to be told not to drive while taking morphine. Always advise patients not to drive for several days after a dose increase.
- Topical morphine may be useful for wound pain. It is usually used as 0.05 to 0.1% morphine [i.e. 0.5 to 1 mg/mL] in Intrasite™ gel, metronidazole gel or KY Jelly™.

*** Drugs that are either not available or not funded in New Zealand**

Movicol™, Lax-sachets™

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

Class: laxative - osmotic

Indications: 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™, Lax-sachet™:

constipation	1 to 3 sachets per day
faecal impaction	8 sachets per day taken within 6 hours for a max. of 3 days. If cardiovascular problems, do not take more than 2 sachets over any 1 hour.

Each sachet should be dissolved in 125 mL. For faecal impaction dissolve 8 sachets in 1 L 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 1 hour.

Each sachet should be dissolved in 60 mL 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

Notes:

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

Naloxone

Class: opioid antagonist

Indications: 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, hydromorphone*

Dosing:

If respiratory rate < 8 per minute, patient unconscious or cyanosed

iv:	0.1 to 0.2 mg every 2 to 3 minutes for reversal of CNS depression
post-op	
	0.4 to 2 mg every 2 to 3 minutes up to 10 mg for opioid overdose
oral:	not available alone
subcut:	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 subcut/im: 15 minutes

Duration: 15 to 90 minutes

Notes:

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

*** Drugs that are either not available or not funded in New Zealand**

Naproxen

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

Indications (NB some may be unlicensed): pain associated with inflammation (including bone pain), dysmenorrhoea, 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 CYP2C8/9 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, ketoconazole, voriconazole**
- *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 **heparin** in combination with naproxen

Dosing:

oral:	normal release	500 to 1,000 mg per day in 2 divided doses or 275 mg every 6 to 8 hours (max 1,375 mg)
	sustained release	750 to 1,000 mg per day as a single dose
subcut:		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

Nortriptyline

Class: antidepressant - tricyclic

Indications (NB some may be unlicensed): depression, smoking cessation, neuropathic pain, itch

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

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

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

Interactions:

- *increased clinical effect/toxicity of nortriptyline* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) **e.g. bupropion, fluoxetine, paroxetine, quinine**
- *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 100 mg at night (max. of 50 mg in elderly)	10 to 50 mg at night
subcut:	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

Notes:

- Metabolite of amitriptyline, less adverse reactions (including sedation) than amitriptyline.
- 25 mg nortriptyline ≈ 75 mg amitriptyline (approx).
- Measurement of blood drug concentrations may be useful to establish compliance or confirm toxicity.

Nystatin

Class: antifungal - polyene

Indications: 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 (1 mL) 4 times a day
gastrointestinal candidiasis:	500,000 to 1,000,000 units 3 times a day
subcut:	not available
rectal:	not available
topical:	apply 2 to 3 times a day
vaginal:	5 g of cream once or twice a day

Syringe driver: not available

Mechanism of action: increases fungal cell membrane permeability

Notes:

- If infection is severe or recurrent use a systemic antifungal e.g. fluconazole.

Octreotide

Class: growth hormone inhibitor

Indications (NB some may be unlicensed): acromegaly, gastro-entero pancreatic endocrine tumours, post pancreatic surgery, emergency treatment to stop bleeding oesophageal varices, 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
subcut:	200 to 600 micrograms/24 hours (max. 1 mg/24 hours) LAR - not usually used in palliative care
rectal:	not available
iv:	not available

Syringe driver: see syringe driver compatibility table

Mechanism of action: blocks somatostatin receptors

Peak effect: 30 minutes

Duration: 12 hours

Notes:

- Long acting octreotide formulations are available. Their use in palliative care has not been fully established.

Olanzapine

Class: antipsychotic, antimanic, mood stabiliser

Indications (NB some may be unlicensed): acute and chronic psychoses including schizophrenia, bipolar disorder, 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, DLB

Adverse reactions: *common* drowsiness, weight gain, dizziness, hallucinations, akathisia and other extrapyramidal side effects, elevated blood glucose and triglycerides, chest pain, oedema, constipation, dry mouth; *less common* angioedema, urticaria, diabetic coma, hepatitis, pancreatitis, priapism, tardive dyskinesia, neuroleptic malignant syndrome, blood disorders, hypotension, mania, seizures

Metabolism/clearance: metabolised mainly in the liver by the metabolising enzymes CYP1A2 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. ciprofloxacin, ketoconazole**
- *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, smoking, 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 20 mg per day as a single dose
subcut:	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

Notes:

- Lower potential for neurological adverse effects than conventional antipsychotics.
- Can be used in acute delirium and behavioural disturbances associated with brain tumours.

Omeprazole

Class: ulcer healing/prophylactic - proton pump inhibitor

Indications (NB some may be unlicensed): duodenal/gastric ulcer, reflux oesophagitis, dyspepsia, NSAID associated gastric and duodenal ulcer/erosion treatment

Contraindications/cautions: renal impairment

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

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

Interactions:

- *increased clinical effect/toxicity of omeprazole* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) **e.g. fluconazole, fluoxetine, ketoconazole**
- *decreased clinical effect/toxicity of omeprazole* (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) **e.g. carbamazepine, phenytoin, rifampicin**
- *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. diazepam**
- *decreased absorption of* **itraconazole** may occur with omeprazole

Dosing:

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

Syringe driver: short infusions only

Mechanism of action: inhibits gastric acid secretion via proton pump blockade

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

Notes:

- Omeprazole is considered the drug of choice for prophylaxis or treatment of NSAID-induced gastro-intestinal damage.
- Oral suspension can be made.

Ondansetron

Class: antiemetic - 5HT3 antagonist

Indications (NB some may be unlicensed): nausea/vomiting post chemo- or radio- therapy, post-operative nausea/vomiting, nausea/vomiting not due to above

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 CYP2D6 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. bupropion, fluoxetine, paroxetine, quinine**

Dosing:

oral:	4 to 8 mg twice a day
subcut:	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 (subcut): 30 minutes

Notes:

- May be of use in nausea and vomiting refractory to all other antiemetics.

Oxycodone

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 mainly in the liver

Interactions:

- *increased clinical effect/toxicity of oxycodone* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) **e.g. bupropion, fluoxetine, paroxetine, quinine**
- *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 1 to 3 mg 4 to 6 hourly
	slow release	initially 5 mg every 12 hours
subcut:	oral:subcut	2:1
rectal:	not available	

Syringe driver: see syringe driver compatibility table

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

Onset: oral: 20 to 30 minutes

Duration: oral: (immediate release): 4 to 6 hours slow release: 12 hours

Notes:

- May be useful in opioid rotation.
- Dose conversion from oral morphine to oral oxycodone is 2:1 i.e. 10 mg oral morphine =
- 5 mg oral oxycodone because oral availability of oxycodone is twice that of morphine.
- The slow release tabs and the immediate release caps should not be opened or crushed/chewed.
- In renally impaired patients, one of oxycodone's active metabolite may accumulate.
- The combination oxycodone+naloxone modified release tablets* are designed to reduce opioid induced constipation.

*** Drugs that are either not available or not funded in New Zealand**

Pamidronate disodium

Class: bisphosphonate calcium regulator

Indications: 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	
subcut:	zoledronic acid is usually used instead	
rectal:	not available	
iv infusion:	bone pain	90 mg every 3 to 4 weeks
	hypercalcaemia	15 to 90 mg depending on corrected calcium concentration

- rate of infusion should not exceed 60 mg/hour (20 mg/hour in renal impairment) and concentration should not exceed 90 mg/250 mL

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

Notes:

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

Pantoprazole

Class: ulcer healing/prophylaxis - proton pump inhibitor

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

Dosing:

oral:	20 to 80 mg once a day
subcut:	inj available but not usually used subcut
rectal:	not available

Syringe driver: not usually used

Mechanism of action: inhibits gastric acid secretion via proton pump blockade.

Onset: oral (antacid effect): 2 hours

Paracetamol

Class: analgesic - non-opioid

Indications: 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 (> 6 g 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 and domperidone**
- *increased risk of* hepatotoxicity may occur with concurrent **carbamazepine, phenytoin**

Dosing:

oral:	500 mg to 1 g 4 to 6 hourly (max. 4 g in 24 hours)
subcut:	infusion available but large volume
rectal:	as for oral

Syringe driver: not used subcut due to high volume

Mechanism of action: thought to have a central effect on pain pathways and not anti-inflammatory

Onset: 0.5 hours

Duration: 4 hours

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

Class: anticonvulsant - barbiturate

Indications (NB some may be unlicensed): seizure control, status epilepticus, pre-op anxiety,

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: may be metabolised by metabolising enzyme CYP2C19 mainly in the liver

Interactions:

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

Dosing:

terminal agitation

oral:	60 to 180 mg per day
subcut:	600 to 1,200 mg/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

Notes:

- Risk of respiratory depression in overdose.

Phenytoin

Class: anticonvulsant - hydantoin

Indications (NB some may be unlicensed): 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 CYP2C8/9 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, ketoconazole, voriconazole**
- *decreased clinical effect/toxicity of phenytoin* (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) **e.g. phenobarbitone, rifampicin**
- *decreased clinical effect/toxicity of some drugs* (due to decreased blood concentrations of them) may occur with phenytoin due to metabolising enzyme induction by phenytoin **e.g. aprepitant, buspirone, amitriptyline, carbamazepine, clonazepam, dexamethasone, diazepam, domperidone, fentanyl, itraconazole, ketoconazole, methadone, midazolam, NSAIDs (e.g. diclofenac), olanzapine, ondansetron, phenytoin, prednisone, quetiapine, triazolam, warfarin**

Dosing:

oral:	100 to 300 mg/24 hours (titrate to plasma concentrations)
subcut:	inj available but not given subcut
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)

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

Class: corticosteroid - glucocorticoid

Indications (NB some may be unlicensed): allergy, asthma, rheumatic disease, inflammatory conditions, 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 CYP3A 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. aprepitant, clarithromycin, fluconazole, fluoxetine, grapefruit juice, itraconazole, ketoconazole, 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, phenobarbitone, phenytoin, rifampicin, St John's wort**
- *increased risk of GI bleed/ulceration* when given with **NSAIDs (e.g. diclofenac)**

Dosing:

oral:	10 to 100 mg usually once a day (max. 250mg/day)
subcut:	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

Notes:

- 0.75 mg dexamethasone has an equivalent anti-inflammatory effect to 5 mg prednisone or
- 20 mg 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 40 mg prednisone (6 mg dexamethasone) per day.
- Corticosteroid induced insomnia responds to benzodiazepines (e.g. temazepam).
- Corticosteroid induced mood disorder is usually depression and rarely mania.
- Metabolised to prednisolone.

Pregabalin* .....

Class: anticonvulsant

Indications (NB some may be unlicensed): neuropathic pain, adjunctive anticonvulsant

Contraindications/cautions: renal disease (reduce dose)

Adverse reactions: *common* dizziness, somnolence, blurred vision, fatigue, dry mouth, headache, tremor, constipation, nausea; *less common* weight gain, ataxia, confusion, suicidal thoughts

Metabolism/clearance: not metabolised, mainly excreted unchanged by the kidneys (fraction excreted unchanged by the kidney = 0.9) so adjust dose in renal dysfunction

Interactions:

- *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:	neuropathic pain/epilepsy	150 to 600 mg/day in 2 divided doses (start with lower dose and increase)
subcut:	not available	
rectal:	not available	

Syringe driver: not available

Mechanism of action: may act through effects on calcium channels in the CNS and reduces release of the neurotransmitters glutamate, noradrenaline and substance P.

*** Drugs that are either not available or not funded in New Zealand**

Quetiapine

Class: antipsychotic - atypical

Indications (NB some may be unlicensed): acute and chronic psychoses including schizophrenia, manic episodes associated with bipolar disorder, nausea and vomiting, delirium

Contraindications/cautions: liver dysfunction, cardiovascular and cerebrovascular disease, hypotension, seizures, Parkinsons, DLB

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 CYP3A

Interactions:

- *increased clinical effect/toxicity of quetiapine* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) **e.g. aprepitant, clarithromycin, grapefruit juice, indinavir, itraconazole, ketoconazole, nelfinavir, ritonavir, telapravir, voriconazole**
- *decreased clinical effect/toxicity of quetiapine* (due to decreased blood concentrations) may occur with some CYP metabolising enzyme inducers (see above) e**.g. carbamazepine, phenobarbitone, phenytoin, rifampicin, St John's wort**
- *possible increase risk of extrapyramidal effects* with **dopamine antagonists e.g. metoclopramide**
- *additive hypotension with* **antihypertensives e.g. propranolol** may occur
- *additive CNS effects* with other **CNS depressants e.g. benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), opioids, alcohol**

Dosing:

oral:	psychosis	initially 50 mg/day increasing daily to 150 to 750 mg per day in 2 divided doses
	mania	initially 100 mg/day increasing daily to 200 to 800 mg per day in 2 divided doses
	tranquillisation, sedation, antiemetic	25 to 100 mg at night
subcut:		not available
rectal:		not available

Syringe driver: not available

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

Notes:

- Lower potential for neurological adverse effects (e.g. extrapyramidal effects) than conventional antipsychotics.
- Can be used in acute delirium and behavioural disturbances associated with brain tumours.

Ranitidine

Class: ulcer healing/prophylactic - H2 antagonist

Indications (NB some may be unlicensed): duodenal/gastric ulcer, reflux oesophagitis, dyspepsia, 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:	150 mg twice a day or 300 mg at night (reduce dose in elderly and renal impairment)
subcut:	100 to 200 mg/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

Notes:

- Pantoprazole or omeprazole is considered the drug of choice for prophylaxis or treatment of NSAID-induced gastrointestinal damage.
- If gastrointestinal reflux is uncontrolled by pantoprazole or omeprazole, adding in a night-time dose of ranitidine may help.

Risperidone

Class: antipsychotic - atypical

Indications (NB some may be unlicensed): schizophrenia, psychosis, behavioural/psychological symptoms of dementia, conduct/behavioural disorders in mentally retarded, autism, mania in bipolar disorder, delirium

Contraindications/cautions: Parkinson's disease, DLB, 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 CYP3A and 2D6 mainly in the liver

Interactions:

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

Dosing:

oral:	schizophrenia	initially 2 mg/day increasing to 4 to 6 mg/day (max 16 mg/day)
	bipolar mania	initially 2 mg/day increasing to 2 to 6 mg/day
	dementia	initially 0.25 mg twice a day increasing to a max. of 1 mg twice a day
	psychosis	0.5 to 4 mg twice a day
subcut/rectal:		not available

Syringe driver: not available

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

Onset: psychosis: 1 to 2 weeks

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 8 mg a day) or in the cerebrally compromised patient extrapyramidal side effects may occur.

Senna

Class: laxative - stimulant

Indications: 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 28 mg) at night with docusate 1 to 2 tabs at night (max. 4 tabs)
subcut:	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

Notes:

- May be useful in opioid induced constipation.

continued

Spironolactone

Class: diuretic - aldosterone antagonist, potassium sparing

Indications (NB some may be unlicensed): oedema, hypertension, congestive heart failure, hirsutism, hyperaldosteronism, 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 200 mg once a day (max. 400 mg daily)
subcut/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

Notes:

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

Tramadol

Class: analgesic - opioid (with extra effect on inhibitory pain pathways)

Indications: step 2 on the WHO analgesic ladder

Contraindications/cautions: epilepsy, drug abuse, respiratory depression

Adverse reactions: *common* nausea, vomiting, diarrhoea, sweating (dose related); *less common* dry mouth, sedation, headache, hypertension, confusion

Metabolism/clearance: metabolised by metabolising enzyme CYP2D6 mainly in the liver to an active metabolite

Interactions:

- *increased clinical effect/toxicity of tramadol* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) **e.g. bupropion, fluoxetine, paroxetine, quinine**
- *additive CNS effects* with other **CNS depressants e.g. benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), other opioids, alcohol**
- *additive risk of serotonin syndrome* (potentially fatal syndrome - symptoms include sweating, diarrhoea, confusion) with other serotonergic drugs **e.g. amitriptyline, carbamazepine, citalopram, fluoxetine, lithium, paroxetine**
- *decreases seizure threshold* so may interact with **anticonvulsants e.g. carbamazepine**

Dosing:

oral:	normal release	50 to 100 mg 4 hourly (max. 400 mg/24 hours)
	slow release	100 to 200 mg twice a day
subcut:		up to 600 mg/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

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

Class: antifibrinolytic, haemostatic

Indications: haemorrhage - surface bleeding from tumours, nose and other organs

Contraindications/cautions: active clotting, urinary tract bleeds (as clots may rarely form in the urinary tract), renal dysfunction, subarachnoid haemorrhage, acquired defective colour vision

Adverse reactions: *common* GI upset; *less common* dizziness (iv), thrombocytopenia, headache, restlessness, impaired colour vision

Interactions:

- *decreased clinical effect of anticoagulants* **e.g. warfarin** may occur with tranexamic acid

Dosing:

haemorrhage

oral:	1 to 1.5 g 3 to 4 times a day
subcut:	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 1 g 2 to 3 times a day

Syringe driver: not applicable

Mechanism of action: interacts with plasminogen to cause antifibrinolysis

Peak effect: 3 hours

Notes:

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

Valproate (sodium)

Class: anticonvulsant, antipsychotic

Indications (NB some may be unlicensed): epilepsy, bipolar disease, neuropathic pain

Contraindications/cautions: liver dysfunction

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

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

Interactions:

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

Dosing:

neuropathic pain

oral:	200 to 1,000 mg twice a day (max. 2,500 mg per day, start low)
subcut:	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

Notes:

- Co-analgesic often used with opioids in the treatment of neuropathic pain although gabapentin or pregabalin have become common alternatives.
- May be used in neuropathic pain when tricyclic antidepressants have failed or in combination with tricyclic antidepressants.
- When switching from carbamazepine to valproate watch for toxicity from other drugs as carbamazepine induces the metabolism of several drugs while 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

Class: antidepressant - bicyclic, SNRI

Indications (NB some may be unlicensed): depression, anxiety disorders, ?neuropathic pain, hot flushes

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

Adverse reactions: *common* nervousness, headache, fatigue, blood pressure changes, dizziness, dry mouth, insomnia, drowsiness, weight gain or loss, GI effects, sexual dysfunction, sweating, weakness, prolongation of the QT interval; *less common* tremor, mania, anxiety, palpitations, heart failure, loss of consciousness, seizures, blood disorders, hepatitis, arrhythmias, neuroleptic malignant syndrome, pancreatitis, extrapyramidal adverse effects, 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. bupropion, fluoxetine, paroxetine, quinine**
- *increased clinical effect/toxicity of some drugs* (due to increased blood concentrations of them) may occur with venlafaxine due to metabolising enzyme inhibition **e.g. codeine** (effect may be decreased due to lack of metabolism to morphine), **nortriptyline**
- *increased risk of serotonin syndrome* with MAOIs **e.g. phenelzine** so avoid venlafaxine within 2 weeks of MAOI therapy
- *increased risk of prolonged QT interval* with other drugs that prolong the interval **e.g. haloperidol**

Dosing:

oral:	modified release	37.5 to 375 mg once a day
subcut:		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

Notes:

- Effectiveness in neuropathic pain is yet to be evaluated.

Warfarin

Class: anticoagulant

Indications: thrombotic disorders prophylaxis

Contraindications/cautions: potential haemorrhagic conditions

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

Metabolism/clearance: metabolised by the metabolising enzymes CYP 1A2, 2C19 and 2C9 mainly in the liver

Interactions:

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

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

Dosing:

oral:	adjusted to INR (see below)
subcut:	not available
rectal:	not available

Syringe driver: not available

Mechanism of action: interferes with vitamin K synthesis

Notes:

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

continued

Treatment in DVT and PE	INR	Duration
Pre and perioperative anticoagulation	1.5 to 2.0	days
Treatment of calf DVT	2.0 to 3.0	4 - 6 weeks
Treatment of provoked DVT	2.0 to 3.0	12 - 26 weeks
Treatment of provoked PE or massive DVT	2.0 to 3.0	26 - 52 weeks
Treatment of unprovoked PE or DVT	2.0 to 3.0	life long
Treatment of recurrent PE or DVT#	3.0 to 4.0	life long
Atrial Fibrillation	2.0 to 3.0	life long
Mechanical heart valves		
Aortic valve replacement	2.0 to 2.5	life long
Mitral valve replacement	2.5 to 3.0	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, 15th Edition 2013, Canterbury District Health Board, New Zealand

Zoledronic acid

Class: bisphosphonate - calcium regulator

Indications (NB some may be unlicensed): osteoporosis treatment and prevention, Paget's disease, prevention of further fracture after hip fracture, hypercalcaemia of malignancy, bone metastases

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	
subcut:	not usual but has been tried	
rectal:	not available	
iv infusion:	hypercalcaemia	4 mg 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

Notes:

- Patients must be adequately hydrated before administration of zoledronic acid, especially the elderly and those on diuretics
- Renal impairment has been noted after a single administration of the drug. Routinely check serum creatinine clearance pre-administration and cease zoledronic acid if creatinine this is becoming impaired.
- Osteonecrosis of the jaw has been noted predominantly in adults receiving bisphosphonate infusions
- Occasionally severe muscle, bone and joint pain is experienced after infusion, mostly this is relieved after stopping treatment

Syringe drivers

A syringe driver is a battery-operated pump which administers drugs subcutaneously- consult a specialist for information on the pump used in your area and how to use it. Many of the drugs administered via the syringe driver are not licensed for subcutaneous use and the responsibility for their use lies with the prescriber

Indications

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

Diluent

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

Compatibility

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

The following drugs should never be given subcutaneously
DIAZEPAM, PROCHLORPERAZINE, CHLORPROMAZINE

Syringe Driver Compatibilty Table

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

Combinations that have been used

Y = compatible	morphine+clonazepam+cyclizine (morphine sulphate and tartrate)
N = incompatible	morphine+clonazepam+dexamethasone (morphine sulphate and tartrate)
SI = sometimes incompatible (usually at higher concentrations)	morphine+clonazepam+haloperidol (morphine sulphate and tartrate)
NA = not usually used together	morphine+clonazepam+ketamine (morphine sulphate and tartrate)
? = unknown	morphine+clonazepam+metoclopramide (morphine sulphate Y, tartrate SI)

Info from:
1) The Palliative Care Handbook 7TH Edition 2014 – 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,

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.

hyoscine butyl bromide(Buscopan™)	hyoscine hydrobromide	ketamine	methotrimeprazine/ levomepromazine (Nozinan™)	methadone	metoclopramide	midazolam	morphine sulphate (normal strengths)	morphine tartrate (high strengths)	octreotide	ondansetron	oxycodone	phenobarbitone
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	?	Y	?
SI	Y	?	Y	?	Y	SI	Y	Y	SI	Y	SI	?
Y	Y	Y	SI	Y	Y	SI	Y	Y	SI	Y	Y	?
Y	Y	Y	Y	?	Y	Y	?	?	Y	Y	?	Y
?	NA	Y	Y	Y	Y	Y	Y	?	Y	Y	Y	N
Y	Y	Y	Y	Y	Y	Y	Y	SI	Y	Y	Y	?
Y	Y	?	Y	?	-	Y	-	-	?	?	-	?
-	NA	Y	Y	?	Y	Y	Y	?	Y	Y	Y	?
NA	-	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	?
Y	Y	-	Y	?	Y	Y	Y	Y	Y	Y	Y	?
Y	Y	Y	-	Y	Y	Y	Y	Y	SI	Y	Y	?
?	Y	?	Y	-	Y	Y	?	?	?	?	?	N
Y	Y	Y	Y	Y	-	Y	Y	Y	Y	Y	Y	?
Y	Y	Y	Y	Y	Y	-	Y	Y	Y	Y	Y	?
Y	Y	Y	Y	?	Y	Y	-	NA	Y	Y	NA	?
?	Y	Y	Y	?	Y	Y	NA	-	?	Y	NA	Y
Y	Y	Y	SI	?	Y	Y	Y	?	-	Y	Y	?
Y	Y	Y	Y	?	Y	Y	Y	Y	Y	-	Y	?
Y	Y	Y	Y	?	Y	Y	NA	NA	Y	Y	-	?
?	?	?	?	N	?	?	?	Y	?	?	?	-

morphine+cyclizine+dexamethasone (morphine sulphate and tartrate)	morphine+dexamethasone+haloperidol (morphine sulphate and tartrate)
morphine+cyclizine+haloperidol (morphine sulphate and tartrate)	morphine+dexamethasone+hyoscine hydrobromide (morphine sulphate and tartrate)
morphine+cyclizine+hyoscine butyl bromide (morphine sulphate, tartrate SI)	morphine+dexamethasone+metoclopramide (morphine sulphate and tartrate)
morphine+cyclizine+metoclopramide (morphine sulphate and tartrate)	morphine+dexamethasone+midazolam (morphine sulphate SI, tartrate SI)
morphine+cyclizine+midazolam (morphine sulphate and tartrate)	morphine+dexamethasone+haloperidol (morphine sulphate and tartrate)

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