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Aotearoa Specialist Adult Palliative Care Guidelines

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The team

A little about us

Roni Taikato

Kia ora tatou.
Ko Mauao me Taranaki oku Maunga.
Ko Tauranga te Moana me Kapuni oku Awa.
Ko Mataatua me Aotea oku waka.
Ko Ngaiterangi me Ngaruahine oku iwi.
Ko te whanau o Tauwhao ki Rangiwaea me Ngati tu oku Hapū.

Ko Roni Taikato ahau.
He noho Ana au ki Te Whanagaui a Tara.
He Neehi Maori ahau ki Mary Potter Hospice.
Kia ora tatou Katoa.

Hello to all,
My mountains are Mauao and Taranaki.
Tauranga is my sea and Kapuni is my river.
Mataatua and Aotea are my waka.
Ngaiterangi and Ngaruahine are my tribes.
Te whanau o Tauwhao and Ngatitu are my sub-tribes.

My name is Roni Taikato
I am a Palliative care nurse currently working at Mary Potter hospice and I live in Wellington.
Thank you all.

Lana Ferguson

Tēnā koutou katoa
Airangi te whakapaparanga mai
Ko Tamaki Makaurau te whenua tupu
Ko Kirikiriroa te kāinga
He Te Tākuta Pairuri au i Hospice Waikato
Ko Lana Ferguson taku ingoa
Tēnā tātou katoa

Greetings
My ancestors are from Ireland
I grew up in Auckland
I live in Cambridge Hamilton
I am a palliative doctor at Hospice Waikato.
My name Lana Ferguson
Greetings to one and all

Denise Hewitt

Tēnā koutou katoa

Ko Peretānia te whakapaparanga mai.

Ko Tāmaki Makaurau me Te Tairāwhiti nga whenua tupu.

Ko Te Papaioea te kāinga.

He kai rongoā pairuri au i Arohanui Hospice.

Ko Denise Hewitt ahau.

Tēnā tātou katoa.

Greetings.

My ancestors ca me from the United Kingdom.

I grew up in Auckland and Gisborne.

My home is Palmerston North.

I am a palliative care pharmacist at Arohanui Hospice.

My name is Denise Hewitt.

Greetings to all.

Abby Earrey

Tēnā koutou katoa.

Ko Kōtarani.

Ko Edinburgh te whenua tupu.

Kei Wanaka, Te Waipunamuau au e noho ana.

He Tapuhi Whai Rēhitatanga au i Otago Tūroro.

Ko Abby Earrey au.

Tēnā tātou katoa.

Greetings.

I am Scottish.

I grew up in Edinburgh.

I live in Wanaka.

I am a registered nurse at Otago Hospice.

I am Abby Earrey.

Greetings to one and all.

Louisa Ingham

Tēnā koutou katoa.

Ko Kōtirana.

Te whakapaparanga mai Ko Kōtirana, Ko Ingarangi, Ko Wēra.

Ko te Waipounamu te whenua tupu.

Kei Ōtepoti au e noho ana

He Mātanga Tapuhi me Kaiwhakahaere Tapuhi me haumanu au i Te kahu Pairuri ki Ōtākou.

Ko Louisa Ingham au.

Tēnā tātou katoa.

Greetings.

I am Scottish.

My ancestry is Scottish, English & Welsh

I grew up in the South Island.

I live in Dunedin.

I am a Nurse Practitioner, and Director of Nursing & Clinical Services at Otago Community Hospice.

I am Louisa Ingham.

Greetings to all.

Jennifer Dawson

Tēnā koutou katoa.	Greetings,
He Ahitereiria ahau.	I am Australian.
Ko Melbourne te whenua tupu.	I grew up in Melbourne.
Ko Tamaki Makaurau te kāinga.	I live in Auckland.
He tākuta pairuri au i Hōhipera Middlemore.	I work at Middlemore Hospital.
Ko Jennifer Dawson au.	I am Jennifer Dawson.
Tēnā tātou katoa.	Greetings to one and all.

Juliet Fleming

Tēnā koutou katoa.	Greetings everyone.
Ko Peretānia.	I am British.
Ko Mahana ahau e noho ana.	I now live in Mahana.
He te tākuta pairuri au i Nelson Tasman Hospice.	I am a palliative care doctor at Nelson Tasman Hospice.
Ko Juliet Fleming tōku ingoa.	My name is Juliet Fleming.
E ki ana te whakatauki	As the saying goes
'Whaowhia te kete mātauranga'.	'Fill the basket of knowledge'.
Tēnā koutou katoa.	Greetings to one and all.

Kathryn Forwood

Tēnā koutou katoa	Greetings.
Ko Ahitereiria	I am Australian.
Ko Tasmania me Queensland te whenua tupu.	I grew up in Tasmania & Queensland.
Ko ōtepoti to kāinga	I live in Dunedin.
He te tākuta pairuri au i Te Kahu Parirui ki Ōtākou.	I am a palliative doctor at Otago Hospice.
Ko Kathryn Forwood au.	I am Kathryn Forwood.
Tēnā tātou katoa.	Greetings to one and all.

Richard McNeill

Tēnā koutou katoa.	Greetings.
Ko Aerana, ko Kōtirana.	I am Irish and Scottish.
Ko Belfast te whenua tupu.	I grew up in Belfast.
Ko Ōtautahi te kāinga.	I live in Christchurch.
He te tākuta pairuri au i Nurse Maude Hospice, Te Whatu Ora Waitaha.	I am a palliative doctor at Nurse Maude.
Ko Richard McNeill au.	I am Richard McNeill.
Tēnā tātou katoa.	Greetings to one and all.

Florry O'Connell

Tēnā koutou katoa.	Greetings.
Ko Aerana.	I am Irish.
Ko Kerry te whenua tupu.	I grew up in Kerry.
Ko Tāmaki Makarau te kāinga.	I live in Auckland.
He te tākuta pairuri au i Te Kahu Pairuri mai I Takatunga ki Te Hana.	I am a palliative doctor at Harbour Hospice.
Ko Florry O'Connell au.	I am Florry O'Connell.
Tēnā tātou katoa.	Greetings to one and all.

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Guideline

Dexamethasone in Palliative Care

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a. Dexamethasone guideline
b. Use of corticosteroids – practise points
c. Corticosteroid comparison chart
d. Ceasing or weaning corticosteroids

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PURPOSE

To provide guidance in the use of corticosteroids (in particular dexamethasone) in palliative care.

SCOPE

Palliative care specialists/palliative medicine physicians, nurse practitioners, hospice medical officers, palliative care pharmacists.

PATIENT GROUP

Patients with a life-threatening or life-limiting illness for who dexamethasone use in indicated.

ABBREVIATIONS

BGL	blood glucose level
CSCI	continuous subcutaneous infusion
GI	gastro-intestinal
GOC	goals of care
INR	international normalised ratio
NSAIDs	non-steroidal anti-inflammatory drugs
PO	per oral
PR	per rectal
SC	subcutaneous
SVC	superior vena cava
ICP	intracranial pressure

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CLINICAL MANAGEMENT

Description
Dexamethasone is a corticosteroid with potent glucocorticoid activity but limited mineralocorticoid activity, suitable for high dose anti-inflammatory therapy.

Approved (licensed) route and indications
Intravenous or oral administration
Relief of raised intracranial pressure due to intra-cerebral malignancy
Therapy specific indications including auto-immune, endocrine, pulmonary or haematological disorders.

Unlicensed route and indications
Subcutaneous administration:
Dexamethasone has a long duration of action and can be given as a once or twice daily SC injection.

To reduce CSCI site irritation, dexamethasone at a dose of 1mg or less is sometimes added to other drugs, only when compatibility data permits.

Indications:

- Spinal cord compression, nerve compression
- Dyspnoea or cough caused by pneumonitis, lymphangitic carcinomatosis, or tracheal or endo-bronchial obstruction.
- Superior vena cava obstruction
- Discharge from a rectal tumour (PO or PR)
- Paraneoplastic fever
- Nausea and vomiting resistant to standard treatments
- Analgesia
  - Pain associated with spinal cord or nerve compression
  - Pain caused by tumour in a confined organ or body cavity (e.g. liver capsule pain)
  - Radiation induced inflammation
- Anti-Cancer Hormone Therapy
  - Prostate Cancer
  - Haematological malignancies
  - Lymphoproliferative disorders
- General “tonic”
  - Improve appetite, enhance sense of wellbeing
  - Hiccup, itch, sweating

Indication and dosing guidance

INDICATION	DAILY DOSE
Spinal cord compression, SVC obstruction	16 mg
Raised ICP, tumour induced airway obstruction	8-16 mg
Obstruction of viscus (bowel, bladder, ureter)	8-16 mg
Hiccups	4-8 mg
Liver capsule, nerve compression, bone pain	4-8 mg
Nausea and vomiting	4-8 mg
Anorexia, general wellbeing, mood	2-4 mg

Contraindications

- Previous hypersensitivity
- Live virus immunisation
- Care with previous corticosteroid induced psychosis

*Relative contraindications**
Hyperglycaemia
Gastro-intestinal ulceration and/or bleeding
Infection

**Need to be considered in context of steroid risk/benefit profile for the individual patient*

Adverse effects

- Fluid and electrolyte disturbances (e.g. hypokalaemia), elevation of blood pressure, oedema
- Hyperglycaemia, increased appetite
- Oral candidiasis
- Glaucoma, increased intraocular pressure
- Increased susceptibility to infection, impaired wound healing
- Psychological disturbances – including insomnia, euphoria and depression
- Peptic ulcer with perforation, oesophageal ulceration (with concomitant NSAIDs or aspirin)
- Muscle and skin atrophy, bruising, proximal myopathy
- Osteoporosis, avascular osteonecrosis

Drug interactions

- Hepatic metabolism
- May be *increased by potent CYP3A4 inducers* such as carbamazepine, phenobarbital, phenytoin, primidone, rifampicin and rifabutin thus reducing the effect of dexamethasone.
- May be *reduced by potent CYP3A4 inhibitors* such as itraconazole, aprepitant, thus increasing the effect of dexamethasone.

Dexamethasone is itself an inducer of CYP3A4.

Concurrent administration of dexamethasone with NSAIDs/aspirin will increase the bleeding risk.

Concurrent administration of dexamethasone with warfarin may cause a significant increase in the INR in about 50% of patients. The INR should be checked weekly for 2 to 3 weeks when a corticosteroid is started or dose altered.

Corticosteroids antagonise the effect of oral hypoglycaemics and insulin (glucocorticoid effect), antihypertensives and diuretics (mineralocorticoid effect).

USE OF CORTICOSTEROIDS – PRACTICE POINTS

Given the many and significant undesirable effects of corticosteroids and the potentially deleterious effect of rapid withdrawal, corticosteroids should be prescribed cautiously and the expected benefits and risks should be discussed with the patient.

The efficacy and dose need to be reviewed at least weekly and instructions documented clearly.

Corticosteroids should be given for a time-limited trial. A duration of 5-7 days is usually enough to assess response. In those with no response, corticosteroids should be stopped. In those who respond, wean to the lowest effective dose, review weekly, aim to get maintenance doses below 4mg.

If a patient is to be on corticosteroids for more than 3 weeks, they should be given a corticosteroid treatment card or similar, warning against sudden cessation. Stress-dosing should be considered in patients who are steroid dependent.

Discontinue if no clinical/symptomatic benefit is seen or weaned to the lowest effective dose, especially if the dose is 4mg or greater.

Consider prophylactic gastric protection in patients taking concomitant aspirin or NSAIDs, or if previous GI bleed. Prophylaxis is not required for steroids alone without other risk factors.

Administer prior to 2pm to prevent sleep disturbance, preferably with or after food.

Monitor BGL closely for hyperglycaemia in patients with diabetes. For non-diabetic patients, high dose and or long-term corticosteroid use can cause hyperglycaemia and corticosteroid-induced diabetes - monitoring of BGL (daily in the afternoon) should be undertaken in this patient cohort.

Consider physiotherapy and occupational therapy referral in the context of steroid induced proximal myopathy.

CORTICOSTEROID COMPARISON CHART

Medication Equivalence	Approximate equivalent anti-inflammatory doses	Duration of Action (hours)	Oral bioavailability (%)
Hydrocortisone	20mg	8-12	96
Prednisone	5mg	12-36	80
Dexamethasone	750microgram	36-54	80

CEASING OR WEANING DEXAMETHASONE

Corticosteroids may be ceased abruptly in those whose symptoms are unlikely to relapse and who have been on doses of 4mg or less for less than 3 weeks, or doses up to 12 mg daily for less than 7 days.

Reducing dose
If used for longer or received repeated courses, reduce dose slowly to avoid adrenal insufficiency due to adrenal suppression and to allow time at new level to assess response, especially whether there is any deterioration:

Dexamethasone dose above 4mg daily:
Reduce by 2mg every 5-7 days until reaching 2mg, then by 0.5mg every 5-7 days, checking for symptoms before each dose reduction

Dexamethasone dose of 4mg or less:
Reduce by 0.5mg every 5-7 days
If a rapid reduction required, may reduce dose every 3-4 days.

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Hypercalcaemia of Malignancy

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OVERVIEW

Hypercalcaemia is a common problem (up to 30%) in patients with malignant disease; particularly associated with multiple myeloma, breast, lung, renal and thyroid malignancies[1]. However, the overall incidence is reducing due to the use of bisphosphonates[2]. The presence of hypercalcaemia can reflect a short prognosis, with refractory hypercalcaemia signifying a very short prognosis of days to short weeks[3].

PURPOSE

To provide guidance in the management of hypercalcaemia of malignancy.

SCOPE

Palliative care specialists/palliative medicine physicians, nurse practitioners, hospice medical officers, palliative care pharmacists.

PATIENT GROUP

Patients requiring management of hypercalcaemia of malignancy.

ABBREVIATIONS

ACE	angiotensin converting enzyme
CSCI	continuous subcutaneous infusion
GOC	goals of care
IU	international units
SC	subcutaneous
RANK	receptor activator of nuclear factor Kappa-B
ICP	intracranial pressure

DEFINITIONS

Hypercalcaemia	Is defined as a serum (corrected) calcium >2.6 mmol/L.
Mild hypercalcaemia	(2.6-2.9mmol/L) may not need correcting, if the patient is asymptomatic. Treatment is required if the patient is symptomatic and/or the corrected calcium is >3.0mmol/L *Serum calcium >4.0mmol/L is life-threatening and requires urgent treatment (provided this is within the patient GOC)*
Refractory hypercalcaemia	is that which is not responsive (serum calcium level does not lower) to usual treatment.

MECHANISMS OF MALIGNANT HYPERCALCAEMIA

- Humoral hypercalcaemia (up to 80%)
  - Secretion of parathyroid-related protein by the tumour
  - Ectopic parathyroid hormone production
  - Minimal to absent metastatic bone disease
- Osteolytic hypercalcaemia (approximately 20%)
  - Skeletal disease (severity of disease does not correlate with degree of hypercalcaemia)
- Impaired gut absorption of calcium and low vitamin D levels
- Reduced renal clearance of calcium

CLINICAL FEATURES OF HYPERCALCAEMIA OF MALIGNANCY

Neurological	• Fatigue & lethargy • Muscle weakness • Delirium • Altered level of consciousness (sedation)* • Seizures*
Renal	• Dehydration (hypovolaemia) • Polydipsia • Polyuria • Progressive renal impairment* • Nephrocalcinosis nephrolithiasis*
Cardiovascular	• Arrhythmias – shortened QT, prolonged PR, heart block, bradycardias*
Gastrointestinal	• Nausea and vomiting • Constipation • Non-specific abdominal discomfort • Pancreatitis

**Features of severe hypercalcaemia*

CLINICAL MANAGEMENT

Serum calcium should always be reviewed in the context of serum albumin.

Method for calculating corrected calcium

Corrected calcium (mmol/L)	=	*measured calcium (mmol/L)*	+	*[0.02 x (40 – measured albumin g/L)]*

Non-pharmacological management

- Check phosphate and renal function, if not already done
- Stop calcium supplements or medications that could worsen hypercalcaemia or contribute to acute kidney injury (e.g. diuretics, ACE-inhibitors).
- Assess volume status – rehydrate if hypovolaemic
  - Usually require 2-3L fluid per day but this needs to be in context of the patient's physiological ability to tolerate a fluid load. Consider pre-existing renal or heart failure.
  - In practical terms often 1 - 2L 0.9% saline IV at 80-100ml per hour is enough to improve mild to moderate hypercalcaemia without causing unnecessary fluid overload.
- Education of patients and family/whānau regarding early signs of hypercalcaemia (extreme fatigue, confusion, constipation, nausea/vomiting) to aide in early identification of hypercalcaemia.

Pharmacological management of hypercalcaemia

Bisphosphonates (zoledronate and pamidronate in New Zealand) remain first line management of hypercalcaemia of malignancy.

- Calcium levels usually take 3-5 days to decrease following bisphosphonate infusion and can take 7-10 days to achieve maximal effect of bisphosphonate.

<table>
<tr><th>DRUG</th><th>DOSING</th><th>COMMENTS</th></tr>
<tr><td>Zoledronate</td><td>3-4mg in 100mL of sodium chloride 0.9% IV over 15 minutes[4]</td><td>Renal dosing:
<table><tr><th>Baseline Creatinine Clearance (mL/min)</th><th>Zometa Recommended Dose</th></tr><tr><td>>60</td><td>4.0 mg</td></tr><tr><td>50-60</td><td>3.5 mg*</td></tr><tr><td>40-49</td><td>3.3 mg*</td></tr><tr><td>30-39</td><td>3.0 mg*</td></tr></table>
Not uncommon to get fever or flu-like symptoms associated with infusion.
Duration of effect on calcium can be up to 4-6 weeks.</td></tr>
<tr><td>Pamidronate</td><td>30-90mg in 250-500ml of sodium chloride 0.9% IV over 60-90 minutes

Can be given subcutaneously if IV route unavailable;

90mg pamidronate in 1L sodium chloride 0.9% SC over 12-24 hours[6]

Dosing dependent on serum calcium level[7]:<table><tr><th>Ca (mmol/L)</th><th>Dose (mg)</th></tr><tr><td>3.0
3.0-3.5
3.5-4.0
>4.0</td><td>30
30-60
60-90
90</td></tr></table></td><td>Renal dosing:
Not recommended in severe renal failure
In mild to moderate, suggest infusion rate of 90mg over 4 hours maximum[7].

Not recommended if creatinine clearance <30mL/min, unless severe life-threatening hypercalcaemia or in clinical context where benefit outweighs risk.

Duration of effect on calcium 3-4 weeks.</td></tr>
<tr><td>Calcitonin</td><td>4-8 IU/kg SC every 6-12 hours</td><td>Not commonly used in palliative care setting
Rapid onset of effect (around 4 hours) but much shorter duration of action (2-3 days) and should be used along with bisphosphates[1].
Useful for rapid lowering of calcium.
Tachyphylaxis can occur at 72 hours.</td></tr>
<tr><td>Corticosteroids</td><td>Dexamethasone 4-8mg PO/SC mane for 3-5 days

Hydrocortisone 200-400mg IV daily for 3 days followed by 7 days prednisone 10-20mg daily</td><td>Not routinely used as first line for management of hypercalcaemia
Slow onset of action – approx. 7 days
Can be useful in the context of hypercalcaemia due to haematological cancers, such as myeloma, lymphomas (1,25(OH)2 D syndrome).
– May lower serum calcium if they have an anti-neoplastic effect on underlying cancer.
NB: corticosteroid adverse effects, see Guideline Corticosteroid use in palliative care.

GUIDELINE
Corticosteroid use in palliative care</td></tr>
</table>

NB: *Denosumab is a RANK ligand monoclonal antibody, it binds with RANK which inhibits osteoclast formation and function, ultimately reducing bone resorption[8]. It is used internationally for the management of hypercalcaemia. While available in NZ it is not funded or indicated for the management of hypercalcaemia of malignancy currently[9].*

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Management of Complex Pain

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OVERVIEW

Management of complex pain in palliative medicine is a core skill. The vast majority of patients with complex pain have an underlying cancer diagnosis, however other non-malignant conditions which may contribute to this group include pain due to ischaemia or underlying vascular disease, patients with a history of chronic (non-cancer) pain, patients with current or previous substance misuse, central/thalamic pain syndromes (e.g., post-stroke). Underlying central sensitisation, as seen in chronic pain, is a contributor to difficult to manage pain, as is opioid-induced hyperalgesia.

Cancer-related pain can be due to the underlying disease process or as a result of cancer treatment. It affects up to 60% of patients with cancer, 40% of these having a neuropathic component[1,2]. Suboptimal pain management is associated with significant distress and impacts greatly on a patient's quality of life (QOL), as well as effecting those caring for them, both whānau and staff[3-5].

This guideline will focus predominantly on the biomedical management of pain, acknowledging that all contributors to pain (social, spiritual, emotional etc.) must be addressed in order to optimally manage this symptom, particularly in those patients with total pain. It also must be acknowledged that the evidence base for the management of cancer related pain is limited, much is extrapolated from the management of non-cancer pain syndromes[5].

With the evolution of cancer treatment, we must consider the concept of chronic cancer pain (both in patients with ongoing disease progression and those for whom treatment has been curative) and how we safely navigate opioid use in this patient cohort[6,7].

Prognosis plays a significant role in the assessment and management of complex pain, particularly in the use of opioids.

PURPOSE

To provide guidance in the management of complex pain in people with palliative care needs.

SCOPE

Palliative care specialists/palliative medicine physicians, nurse practitioners, hospice medical officers, palliative care pharmacists.

PATIENT GROUP

Patients with a life-threatening or life-limiting illness associated with pain that is complex such as neuropathic pain or poorly opioid-responsive pain.

ABBREVIATIONS

AV	Atrioventricular
ARC	Aged residential care facility
COX	Cyclo-oxygenase
CNS	Central nervous system
EOL	End of life
FDA	Federal Drug Administration
IV	Intravenous
IT	Intrathecal
ICP	Intracranial pressure
NSAID	Non-steroidal anti-inflammatory
NMDA	N-methyl-D aspartate
MEGX	Monoethylglycylxylidide
OIH	Opioid induced hyperalgesia
OME	Oral morphine equivalent
OST	Opioid substitution therapy
PO	Per oral
PR	Per rectal
QOL	Quality of life
SC	Subcutaneous
SL	Sublingual
SSRI	Selective serotonin reuptake inhibitor
SNRI	Serotonin-noradrenalin reuptake inhibitor
TCA	Tricyclic antidepressant

DEFINITIONS

Neuropathic pain	"Neuropathic pain is defined as pain caused by a lesion or disease affecting the somatosensory system"[5,6].
Nociception (nociceptive pain)	The perception of stimuli (usually painful) that causes or has the potential to cause tissue damage[8].
Mixed pain	Complex overlap of neuropathic and nociceptive pain types[9].
Central sensitisation	"Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input"[10].
Adjuvant analgesic	Medications used for pain management, for which the primary indication is not analgesia. Sometimes called "co-analgesic".
Opioid induced hyperalgesia	Nociceptive sensitisation resulting in hyperalgesia and/or allodynia associated with use of high dose opioids and or rapid escalation of opioids. Pain is potentiated by addi-tional doses of opioids[11,12].
Thalamic pain syndrome/ central post-stoke pain	Central neuropathic pain syndrome often seen following stoke affecting the thalamus.

KEY PAIN CONCEPTS

Central sensitisation

Ongoing stimulation of nociceptors can cause a heightened excitability and efficacy in pain pathways throughout the nervous system, this results in increased sensitivity of the pain system. Painful stimulation results in hyperalgesia and normally non-painful stimuli causes pain (allodynia).

Reduced or deficient descending inhibition

Inhibitory pathways help modulate pain. If there is reduced descending inhibition pain perception is intensified.

Opioid tolerance

The need for escalating opioid dose to achieve the same degree of analgesia. Opioid tolerance is defined by the FDA as anyone taking opioids daily for more than a week and receiving doses equivalent to morphine 60mg per day, oxycodone 30mg per day or 25mcg/hr fentanyl patch[13]. By this definition, the majority of patients known to palliative care would be considered to have opioid tolerance.

Opioid induced hyperalgesia

OIH is defined as hyperalgesia directly related to high or rapidly escalating opioid doses. Subsequent dose increases exacerbate hyperalgesia. The underlying mechanism is unclear, with several proposed theories, the most common being the role of the central glutaminergic system. Increasing exposure to opioids is thought to trigger NMDA activity centrally, spinal glutamate receptors are down-regulated with prolonged opioid exposure causing spinal sensitisation[12]. OIH tends to be diffuse pain, patients often describing “pain all over”, rather than pain localised to site of disease[14]. It is also important to note that OIH can occur acutely and is not always associated with chronic opioid use[14].

PAIN MANAGEMENT TECHNIQUES

Opioid rotation

The act of switching between opioids, including an overall dose reduction to improve the efficacy of opioids in pain management. It is generally advised to dose reduce by 25% when rotating to another opioid to account for cross-tolerance[15].

Multimodal analgesia

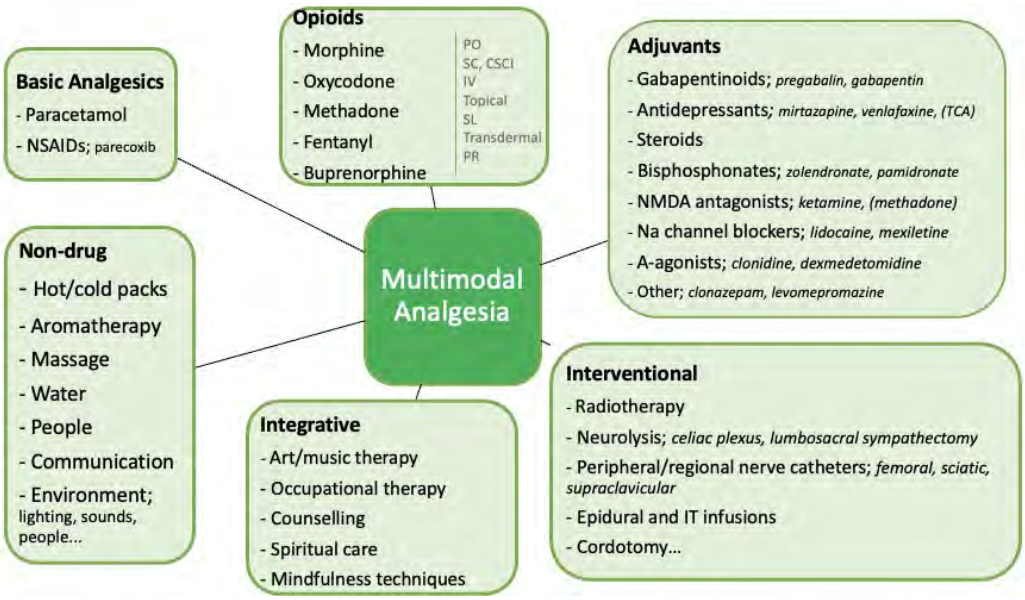

Figure 1: Multimodal approach to cancer pain management

COMMON CANCER PAIN SYNDROMES AND SUMMARY OF RECOMMENDED PHARMACOLOGICAL OPTIONS

Bone pain	• NSAIDS, corticosteroids, paracetamol • Bone-modifying agents (bisphosphonates) • Interventional options; radiation therapy, ablative techniques (e.g., cryoablation), vertebroplasty etc.
Nerve pain	• Compression/inflammation: – Corticosteroids, NSAIDs • Neuropathic pain: – TCAs as tolerated (side effect profile) – Gabapentinoids; consider rotation between gabapentin/pregabalin – SNRI or SSRI particularly if co-existing anxiety or mood condition. – Trial ketamine infusion and/or lidocaine infusion • Interventional options; radiation therapy, cryotherapy, regional/neuraxial analgesic techniques, plexus ablation (e.g., celiac plexus ablation).
Liver capsular pain	• Corticosteroid, NSAID
Skin; fungating tumors/ulceration	• In addition to systemic analgesic consider topical preparations including
Raised ICP headache	• Corticosteroids • Acetazolamide

ASSESSMENT

A key component of successful cancer pain management is thorough and targeted pain assessment to determine the underlying cause and nature of the pain. This includes review of recent radiological imaging and assessing for features of pain sensitisation and opioid-induced hyperalgesia. It is important to determine if pain is due to cancer, versus a consequence of cancer-related treatment or due to co-morbid conditions, as the management of the latter two is quite different[6]. A common error in pain management in patients with cancer, is the assumption that all pain is cancer-related pain. Accurate pain diagnosis has been found to benefit patients in multiple ways. These include the development of a targeted management plan (including analgesic medication, use of anticancer treatment), triggering education, support and promotion of non-drug/integrative therapies and improving interdisciplinary approach to pain management e.g. referral for interventional analgesic techniques such as celiac plexus neurolysis[6].

See figure 1 – Multimodal approach to cancer pain management

NON-PHARMACOLOGICAL MANAGEMENT OF PAIN

As outlined in the above figure, there are many non-pharmacological modalities important to the holistic management of complex pain. Resource constraints and limited accessibility can make routine utilisation of these techniques challenging, however, wherever possible non-pharmacological strategies should be employed in addition to pharmacological strategies[16,17,18].

PHARMACOLOGICAL MANAGEMENT OF PAIN

Generally, the concept of multimodal analgesia should be employed when managing complex cancer (or non-cancer) pain. In particular, recognising that complex pain is often poorly opioid responsive and escalating opioids may result in harm.

With the change in cancer trajectories and the evolving concept of cancer as a chronic illness, pain management techniques must also adapt. Opioids have been the mainstay of cancer pain management for many years and continue to be an important tool in managing pain in these patients. However, consideration must be made to ensure patients are not being exposed to unnecessary side-effect burden and long-term consequences of opioid use particularly in those patients for whom prognosis is in the region of long months to years.

In this setting skilled use of opioid-sparing techniques such as use of adjuvant medication, co-analgesics, opioid rotation, addressing the non-physical issues contributing to pain (emotion/mood/sleep/social etc), promotion of function, and use of interventional pain management techniques are paramount to avoid opioid tolerance and rapid escalation of opioid medications.

Many of the adjuvant analgesics that are used in the pharmacological management of pain are effective by reducing central sensitisation and increasing descending inhibition, i.e. “turning down the volume of pain”[19].

OPIOID ANALGESICS

NB: *This guideline only covers second-line (or those less commonly used) opioids in keeping with the theme of complex pain management. The assumption being that standard opioids have been trialed and are either ineffective or have caused an intolerable side effect burden.*

Regarding opioid equivalence/conversion advice please see links below:

https://nzf.org.nz/nzf_70672#nzf_70708

https://www.bettersafercare.vic.gov.au/sites/default/files/2021-02/GUIDANCE_Opioid%20Conversion%20FINAL_0.pdf

Methadone

Methadone is a μ-opioid receptor agonist (and possibly δ-opioid receptor agonist), N-methyl-D aspartate (NMDA) receptor channel blocker and a pre-synaptic blocker of serotonin reuptake.

Methadone can be challenging to use due to its long and variable plasma half-life (mean 20-35 hours, range 5-130 hours)[15]. It is highly lipophilic (high volume of distribution and high protein-binding).

Methadone accumulates in tissues creating an extensive reservoir which contributes to the complexity associated with its use. Multiple CYP450 enzymes are involved in methadone metabolism with CYP3A4 being the most clinically relevant[20]. Methadone is extensively metabolized by CYP3A4 to inactive metabolites. There is no single potency ratio between methadone and morphine.

> ***Caution:*** *risk of QT prolongation on methadone, ECG should be considered prior to initiation (depending on the clinical context), particularly if the patient is prescribed other QT prolonging medications.*

Available preparations:
Tablets 5mg
Oral liquid 2mg/mL, 5mg/mL, 10mg/mL
Injection 10mg/1mL
Methadone has high oral bioavailability (85%); safe conversion between oral and subcutaneous is 1:0.5 however, ranges from 1:1 to 1:0.7 (specialist preference)[21,22].

Patient selection for methadone[23]

- Moderate to severe pain
- Pain that is poorly opioid responsive/refractory to other opioids
- Intolerance to or significant side effect burden from other opioids
- High opioid tolerance, escalating opioid dosing
- Significant renal impairment
- No history of prolonged QTc
- Ideally prognosis longer than expected time for methadone to reach steady state

Considerations for initiating methadone in a home or community environment:
Methadone initiation and titration (especially conversion to methadone from another opioid) is ideally done in a monitored environment, however there are many factors that may necessitate the use of methadone outside of this environment to facilitate optimal pain control.

When initiating methadone in a community setting (e.g., home, ARC facility) the following should be considered.

- Patient safety – ensure patient has adequate cognition to follow dosing adjustments and ideally a responsible caregiver in the home (i.e., patient not living alone)
- The clinician initiating methadone needs to be able to regularly follow up until steady state is established (this is also true for any future dose adjustments)
- Ideally dose adjustment should be no more frequent than every 5-7 days
- Consider any risk factors for increased chance of methadone toxicity occurring
  - e.g., is the patient concurrently taking CYP450 inhibitors or potentially stopping CYP450 inducers during methadone initiation and titration? (These include over-the-counter medications and natural preparations such as turmeric).
- History of substance misuse or medication nonadherence may increase risk profile for community initiation.

QTc screening and monitoring of methadone for pain management in outpatient settings for patients with long prognosis (> 6 months)

1. Counsel patients about risks and benefits before initiating trial of methadone
2. Screen patients for Torsade's de Pointes risk factors, syncope or family history of sudden death
3. Review medications and reduce or stop as able
4. Baseline ECG
5. Avoid methadone in patients with QTc >500ms
6. Correct QTc prolongation reversible causes in patients with interval 450-500ms
7. Follow up ECG in 2-4 weeks post initiation of methadone in the following patients:
   - QTc >450ms at baseline
   - Patient taking two or more QTc prolonging drugs
   - Methadone doses reaching 30-40mg/day and again when methadone dose reaches 100mg/day

Dosing:
Establishing a stable methadone dose can take several days (7-10) even up to 2 weeks due to the drug's variable half-life. Patients must be monitored for methadone accumulation.

When methadone is used as background analgesia a second opioid (morphine or oxycodone) is generally used as the breakthrough analgesia to reduce the risk of methadone accumulation. In some situations (pain unresponsive to alternate opioids, renal failure with eGFR <10, OIH etc.), it may be reasonable to use methadone as the PRN medication, as a general rule it should not be given within 2 hours of the regular methadone dose. PRN methadone doses should be prescribed no more than every 3 hours with a maximum of 4 doses in a 24-hour. A safe starting PRN dose is calculated as 1/10th of the total 24-hour dose and titrated to effect[24]. In practical terms and in a monitored environment (e.g., IPU or hospital setting) a PRN dose of 2.5mg PO is reasonable.

Initiation of methadone:
Methadone can be started either by addition to a pre-existing opioid (adjuvant methadone) or through full rotation (methadone conversion).

Adjuvant methadone	• In general, it is safe to start methadone 2.5mg PO BD in addition to the patient's background opioid. • This can be increased in 2.5mg increments every 3 days (longer, 5-7 days, if in a community setting). • Close observation for opioid accumulation is necessary and it may be appropriate to reduce the background opioid as you up-titrate methadone (this is individual to the patient). • Caution in elderly/frail, it may be more appropriate to initiate adjuvant methadone at lower dose e.g., 1mg PO BD
Methadone conversion	• There are several methods available to guide methadone conversion. • The Edmonton method is a reliable and safe means of rotating to methadone over a 3-day period (note this should only be done in an inpatient facility). • Stop & Go Approach (Morley/Makin) – see below • Direct switch

1. Edmonton method for conversion to methadone:

- Calculate patients daily OME (do not include PRN use in this)
- Use the methadone conversion nomogram (see below) to determine target methadone dose.
- Over 3 days dose reduce the primary opioid by 1/3rd each day until stopped, at the same time start up-titrating methadone by 1/3rd until target dose achieved (or pain controlled)[23,25,26].

For example: patient taking oxycodone 120mg BD, convert to morphine using 1:1.5 conversion gives an OME of 360mg. Plot this on the nomogram to calculate a methadone target dose of approximately 35mg PO daily.

Example plan for a 3-day rotation in this patient:

DAY	OXYCODONE	METHADONE
Day 0	120mg BD	0 mg
Day 1	80mg BD	5mg TDS
Day 2	40mg BD	7.5mg, 10mg, 7.5mg
Day 3	0mg	12.5mg, 10mg 12.5mg

Key considerations when using this method:
The target methadone dose is just a guide to begin conversion, the final effective dose may be more or less than this dose. It is important that the patient is monitored closely for accumulation during the 3-day rotation and in the subsequent days until steady state is reached. In some patients, for whom methadone proves very effective, it may be appropriate to stop the methadone component of the above rotation at "day 2", i.e., on day 3 oxycodone would be stopped but the methadone dose would stay at 7.5mg, 10mg, 7.5mg. For other patients, titration beyond the calculated "day 3" target may be needed.

It may be appropriate to extend the time between dose titrations depending on the clinical scenario, for example rather than switching over 3 days, changing over 9 days (i.e., titrate every 3 days may be more suitable) particularly in a less monitored environment.

For a community/outpatient setting, it is possible to do a slow methadone rotation using the Edmonton methadone over 3 weeks, with each step taking place on weekly basis[27].

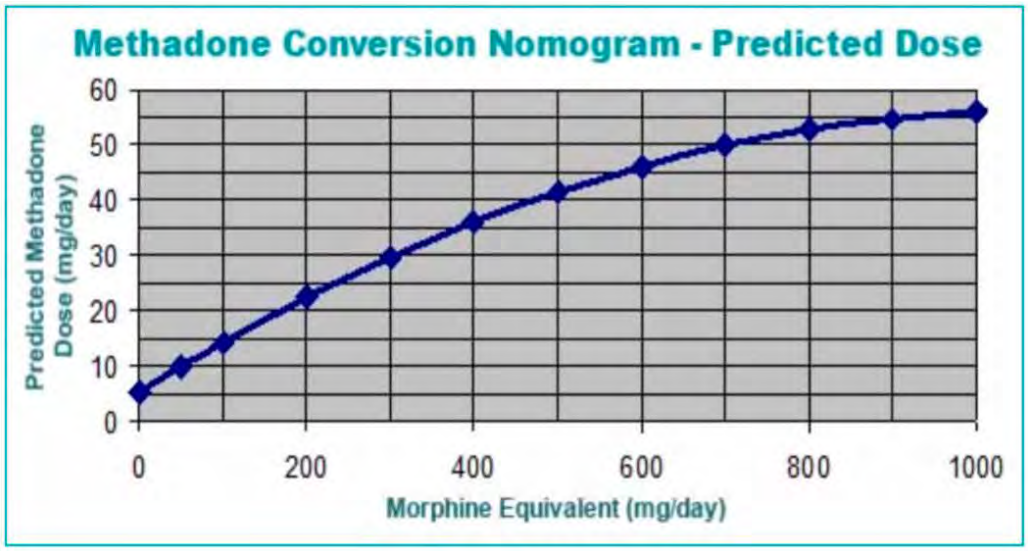

Figure 2: Methadone conversion nomogram (ref)

2. "Stop and Go" method for conversion to methadone:

PALLIATIVE CARE FORMULARY 'STOP AND GO' APPROACH:

The initial opioid is discontinued when methadone is started. Calculate the total 24-hour oral morphine equivalent dose the patient has been taking.

Give a single **loading dose** of oral methadone **one-tenth** of the total 24-hour oral morphine equivalent dose up to a maximum of **30mg** of methadone.

A three hourly '**as required**' dose of methadone **one-thirtieth** of the total 24-hour oral morphine equivalent dose is prescribed, up to a maximum of **30mg** of methadone.

If additional analgesia is required for breakthrough pain, i.e., for patients in severe pain, an alternative opioid may be prescribed 'as required' for second line use. This dose should be 50–100% of the PRN dose used before switching and can be administered hourly.

On **day six**, the amount of methadone taken in total over the previous 48 hours is calculated and divided by 4 to give a regular twice daily dose.

Write a care plan for 'Methadone Initiation' emphasising the need to monitor for opioid toxicity (RR, O2Sats, level of consciousness) for next 10 days.

Cautions with this method:
Patients who are too unwell/confused to report pain accurately and request as required analgesia

Oral dose conversion – worked examples of stop and go approach

- *Example 1:* Patient receiving the equivalent of 120mg oral morphine in 24 hours, loading dose = 12mg oral methadone, 'As required' dose = 4mg oral methadone
- *Example 2:* Patient receiving the equivalent of 450mg oral morphine in 24 hours, Loading dose = 30mg oral methadone (one-tenth equates to 45mg however this exceeds the maximum dose advised), 'As required' dose = 15mg oral methadone
- *Example 3:* Patient receiving the equivalent of 1200mg oral morphine in 24 hours, Loading dose = 30mg oral methadone (one-tenth equates to 120mg however this exceeds the maximum dose advised), 'As required' dose = 30mg oral methadone (one-thirtieth equates to 40mg however this exceeds the maximum dose advised)

Figure 3: PCF: Stop and go approach[15]

3. Straight switch:
This method involves stopping the primary opioid and starting the patient on the calculated "target" methadone dose. This is a useful method if the patient is only on low dose primary opioid or in the setting where prognosis is short and time for rotation is limited. The disadvantages include risk of precipitating withdrawal symptoms (rare) and suboptimal analgesia until steady state is reached. It may be useful in the setting to also use methadone as a 2nd line PRN (e.g., methadone 2.5mg Q3H, maximum of 4 doses per 24 hours). In this setting it may also be helpful to "bridge" the patient with a ketamine infusion for a few days, to allow methadone to reach steady state (see ketamine infusion below).

Buprenorphine:
Buprenorphine is a semi-synthetic partial mu-opioid agonist and a kappa/delta-opioid antagonist. Analgesia is achieved via agonistic action on the mu-opioid receptor. In New Zealand the only available preparation for use in palliative care is transdermal (TD) (Norspan patch 5, 10 and 20mcg/hr), however this is not funded and increasingly, sourcing this product is challenging[28].

Buprenorphine's effect on respiratory function plateaus, there is a ceiling on respiratory depression once a certain dose is achieved i.e., increasing dose beyond this does not increase risk of respiratory depression. This is thought to be due to its partial agonistic effect. Potency compared with morphine is complicated, however a safe conversion ratio for PO morphine to TD buprenorphine is 100:1, which can be extrapolated to suggest equipotency between TD fentanyl and TD buprenorphine, however some studies suggest TD fentanyl to be 1.4 times more potent than TD buprenorphine[15,29].

For practical application of dose equivalence a 5mcg/hour Norspan patch is equivalent to approximately 10mg oral morphine in 24 hours.

Approximate cost of Norspan patches (each patch lasts 1 week):

- 5mcg/hr $26.00 (2 patches)
- 10mcg/hr $47.00 (2 patches)
- 20mcg/hr $72.00 (2 patches)

Tramadol
This is a weak synthetic opioid with selective serotonin reuptake action, not commonly used in palliative care due to side effect profile and potential drug interactions, however there are some instances (particularly neuropathic pain) when it can be a very effective analgesic[30]. Tramadol is approximately 1/6th as potent as oral morphine (60mg PO tramadol equal 10mg PO morphine) and metabolised by CYP2D6 to an active metabolite which is renally cleared[31]. Use with caution in patients with renal failure.

Risk of serotonin syndrome (use with caution if patient is taking other serotonergic medications), tramadol should not be used concurrently with SSRI's or SNRI's due to the risk of serotonin syndrome and/or seizure precipitation[32].

NB: *Concurrent use with other opioids (fentanyl and methadone) can also precipitate serotonin syndrome and caution is recommended in patients with seizure disorders (tramadol can lower seizure threshold).*

Dosing:

- 50-100mg PO QID PRN tablet or liquid preparation
  (**NB:** *liquid preparation not funded)*
- IR preparation available in 50mg dose
- SR preparation (BD dosing) available in 100mg, 150mg and 200mg doses
- 25-50mg IV QID PRN

NON-OPIOID ANALGESICS/ADJUVANT ANALGESICS

Non-opioid analgesics are important in the management of complex pain, particularly in those patients with a prolonged prognosis (long months to years) due to the importance of minimising risks associated with long-term opioid use[19]. The following will discuss the use of corticosteroids, NSAID's, antiepileptics, antidepressants, bisphosphates, NMDA inhibitors (ketamine), sodium channel blockers (lidocaine and mexiletine), a-agonists (clonidine, dexmedetomidine). Due to the nature of complex pain, use of multiple adjuvant analgesics simultaneously may be needed to optimise pain control, this is a careful balance between analgesic benefit and side effect burden that must be closely monitored by the treating physician and carefully aligned with the patients' goals of care.

Corticosteroids

Dexamethasone is the most commonly used steroid in palliative care. Steroids are particularly useful for pain related to:

- Raised intracranial pressure
- Spinal cord compression
  Tumour compression or invasion of the brachial or lumbosacral plexus, nerve roots or individual peripheral nerves
- Capsular stretching by liver metastases.
- Soft tissue infiltration, e.g., head and neck, intra-abdominal; superior vena cava obstruction and lymphoedema.

It is advisable to use a high dose initially in order to gain symptomatic benefit as soon as possible, e.g., dexamethasone 8mg mane (PO or SC). This can be given as a 3-5-day trial and then stopped if not effective. If continued longer than 2 weeks dose must be tapered, not stopped immediately. If effective, the dose should be reduced as low as possible to minimise side effects of long-term use.

Patients should **NEVER** be prescribed steroids for pain without an endpoint or weaning plan.

Corticosteroids have multiple short and long-term side effects, a few to be aware of include:

- Risk of hyperglycaemia (particularly in patients with diabetes); consider checking afternoon blood glucose level during steroid treatment; oral hypoglycaemics and/or insulin regime may need to be adjusted.
- Insomnia - avoid administering after midday
- Hypomania/mania, psychosis or depression with high dose steroids (usually evident within first few doses).
- Immunosuppression – use with caution in patients on other immunosuppressive treatment and those on cancer immunotherapy (for patients taking immunotherapy or about to commence, discussion should be had with the patient's oncologist prior to initiating corticosteroids[13].

NB: *Dexamethasone can be used at low dose (0.5-1mg) via CSCI for site protection.*

NSAIDs
These should be used with caution and for a short duration due to side effect profile, specifically nephrotoxicity and gastritis. NSAIDs should generally be prescribed with gastric protection (proton pump inhibitor)[13]. It is recommended that non-selective NSAIDs should be used with caution in patients with gastric disorders, ischaemic heart disease, heart failure, renal impairment, or platelet disorders. Naproxen appears to have the safest cardiovascular risk profile and should be first in preference to other non-selective NSAIDs in patients with a history of ischaemic heart disease if no alterative analgesia is effective[33]. As with any medication, risk and benefit must be considered as it relates to the individual patient, for example it may be entirely appropriate to prescribe a NSAID to a patient with complex pain and a history of ischaemic heart disease, if the analgesic benefit they receive outweighs the potential cardiac risk[34,35]. Equally if a patient has end-stage renal failure and is on renal replacement therapy, the risk of nephrotoxicity is largely academic in this context and NSAIDs may be an appropriate analgesic alterative or adjunct to opioids.

Selective COX-2 inhibitors e.g., celecoxib, do not affect platelet function and can be used in patients with thrombocytopenia or platelet function disorders without increasing bleeding risk[36].

Concurrent use of NSAIDs with corticosteroids should generally be avoided due to gastro-intestinal bleeding risk, however in some situations whereby analgesic benefit outweighs bleeding risk, it may be appropriate to use concurrently.

Parecoxib (Dynastat):
This is a parenteral COX-2 inhibitor which can be safely administered subcutaneously or intravenously[37-39]. Maximum dose of 80mg per 24 hours, 20-40mg bolus doses BD SC or IV. This is not funded in the community (there are no funded SC/IV preparations of NSAIDs in New Zealand).

Approximate cost of parecoxib (40mg vial), 10 pack is $150.00

Antidepressants
The evidence available for the role and efficacy of antidepressants in cancer pain management is very limited. Most data is extrapolated from non-cancer neuropathic pain studies. However, antidepressants are used not infrequently in the management of complex cancer pain and anecdotally are effective.

Analgesic effect of antidepressants is independent of antidepressant effect and dose required to improve pain control is often less than needed for antidepressant effect[13].

There is evidence for use of tricyclic antidepressants (nortriptyline and amitriptyline) in neuropathic pain (NNT = 3), however the side effect profile (particularly anti-cholinergic effects) may limit the use of TCAs in patients[40]. Start with nortriptyline 10mg nocte for 5-7 days and increase to 25mg nocte if tolerated, dose can be titrated to 75mg nocte, however side effect burden may prohibit this (e.g., dry mouth, constipation, drowsiness)[41]. TCAs are often sedating, hence, nocte administration, this sedating effect can be advantageous if the patient is also struggling with sleep.

There is some evidence for selective-noradrenalin reuptake inhibitors (SNRI's), in particular duloxetine and venlafaxine for neuropathic pain, however duloxetine is not available in New Zealand. Venlafaxine should be started at low dose 37.5mg mane and increased to 75-225mg daily[7,13,40].

Mirtazapine may be a helpful adjuvant for complex pain, particularly in the setting of anxiety. Start at 15mg nocte and titrate to a maximum of 45mg nocte[41].

NB: *lower doses can be associated with sedation; this resolves as dose is titrated[42].*

NB: *Antidepressant discontinuation syndrome is well documented as occurring with abrupt cessation of antidepressants. Symptoms are unpleasant and can be very distressing for patients[40]. This may occur if a patient loses their oral route and needs to be switched to SC route. Mirtazapine has a low risk of causing discontinuation symptoms if stopped abruptly[43]. Benzodiazepines can be helpful to reduce the severity of withdrawal syndrome symptoms. The addition of midazolam 10mg per 24 hours to a CSCI may be helpful[43].*

See appendix for information on rotating between antidepressants.

Anticonvulsants (Gabapentinoids – Gabapentin and Pregabalin)
Gabapentinoids are commonly used for the management of neuropathic pain and have become a useful adjuvant in the management of complex pain in palliative care[44]. Both gabapentin and pregabalin have their advantages and disadvantages, however overall pregabalin appears to be better tolerated than gabapentin[44]. There does not seem to be a significant difference in analgesic efficacy[45]. Due to dosing schedule, pregabalin allows for a reduced tablet burden which is an important consideration. Gabapentin can be made into a suspension (compounding pharmacy) which may be advantageous for some patients.

Gabapentin should be started at low dose (100mg TDS) and increased slowly (every 3 days) to avoid side effects[45].

Pregabalin is approximately 4 times more potent than gabapentin, however equipotency is complicated by differences in bioavailability kinetics (gabapentin having nonlinear bioavailability, pregabalin having fixed bioavailability)[46,47]. The recommended starting dose is 75mg BD (however, some patients may require lower starting doses e.g., 25-50mg BD) and increase, if necessary, after 3-7 days to 150mg BD.

Further dose increases can be made at 7-day intervals. Maximum recommended dose is 300mg BD[45,15].

Caution with gabapentinoids in renal failure – dose reduction is required (see tables below).

Gabapentin dosing according to eGRF[48]:

Creatinine Clearance (mL/min)	Target Total Daily Dosing Regime
>80	300 - 1200mg TDS
50-79	300mg BD - 600mg TDS
30-49	300mg daily -TDS
15-29	100mg daily to 300mg BD
<15	100mg daily - BD

NB: *In patients with severe renal failure alternate day dosing of gabapentin may be appropriate.*

Pregabalin dosing according to eGFR[49]:

Creatinine Clearance (mL/min)	Starting dose	Maximum Total Daily Dose (mg/day)
>60	150	600
30-60	75	300
15-30	25-50	150
<15	25	75

When rotating between gabapentinoids, there are 3 methods described[46,47,50].

Stop/start	Two options; • Take the last dose of gabapentin nocte and start pregabalin the next morning. • Make the afternoon the last dose and give the first dose of pregabalin nocte (this may be preferable for some patients, any sedation or other side effects they may experience with the first dose of pregabalin will be overnight rather than during the day – this may improve compliance).
Cross taper	50% of gabapentin dose and 50% of pregabalin dose given over four days, day five give 100% pregabalin dose.
Down taper and stop gabapentin then up titrate pregabalin	This method is recommended by manufacturers but is time consuming and runs the significant risk of loss of analgesic control.

In practice the direct stop/start method works well without significant issues and less complexity than the other two options. However, an individualised approach to the patient is always advised. Conversion between gabapentin and pregabalin is described in the table below:

Gabapentin dose	Pregabalin dose
100mg tds	50mg bd
200mg tds	75mg bd
300mg tds	100mg bd
400mg tds	125mg bd
500mg tds	150mg bd
600mg tds	150mg m and 175mg n
700mg tds	175mg bd OR 175mg m and 200mg n
800mg tds	200mg bd
900mg tds	200mg m and 225mg n
1,000mg tds	225mg bd
1,100mg tds	225mg m and 250mg n
1,200mg tds	250mg bd
1,600mg tds	300mg bd

Figure 3: Proposed conversion doses gabapentin to pregabalin[46].

Bisphosphonates
These are bone modifying agents which inhibit osteoclast-mediated bone resorption. There is evidence for their use in prevention of skeletal related events associated with bony metastatic disease however there is limited evidence for their analgesic benefit in the management of bone pain. Bisphosphonates should not be first-line therapy for bone pain, but may be a useful addition[51, 52].

NB: *risk of hypocalcaemia (calcium should be checked pre and post infusion), unless being used for treatment of hypercalcaemia; oral calcium and vitamin D supplements are recommended[53,54].*

Osteonecrosis of the jaw is associated with bisphosphonates, patients should undergo dental examination prior to starting regular bisphosphonate infusions[55].

Dosing:

- Pamidronate 90mg in 250 – 500 mL sodium chloride 0.9% IV
- Can be given subcutaneously if IV route unavailable; 90mg pamidronate in 1L sodium chloride 0.9% over 12 – 24 hours[15].
- Zoledronate (Zoledronic acid Mylan, funded) 4mg in 100mL sodium chloride 0.9% IV over 15 minutes[55].

Adjustment for renal function is advised[55]:

Creatinine clearance (mL/min)	Zoledronate dose (mg)
>60	4
50 – 60	3.5
40 – 49	3.3
30 – 39	3

Ketamine
Ketamine is a non-competitive inhibitor of the NMDA receptor with some opioid receptor activity and psychomimetic properties. It is commonly used in the non-malignant, post-operative pain setting at sub-anaesthetic doses for the management of pain as an adjunct to opioids (allowing opioid-sparing). Anecdotally it is effective in the management of complex neuropathic cancer pain and opioid-induced hyperalgesia, however several randomised control trials have failed to reproduce this efficacy. It can also allow the reduction of opioids and may be useful as an analgesic bridge while methadone steady state is being established.

Recently a prospective single arm study showed the positive effect of ketamine on pain management when used in a stepwise titration protocol (similar the commonly used “burst” ketamine regime). This study demonstrated improved pain scores, overall reduction in morphine equivalent daily dose following administration of a 5-day ketamine infusion with step-wise titration[56]. The infusion was well tolerated with minimal side effects (haloperidol being used to reduce psychomimetic effects).

Patient selection is important and may be part of the reason for previous negative trial results. Ketamine should be considered in the following clinical scenarios[56-58]:

- Neuropathic pain poorly responsive to increasing opioid doses and oral adjuvant analgesics
- Pain due to ischaemia (e.g., critical limb ischaemia, ischaemic bowel)
- Complex abdominal or visceral pain with neuropathic component
- "Bridging" e.g., during methadone rotation while titrating and allowing methadone to reach steady state (inpatient only)
- Presence of allodynia or hyperalgesia
- Opioid-induced hyperalgesia
- Features of central sensitisation

Ketamine can be used as a continuous subcutaneous infusion either via gradual titration or over a 3-5 day "burst" regime. Ketamine can be given as a SC bolus PRN for pain management, this may be useful as a trial for efficacy prior to commencing infusion or as part of procedural analgesia (e.g., painful change of) dressing, doses of 10-50mg SC Q2H can be used, depending on ketamine tolerance, use of background infusion and indication[15].

Ketamine can also be used orally.

PROTOCOL
Ketamine

See **Ketamine Protocol** for further information.

Lidocaine (formally known as lignocaine)
Lidocaine is a sodium channel blocker typically used for local anaesthesia. The mechanism by which lidocaine relieves pain is not fully understood but presumably components of the nervous system involved in chronic pain maintenance are sensitive to the partial blockade of sodium channels caused by systemic lidocaine[59,60]. It also influences the priming of polymorphic neutrophils and as such reduces the inflammatory stress response[61]. Using subcutaneous lidocaine to provide analgesia over a few days is intended to 'reset' the pain system, allowing analgesia to persist for an extended period after the infusion ceases (weeks to months). Use can also dramatically reduce opioid requirements, allowing for the reduction in background opioids during the course of the infusion[62]. The infusion can be run for an extended period of time, or conversion to oral mexiletine can also be considered (see below).

Concerns regarding the cardiovascular effects of lidocaine in this context are largely unfounded due to the dosing schedule and monitoring described. Several studies have demonstrated the safe use of systemic lidocaine infusions in palliative care populations[59,60,63-65]. Central nervous system toxicity (confusion, tinnitus, metallic taste etc.) generally occurs well before cardiovascular toxicity, lidocaine has a high cardiovascular collapse to CNS toxicity ratio. Mild CNS toxicity may be apparent at plasma levels of 6mcg/mL whereas plasma levels generally need to be >10mcg/mL before progression to significant cardiovascular compromise occurs[66]. Lidocaine (and its active metabolite MEGX) has a short plasma half-life allowing for rapid titration and equally rapid resolution of any adverse effects on dose reduction or cessation of the infusion.

Patient selection is important, lidocaine should be considered in the following scenarios:

- Opioid refractory pain or intolerable opioid side effects
- Previous response to lidocaine (lasting longer than 2 weeks)
- Insufficient response to other analgesics (including adjuvants)
- Neuropathic pain, including hyperalgesia and allodynia
- Opioid-induced hyperalgesia
- History of chronic pain or previous opioid misuse
- Features of central sensitisation

PROTOCOL
Lidocaine infusion protocol

See **Lidocaine Infusion Protocol**.

NB: *Indications for the use of both ketamine and lidocaine infusions are very similar. Both drugs have benefits in complex pain and use of each should not be seen as an either/or option, it is possible to use both either in separate episodes of care, or simultaneously if the combination of both provides the best analgesia for the patient. There is randomised control data supporting the use of lidocaine in complex pain, whereas this has yet to be produced for ketamine. The side-effect profile of lidocaine is also, generally, more favourable than ketamine.*

Mexiletine
Mexiletine is an oral sodium channel blocker (class 1b anti-arrhythmic) with a bioavailability of 80-90%[15]. Evidence for use in cancer pain is limited. Consider using it in patients who have had a positive response to lidocaine therapy. There is no data published on the conversion of lidocaine to mexiletine in pain and palliative care cohorts[67]. Mexiletine is contra-indicated in patients on flecainide or who have 2nd or 3rd degree AV block (unless pacemaker in-situ). Caution in patients with cardiac conduction abnormalities and seizure disorders. Side effects include nausea, vomiting, dizziness, tremor, and ataxia. It does not prolong the corrected QT interval.

Recommended dosing

- Start with 150mg BD and titrate to effect up to 250mg TDS, dosing >900mg/day are associated with side effects and no increase in analgesic efficacy[67].
- Dose reduction should be considered if patients are prescribed medications that are CYP3A4, CYP2D6, CYP1A2 inhibitors or in patients with hepatic dysfunction (mexiletine undergoes biliary excretion)
- When used in a chronic (non-malignant pain setting), monitoring of plasma levels and serial ECGs are recommended.

Proposed protocol for cross-titration (lidocaine dose reduction every 24 hours)[67]:
If considering cross-titration from lidocaine infusion to mexiletine, the short half-life of lidocaine needs to be taken into consideration, allowing mexiletine to reach steady state (half-life of mexiletine is 9-12 hours, with steady state in 3.3-5 half-lives).

Day 1 (0 hours)	start mexiletine at 150mg PO Q8H and reduce lidocaine by 50% of its mg/kg/hr dose
Day 2 (24 hours)	Discontinue lidocaine infusion, continue mexiletine at 150mg PO Q8H
Day 3 (48 hours)	mexiletine will have reached steady stage, can consider increasing to 200mg PO Q8H if pain is not controlled, and no side effects are present.

ALPHA-2 AGONISTS

Dexmedetomidine
Dexmedetomidine is a selective alpha-2 adrenoceptor agonist with sedative, anxiolytic and analgesic properties[68,69]. It is commonly used in anaesthesia and ICU settings for sedation and increasingly in pain medicine as an analgesic adjuvant.
Dexmedetomidine's use in palliative medicine is increasing internationally and it appears to be a promising drug in the context of delirium and complex pain[14,70-75].
Dexmedetomidine is not funded and is a hospital-only medication.

NB: *Withdrawal syndrome can occur if stopped abruptly (taper over 2-4 days), this includes rebound hypertension, agitation/restlessness/anxiety, headache.*

Dexmedetomidine should be considered in the following scenarios:

- Opioid refractory pain or intolerable opioid side effects
- Pain refractory to analgesic adjuvants (ketamine, lidocaine, methadone), or adjuvant use has resulted in intolerable side effects, or adjuvants are contra-indicated.
- Bridge to therapy while considering other analgesic options
- Option for rousable sedation in clinical scenarios where traditional palliative sedation methods are not appropriate.

Clonidine

Clonidine is an alpha-2 agonist with analgesic activity. It is generally ineffective as an analgesic in isolation but as an adjuvant can improve analgesia and be opioid-sparing. Proposed pain modulation is thought to be through change in autonomic function and reduction in anxiety levels. It has been used in both cancer pain and post-operative pain[76]. Clonidine acts on dorsal horn alpha-2 receptors and improves descending pain inhibition as well as reducing anxiety levels and increasing parasympathetic activity, both of which have been shown to reduce pain perception[77,78].

Clonidine can be administered orally, transdermally, subcutaneously, intravenously and neuraxially (IV and neuraxial administration are beyond the scope of this document).

NB: *clonidine can be useful in the context of co-existing anxiety (as an alternative to benzodiazepines or in the benzodiazepine tolerant patient) or in the context of opioid withdrawal[79].*

Dosing;

- Oral 25-75mcg TDS
- Transdermal preparations; 100, 200, 300mcg/hr (weekly)
- CSCI 150mcg over 24 hours, typically effective dose 300-600mcg over 24 hours
- Subcutaneous bolus 75-150mcg Q8H/PRN
- PO:SC dose ratio 1:1

NB: *withdrawal syndrome can occur if stopped abruptly (taper over 2-4 days), this includes rebound hypertension, agitation/restlessness/anxiety, headache.*

AUDIT INDICATORS

- Accurate identification of pain
  - Clear and detailed pain history
  - Ensure the nature of the pain is understood and documented.
- Evidence of documentation of additional information in patients with complex pain
  - Previous pain syndromes (e.g., migraine, low back pain, irritable bowel syndrome)
  - Previous treatments and efficacy
  - Emotional and spiritual factors, previous mental illness (total pain)
  - Past history of alcohol or recreational drug use
  - History of trauma - childhood, domestic (as appropriate)
- Evidence of documentation of a clear plan for pain management
- Evidence of multimodal analgesia use
- Documentation of response to analgesia
- Documentation of side effects

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APPENDIX

Rotation between antidepressants

Antidepressant Switching Table

Changing from \ Changing to	short-acting SSRI [a]	fluoxetine	TCAs [b]	venlafaxine	mirtazapine (or mianserin)	bupropion	moclobemide	irreversible nonselective MAOIs [c]
short-acting SSRIs [a]	Stop 1st SSRI [d] then start 2nd SSRI the following day	Stop 1st SSRI [d] then start fluoxetine	Cross taper cautiously with very low dose TCA [f] [g]	Stop SSRI [d] then start venlafaxine the next day at 37.5mg/day and increase very slowly	Withdraw before starting mirtazapine cautiously	Withdraw then start bupropion	Withdraw, wait 1 week, start moclobemide	Withdraw and wait 1 week
fluoxetine [h]	Stop fluoxetine, wait 4-7 days, start SSRI at low dose [e]	—	Stop fluoxetine, wait 4-7 days, start TCA at very low dose and increase very slowly [f][g]	Stop fluoxetine, wait 4-7 days, start venlafaxine at 37.5mg/day and increase very slowly	Stop fluoxetine, wait 4-7 days, start mirtazapine cautiously	Stop fluoxetine, wait 4-7 days, start bupropion	Stop fluoxetine, wait 5 weeks, start moclobemide	Stop fluoxetine and wait 5 weeks [h]
TCAs [b]	Halve dose, add SSRI, then slowly withdraw TCA [g]	Halve dose, add fluoxetine, then slowly withdraw TCA [g]	Cross taper cautiously	Cross taper cautiously starting with venlafaxine 37.5mg/day [g]	Withdraw, start mirtazapine cautiously	Cross taper cautiously	Withdraw, wait 7 days, start moclobemide	Withdraw and wait 7 days
venlafaxine	Cross taper cautiously starting with low dose SSRI [e]	Cross taper cautiously starting with fluoxetine 20mg on alternate days	Cross taper cautiously with very low dose TCA [g]	—	Withdraw, start mirtazapine cautiously	Withdraw, start bupropion cautiously	Withdraw, wait 7 days, start moclobemide	Withdraw and wait 7 days
mirtazapine/ mianserin	Withdraw then start SSRI	Withdraw then start fluoxetine	Withdraw then start TCA	Withdraw then start venlafaxine	—	Withdraw, start bupropion cautiously	Withdraw, wait 7 days, start moclobemide	Withdraw and wait 7 days
bupropion	Withdraw then start SSRI	Withdraw then start fluoxetine	Withdraw then start TCA at a low dose.	Withdraw, start venlafaxine at 37.5mg and increase slowly	Withdrawn, start mirtazapine cautiously	—	Withdraw, wait 7 days, start moclobemide	Withdraw and wait 7 days
moclobemide	Withdraw, wait 24 hours, start SSRI	Withdraw, wait 24 hours, start fluoxetine	Withdraw, wait 24 hours, start TCA	Withdraw, wait 24 hours, start venlafaxine	Withdraw, wait 24 hours, start mirtazapine	Withdraw, wait 24 hours, start bupropion	—	Withdraw and wait 24 hours
irreversible nonselective MAOIs	Withdraw and wait 2 weeks	Withdraw and wait 2 weeks	Withdraw and wait 2 weeks	Withdraw and wait 2 weeks	Withdraw and wait 2 weeks	Withdraw and wait 2 weeks	Withdraw and wait 2 weeks	Withdraw and wait 2 weeks

[a] Short-acting SSRIs are citalopram, escitalopram, paroxetine, and sertraline.
[b] TCAs are amitriptyline, clomipramine (refer to note g), dothiepin, doxepin, imipramine, nortriptyline, trimipramine.
[c] Irreversible nonselective MAOIs (phenelzine or tranylcypromine) should be commenced with caution after all other antidepressants because of the risk of hypertensive crisis and serotonin toxicity. Allowance should be made for the washout period (5 half-lives) and individual patient differences in pharmacokinetics.
[d] Abrupt withdrawal is usually possible, however if patients are likely to experience problems with discontinuation symptoms then a slower withdrawal may be required.
[e] Low Dose= citalopram 10mg/day; escitalopram 5mg/day; paroxetine 10mg/day; sertraline 25mg/day; fluoxetine 20mg on alternate days
[f] If changing from paroxetine or fluoxetine, TCA concentration may be elevated for at least several weeks due to persisting SSRI-induced cytochrome P450 inhibition.
[g] Do not co-administer clomipramine with SSRIs or venlafaxine.
[h] Care is required when changing from fluoxetine to another antidepressant as it has a longer half-life than other SSRIs, leading to significant concentrations of fluoxetine or its active metabolite being present for about five weeks after cessation.

https://bpac.org.nz/bpj/2012/december/docs/bpj_49_nzf_pages_34-35.pdf

Patient selection for methadone therapy

Potentially Appropriate Candidates for Methadone in HPC	Potentially Inappropriate Candidates for Methadone in HPC
• Moderate to severe pain (especially as a second-line opioid choice) • Pain refractory to other opioids • True phenanthrene (e.g., morphine) allergy • Significant renal impairment Need for a long-acting opioid (particularly as an oral concentrate solution) • High opioid tolerance • Poorly controlled opioid-induced adverse effects with other opioids • History of dysphagia, inability to swallow, or feeding tube placement	• Patient lives alone, or poor cognitive functioning, without aresponsible caregiver • Lack of knowledgeable practitioner on transfer • History of opioid/medication nonadherence • History of substance misuse or SUD (patient or family) Multiple risk factors for methadone toxicity (e.g., clinical instability, multiple transitions in care, history of transplant) • History of QTc prolongation or at high risk for such Prognosis less than projected time to methadone steady state (i.e., five to seven days) • Obstructive or central sleep apnea Determined to be medically inappropriate after risk assessment (see next section)

HPC = hospice and palliative care.

Figure 1: Macpherson et al.[23]

ECG monitoring requirement and action needed in methadone therapy.

Level of Vigilance	Goals of Care	Methadone Role	Baseline ECG	Follow Up ECG
High	Curative, life-prolonging	First line	Obtain baseline ECG: • Positive risk factors" • Prior QTc >450 ms • History suggestive of prior ventricular arrhythmia Consider baseline ECG: • No risk factors • QTc <450 ms in the previous year Recommendation: • QTc >500 ms-do not use methadone QTc 450-499 ms – consider alternate opioid (or correct reversible causes of QTc prolongation and reassess)	Obtain ECG within two to four weeks: • Positive risk factors • Prior ECG with QTc > 450 ms • History of syncope Obtain additional ECG: • TDD methadone reaches 30-40 mg • TDD methadone reaches 100 mg • New risk factors or signs/ symptoms suggesting arrhythmia Recommendation: • QTc > 500 ms – switch to alternative opioid or reduce methadone dose • QTc 450-499 ms – consider switching to alternative opioid or reduce methadone dose
Moderate	Curative, life-prolonging	Second line	• Discuss risks and benefits with patient/family in light of goals of care	• Reinitiate discussion of risks/benefits if goals of care change
	Comfort measures	First line	• Routine baseline ECG monitoring not recommended; may consider ECG depending on patient's risk status, wishes, and goals of care (e.g., curative) • Document informed consent if no ECG • If ECG obtained, follow recommendations above	• Routine follow-up ECG monitoring not recommended; may consider ECG depending on patient's risk status, wishes, and goals of care • Document informed consent if no ECG • If ECG obtained, follow recommendations above
Low	Comfort measures only	Second line	• No ECG unless compelling indication • If ECG obtained, follow recommendations above	• No ECG unless compelling indication • If ECG obtained, follow recommendations above

"Clinical risk assessment is always indicated and may alter recommendation for ECG monitoring. Risk factors include hypokalemia, hypomagnesemia, impaired liver function, structural heart disease (congenital heart defects, history of endocarditis, or heart failure), and genetic predisposition including patient or family history of congenital OT syndrome, use of OTc-prolonging medications.

Figure 1: Macpherson et al.[23]

Methadone – CYP450 interactions

Supplemental Table 1

Medications With Potential to Impact Methadone Levels[a]

Drug	Net Effect on Methadone Level	Effect on Major Metabolic Enzymes			Effect on Minor Metabolic Enzymes			Effect on QTc interval[b]/TdP[c] Reported With Concomitant Methadone Use
		CYP2B6	CYP2C19	CYP3A4	CYP2D6	CYP2C9	CYP2C8	
Anti-infectives								
Amprenavir	↑			↓↓↓				
Atazanavir	–[d]			↓↓↓				Possible[c]
Azithromycin								Risk[c]
Boceprevir	↑			↓↓↓				
Ciprofloxacin	↑			↓				Risk[c]
Clarithromycin	↑			↓↓↓				Risk[c]
Cobicistat	–[e]			↓↓↓	↓			
Delavirdine	↑			↓	↓↓↓			
Efavirenz	↓			↑↑				
Erythromycin	↑			↓↓				Risk[c]
Fluconazole	↑		↓↓↓	↓↓		↓↓		Risk
Nevirapine	↓	↑↑↑						
Efavirenz	↓	↑	↓↓	↑↑		↓↓	↓↓	
Isavuconazonium sulfate	↑		↓	↓↓	↓			
Isoniazid	↑		↓↓	↓	↓↓	↓		
Itraconazole	↑			↓↓↓				Conditional[c]
Ketoconazole	↑	↓	↓↓	↓↓↓	↓↓	↓↓	↓	Conditional
Levofloxacin								Risk[c]
Posaconazole	↑			↓↓↓				Conditional
Ritonavir	↓	↑↑↑	↓↑	↓↓↓	↓↓	↓↑	↓↓	Conditional[c]
Rifampin	↓	↑↑↑	↑↑↑	↑↑↑		↑↑↑	↑↑↑	
Saquinavir	↓[e]	↓		↓↓↓	↓	↓		Possible
Terbinafine	↑				↓↓↓			
Tipranavir	↓[e]				↓↓↓			
Voriconazole	↑	↓↓	↓↓	↓↓↓		↓↓		Conditional[b]
Central nervous system								
Alprazolam	↑			↓				
Amitriptyline								Conditional
Aripiprazole								Possible
Asenapine	↑				↓			Possible
Buprenorphine	↑		↓↓		↓↓			
Bupropion	↑				↓↓↓			
Carbamazepine	↓	↑↑↑	↑↑↑	↑↑↑		↑↑↑	↑↑↑	
Chlorpromazine	↑				↓↓			Risk
Citalopram	↑	↓	↓		↓			Risk
Clomipramine	↑				↓↓			Possible
Clozapine								Possible
Cocaine	↑				↓↓↓			Risk[c]
Desipramine	↑	↓↓			↓↓			Possible
Dexmedetomidine								Possible
Diazepam	↑		↓					
Doxepin								Possible[c]
Droperidol								Risk[c]
Duloxetine	↑				↓↓			
Escitalopram	↑				↓			Risk
Fluoxetine	↑	↓	↓↓		↓↓↓	↓		Conditional[c]
Fluvoxamine	↑	↓	↓↓↓	↓	↓	↓		Conditional[c]
Haloperidol	↑				↓↓			Risk
Imipramine								Possible
Midazolam	↑					↓	↓	
Mirtazapine								Possible
Modafinil	↓	↑	↓↓	↑↑		↓		
Nefazodone	↑	↓		↓↓↓	↓		↓	
Nortriptyline								Possible
Olanzapine								Possible
Paroxetine	↑	↓↓	↓		↓↓↓	↓		Conditional[c]
Phenytoin	↓	↑↑↑	↑↑↑	↑↑↑		↑↑↑	↑↑↑	
Phenobarbital	↓	↑↑↑		↑↑↑		↑↑↑	↑↑↑	
Primidone	↓	↑↑↑		↑↑↑		↑↑↑		
Quetiapine								Conditional[c]
Risperidone								Possible

(*Continued*)

Supplemental Table 1
Continued

Drug	Net Effect on Methadone Level	Effect on Major Metabolic Enzymes			Effect on Minor Metabolic Enzymes			Effect on QTc interval[b]/TdP[c] Reported With Concomitant Methadone Use
		CYP2B6	CYP2C19	CYP3A4	CYP2D6	CYP2C9	CYP2C8	
Sertraline	↑	↓↓	↓↓	↓	↓↓	↓	↓	Conditional[c]
Thioridazine								Risk
Tizanidine								Possible
Trazodone								Conditional
Venlafaxine								Possible
Ziprasidone								Conditional[c]
Cardiovascular								
Amiodarone	↑		↓	↓	↓↓	↓↓		Risk[c]
Clopidogrel	↑	↓↓				↓	↓↓↓	
Diltiazem	↑			↓↓	↓	↓		
Furosemide								Conditional[c]
Hydrochlorothiazide								Conditional
Indapamide								Conditional
Nicardipine	↑		↓↓	↓	↓↓	↓↓↓		Possible
Nifedipine	↑			↓	↓	↓		
Ticlopidine	↑	↓↓	↓↓↓		↓↓	↓		
Torsemide								Conditional
Verapamil	↑			↓↓	↓	↓		
Chemotherapeutics								
Abiraterone	↑		↓↓		↓↓	↓↓	↓	
Anastrozole	↑					↓	↓	
Doxorubicin	↑	↓↓			↓			
Imatinib	↑			↓↓	↓	↓		
Endocrine								
Estradiol	↓	↑					↑	
Gastrointestinal								
Cimetidine	↑		↓↓	↓	↓↓	↓		
Esomeprazole	↑		↓↓					
Lansoprazole	↑		↓		↓	↓		
Omeprazole	↑		↓↓		↓	↓↓		
Pantoprazole	↑		↓					Conditional
Ranitidine	↑				↓			
Famotidine								Conditional
Anti-emetics								
Aprepitant	↑		↓	↓↓		↑↑↑		
Dolasetron								Possible
Granisetron								Possible
Metoclopramide								Conditional
Ondansetron								Risk[c]
Other								
Celecoxib	↑				↓↓		↓↓	
Chlorpheniramine	↑				↓			
Cinacalcet	↑				↓↓↓			
Clemastine	↑				↓			
Cyclosporine	↑			↓		↓		
Darifenacin	↑				↓↓			
Dexamethasone	=/↓	↑		↑		↑	↑	
Diphenhydramine	↑				↓↓			Conditional
Grapefruit juice	↑			↓↓↓				
Hydroxyzine	↑				↓			Conditional
St. John's Wort (hypericum perforatum)	↓		↑↑	↑↑↑				

[a]The table describes the major CYP450 enzyme interactions and identifies those with QTc risk. ↑, inducer; relative strength weak, ↑, moderate, ↑↑, or strong ↑↑↑. ↓, inhibitor; relative strength weak, ↓, moderate, ↓↓, strong, ↓↓↓. A weak inhibitor causes a >1.25-fold but <2-fold increase in the plasma AUC values or 20%–50% decrease in clearance. A moderate inhibitor causes a > 2-fold increase in plasma AUC values or 50% to 80% decrease in clearance. A strong inhibitor causes a > 5-fold increase in plasma AUC values or more than 80% decrease in clearance. (FDA) Classification of inducers is not as clearly defined owing to a history of methodological variability in the pharmaceutical industry.[86–88] Therefore, literature was reviewed for each medication, and the consensus qualifier was used to define weak, moderate, or strong effect using relative induction score, if available.[89] QTc risk definitions: Risk, substantial evidence supports the conclusion that these drugs prolong the QTc interval and are clearly associated with a risk of TdP, even when taken as directed in official labeling; possible, substantial evidence supports the conclusion that these drugs can cause QTc interval prolongation but there is insufficient evidence that these drugs, when used as directed in official labeling, are associated with a risk of causing TdP; conditional, substantial evidence supports the conclusion that these drugs are associated with a risk of TdP but only under certain conditions (e.g., excessive dose, hypokalemia, or congenital long QTc interval or by causing a drug-drug interaction that results in excessive QTc interval prolongation).[90]
[b]Definitions from CredibleMeds.org.[90]
[c]Evidence reports TdP with concomitant methadone use.
[d]No effect on methadone levels.[91]
[e]Boosted with ritonavir: net effect is lower levels.

Figure 1: Macpherson et al.[23]

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OVERVIEW

Cough is a common and frustrating symptom for many patients which is often undertreated and challenging to manage[1]. Cough is a frequently experienced symptom in patients with advanced lung cancer and end stage chronic lung conditions. Untreated cough can contribute to suffering and poor quality of life[2-4].

PURPOSE

To provide guidance in the management of cough.

SCOPE

Palliative care specialists/palliative medicine physicians, nurse practitioners, hospice medical officers, palliative medicine advanced trainees.

PATIENT GROUP

Patients with a life-threatening or life-limiting illness.

ABBREVIATIONS

BD	twice daily
CSCI	continuous subcutaneous infusion
GOC	goals of care
LRT	lower respiratory tract
MND	motor neuron disease
NAC	N-acetyl-cysteine
NaCl	sodium chloride
OME	oral morphine equivalent
PO	per oral
SC	subcutaneous

DEFINITIONS

Cough is normally a protective physiological process to prevent the movement of mucus and/or foreign material from the upper airways into the lower respiratory tract[5].

Chronic cough is defined as being present for 8 weeks or more[5,6].

Prolonged episodes of coughing can result in dyspnoea, vomiting, pain or haemoptysis. Untreated cough impacts quality of life through disrupted sleep, impact on socialisation, physical exhaustion and potential for urinary incontinence.

CLINICAL MANAGEMENT

Potential causes of cough in cancer and non-cancer conditions
There are many potential causes of cough in patients with life-limiting conditions, the cause is often multifactorial. Initial treatment of cough involves careful assessment for reversible causes and an attempt at treatment of these (if appropriate within patients GOC).

CAUSE	POTENTIAL MANAGEMENT OPTIONS
Infection	Antimicrobials (if appropriate)
Gastro-oesophageal reflux	Proton-pump inhibitor, H2 antagonist, prokinetics
Airways disease	Corticosteroids, optimatisation of inhaler therapy
Pulmonary oedema	Diuretics
Tumour obstruction	Corticosteroids, systemic anti-cancer therapy, radiation therapy, stenting, surgery
Bronchorrhea	Anti-secretory agents, octreotide, *see management of bron-chorrhea in* **Management of Oropharyngeal and Respiratory Secretions in Palliative Care** **GUIDELINE** Management of Oropharyngeal and Respiratory Secretions in Palliative Care
Parenchymal lung disease	Systemic anti-cancer therapy, radiation therapy
Pleural disease, effusion	Drainage of effusion, corticosteroids
Post radiation or chemotherapy associated cough	Corticosteroids
Lymphangitis	Corticosteroids

Management of cough
There is limited evidence for the management of chronic cough in the palliative care setting.

Non-pharmacological options[2,7,8]:

- Avoidance of potential triggers (e.g. cold air, smoke etc)
- Positioning
- Assessment by speech language therapy
- Fan therapy
- Appropriate oral care
- Over the counter “cough drops”/hard boiled sweets etc. (there is no evidence to support this, however a therapeutic trial is unlikely to cause any harm provided there is not a significant financial burden associated with their use).

Pharmacological options:

CLASS	DRUG	DOSING	COMMENTS
Mucolytics *Consider in cough secondary to tenacious secretions*	Nebulised sodium chloride 0.9%	**NaCl 0.9%** 3-5mL via nebuliser 3-4 times per day	Aim to reduce sputum viscosity and ease clearance. Minimal evidence on the use of mucolytics
	Nebulised acetylcysteine	**Acetylcysteine** 2000mg/10mL ampules (20%) ***Standard dose:*** 3-5mL via nebuliser 3-4 times daily (use air not oxygen) ***If concerns with bronchospasm:*** Dilute 1mL acetylcysteine 20% in 5mL NaCl 0.9% and nebulise 3-4mL[9]	**Acetylcysteine:** Improved mucous clearance, reduced viscosity, oxygenation with acetylcysteine compared with sodium chloride. Some data on the use in MND secretion management.[10-12] Acetylcysteine can cause bronchospasm (use at lower dose or pre-administer bronchodilator to mitigate this). Concentrated oxygen can cause degradation of acetylcysteine.
Anti-tussive agents	**Centrally acting:** Opioids - Morphine most studied, however any opioid can be used, e.g. anecdotal evidence for low dose methadone nocte[13]. Dextromethorphan[14]	**Low dose morphine** 1-2.5 mg Q4H PRN **Methadone** 1-2 mg PO daily (nocte) to BD **Dextromethorphan** 10-15mL PO TDS	**Opioids:** Act centrally to reduce or suppress the cough reflex. If effective, consider long-acting preparation at low dose, no evidence for doses greater than 10mg BD OME. If a patient is already on opioids and is getting no benefit (cough suppression), no role for additional opioids.
	Peripherally acting: Nebulised lidocaine 2%	**Nebulised lidocaine** 5ml lidocaine 2% TDS *Caution: eating - swallow reflex may be impaired immediately post nebulisation; aspiration risk.*	
	Cromoglycate	**Cromoglycate** 10mg nebulised/inhaled TDS *(not funded in NZ, oral preparation and eye drops are available and funded).*	**Cromoglycate:** Mast cell stabiliser, prevents bronchoconstriction. Shown to be effective in reducing cough in lung cancer[15].
Other	Gabapentin Pregabalin Baclofen Amitriptyline Paroxetine Aprepitant *(hospital only, unfunded)*	There is no formal dosing guidance on the use of alternate agents for opioid resistant cough. Generally recommend low dose therapeutic trial. Aprepitant – 3 day course as for antiemetic therapy.	Consider in opioid-resistant cough. Target cough hypersensitivity, similar to the concept of sensitisation in complex pain, ie reduce sensitisation therefore reduce cough[16-19]. Limited evidence on the use of paroxetine[20,21]. Aprepitant, NK-1 and substance P thought to be implicated in cough reflex[22-25].

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Aotearoa Specialist Adult Palliative Care Guidelines.
Guideline: Management of Dyspnoea and Respiratory Distress.
Version 1.0. July 2023

OVERVIEW

Dyspnoea is a common symptom, particularly in malignant disease, which can be challenging to manage. It is an unpleasant subjective experience of breathlessness or breathing discomfort, often multifactorial in nature. There may be significant psychological, emotional or social factors which influence perception of dyspnoea.

Dyspnoea is not always associated with tachypnoea or hypoxaemia, physiological measures may only weakly correlate with a patient's subjective experience[1].

Reversible causes of dyspnoea should be identified and treated as part of dyspnoea management, within the shared goals of care.

PURPOSE

To provide guidance in the management of dyspnoea in palliative care

SCOPE

Palliative care specialists/palliative medicine physicians, nurse practitioners, hospice medical officers.

PATIENT GROUP

People with a life-threatening or life-limiting illness experiencing dyspnoea.

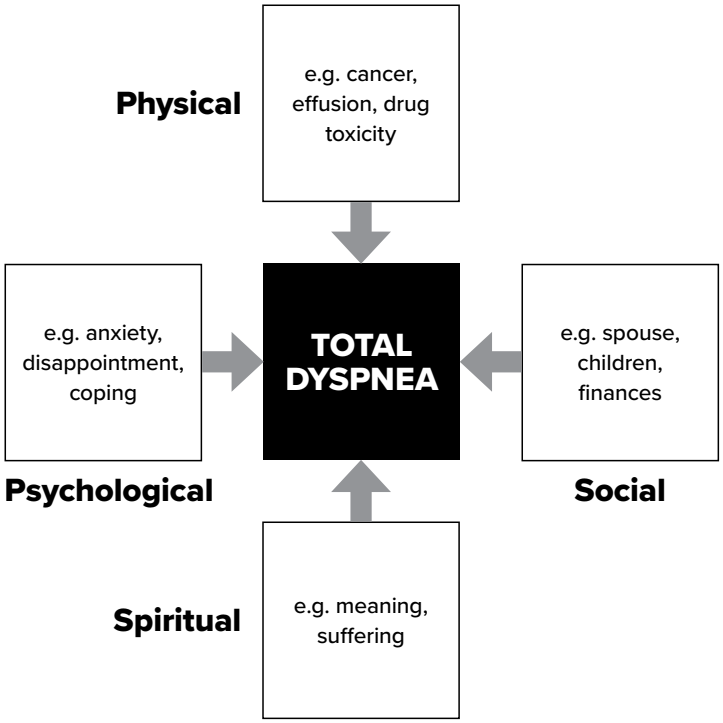
ABBREVIATIONS

BIPAP	bi-level positive airway pressure
CPAP	continuous positive airway pressure
CSCI	continuous subcutaneous infusion
COPD	chronic obstructive pulmonary disease
DNI	do not intubate
EPAP	expiratory positive airway pressure
FiO2	fraction of inspired oxygen
HFNT	high flow nasal therapy
IPAP	inspiratory positive airway pressure
GOC	goals of care
IMV	invasive mechanical ventilation
MND	motor neuron disease
OME	oral morphine equivalent
PST	palliative sedation therapy
SC	subcutaneous

DEFINITIONS

Concept of total dyspnoea

Total dyspnoea, analogous to the concept of total pain, describes the interplay between factors that influence the experience of dyspnoea as shown in the diagram below[2]. It is useful to consider this when assessing dyspnoea and developing an ongoing management plan, particularly when identifying non-pharmacological management strategies. There may be an interplay between dyspnoea and other symptoms (such as pain), which can highlight the multifactorial nature of breathlessness and the significant impact it can have on suffering and quality of life[1].



Chronic breathlessness syndrome

Refractory breathless or "breathlessness which persists despite optimal treatment of the underlying pathophysiology and results in disability"[3].

Types of dyspnoea[4]

Type of Dyspneic Sensation	Origin of the Dyspneic Sensation	Example of Disease	Possible Treatment
Air hunger	Chemoreflex activity	Pulmonary hyperinflation (COPD, advanced phase of asthma attack)	CPAP, NIV, bronchodilators
Increased work of breathing	Activity of cerebral motor cortex	Muscle weakness (neuromuscular diseases)	NIV, IMV
Chest tightness	Stimulation of slowly adapting receptors in the large airways	Bronchospasm (first phase of asthma attack)	Bronchodilators
Rapid breathing, tachypnea	Stimulation of pulmonary C fibers	Interstitial lung disease, pulmonary venous congestion	Opioids, HFNT

HFNT = high-flow nasal therapy; IM= invasive mechanical ventilation; NIV = noninvasive ventilation.

CLINICAL MANAGEMENT

Potentially reversible causes of dyspnoea

It is important to consider reversible causes of dyspnoea and address these within the shared GOC. However, in some cases chronic refractory breathlessness will be present despite optimal treatment of reversible causes of dyspnoea. Below is a table highlighting common, potentially reversible, causes of dyspnoea and management options.

CAUSE	MANAGEMENT OPTIONS
Infection	Antimicrobials
Pleural effusion	Pleural drainage, pleurodesis
Pulmonary oedema	Diuresis (+/- optimisation of heart failure therapy)
Pulmonary embolism	Anticoagulation
Lymphangitis	Corticosteroids
Superior vena cava obstruction	Corticosteroids, radiation, stenting
Malignant airway obstruction	Corticosteroids, radiation, stenting
Anaemia	Transfusion
Pain	Adequate analgesia
Anxiety	Non-pharmacological approach +/- anxiolytic medications
Cardiac ischaemia	Opioids, nitrates, optimisation of medical management
Pericardial effusion	Drainage
Ascites	Drainage

Non-malignant disease

In the setting of non-malignant disease (e.g. end stage cardiac or respiratory disease, neurodegenerative/neuromuscular disorders e.g. MND) dyspnoea may be less reversible, progressive and with episodes of increased severity (e.g. in the setting of exacerbation of COPD). These episodic changes may or may not be reversible, but often represent an overall deterioration in condition.

Non-pharmacological management

After the identification and management of reversible causes of dyspnoea (or optimisation medical management in the setting of chronic cardio-respiratory disease), first line symptomatic management should begin with a *non-pharmacologic* approach.

- Air flow – use of fans (particularly hand-held)
  - The use of a fan or open windows allowing air movement can improve the sensation of dyspnoea. Stimulation of the trigeminal nerve is thought to be the mechanism behind this. There is a reasonable body evidence supporting the use of hand-held fan in dyspnoea management[1,5-7]. The fan should be particularly aimed at the face.
- Patient and family/whānau education
  - Encourage activity within tolerance level and awareness of activities which may trigger dyspnoea.
  - Ensure patient and family/whānau know how and when to use medications
- Pulmonary rehabilitation (non-malignant disease)
- Anxiety reduction and distraction techniques
- Breathing techniques – referral to physiotherapist may be helpful
- Positioning; e.g. forward leaning8, prone etc
- Acupuncture[9-11]
- Smoking cessation (if in line with shared GOC)

Pharmacological Management

DRUG	DOSING GUIDANCE	COMMENTS
Opioids: Low dose opioids are the mainstay of dyspnoea management, with robust evidence to support their routine use. Opioids reduce the sensation of dyspnoea in both malignant and non-malignant disease. Morphine remains the most studied opioid. Most recent studies have used long-acting preparations, even in opioid naïve patients.	**Opioid naïve patients:** Morphine elixir 1-2 mg PO Q1H PRN **Opioid tolerant patients:** Use 1/10th of their total daily opioid dose PRN Q1H as a starting dose and titrate to effect. May benefit from background opioid starting but rarely need >40 mg/day OME for dyspnoea alone*. Fentanyl nasal spray may be useful in some patients (particularly if they are opioid naïve or sensitive to opioids, due to the very low dose per application). *See appendix*	Encourage pre-emptive use, i.e., 20-30 minutes pre-activity. Appropriate use of opioids does not lead to CO_2 retention. Respiratory depression associated with opioids is very rare when opioids are appropriately titrated[4]. *Doses > 40mg/day OME may result in a greater side effect burden.
Benzodiazepines: Consider as a 2nd or 3rd line options when opioids and non-pharmacological methods have failed[12]. **NB:** *The prolonged use of short-acting anti-anxiety medications, such as benzodiazepines, should be discouraged in patients with long-term anxiety disorders or a prolonged prognosis (e.g. in the context of non-malignant disease) due to the risk profile of long-term benzodiazepine use.*	**PRN dosing:** Midazolam 2.5 mg SC Q1H PRN Lorazepam 0.5 mg PO TDS PRN Midazolam nasal spray *See appendix* **Regular dosing:** Lorazepam 0.5 mg PO BD Clonazepam 0.25-0.5mg PO BD	There is no evidence that benzodiazepines directly reduce breathlessness and they should be used with caution[13]. Tolerance, dependence[14] • To help mitigate this risk aim to prescribe lowest effective dose, ideally for short course Higher AE profile compared with opioids (e.g. drowsiness)
Oxygen: There is no role for supplemental oxygen in the non-hypoxaemic patient, where oxygen saturations are generally >90% at rest. There is no robust evidence that providing ambulatory oxygen for those that desaturate on exertion alters symptoms or exercise tolerance. If used at high flow or for long periods of time, it should be humidified to prevent drying of mucous membranes. May be life-prolonging in the context non-malignant conditions[4]		
Antidepressants: The use of SSRI and SNRI antidepressant medications have been proposed in the management of chronic breathlessness. Their effect is thought to be anxiolysis and improved anxiety control[15]. Studies on their benefit are mixed and further work is likely needed this area, currently there is insufficient evidence to support the routine use of antidepressants for the management of chronic breathlessness[16,17]. In practical terms, a patient with underlying anxiety and chronic breathlessness may benefit from a trial of antidepressant as an adjunct to anxiety and dyspnoea management. In addition a holistic approach to anxiety management should be undertaken, with a focus on non-pharmacological interventions in the first instance.		
Pregabalin: There is no data on the use of pregabalin for anxiety related to dyspnoea. However, pregabalin can be used in the setting of generalised anxiety disorder (usually when SSRI/SNRI ineffective)[18]. A therapeutic trial may be beneficial particularly if the patient has neuropathic pain alongside dyspnoea with anxiety.		

Management of acute respiratory distress or severe dyspnoea at the end of life

DRUG	DOSING GUIDANCE	COMMENTS
Opioids: Morphine, oxycodone or fentanyl can be used (morphine remains the most studied of the opioids).	**Opioid naïve patients:** Morphine 5-10mg SC Q15 minutes, titrated to effect. Consider starting a CSCI; a reasonable starting CSCI is morphine 10-20mg, midazolam 10-20mg over 24 hours **Opioid tolerant patients:** Titrate usual PRN dose to effect, ensure background opioids converted to CSCI.	
Benzodiazepines:	Midazolam 2.5-5 mg SC Q15 minutes, titrated to effect for sensation of anxiety or panic associated with respiratory distress.	Benzodiazepine-tolerant patients may require significantly higher doses to achieve anxiolysis. Risk of respiratory depression
Other (sedating): Levomepromazine Phenobarbitone Dexmedetomidine	See **Palliative Sedation Therapy Guideline** GUIDELINE Palliative Sedation Therapy	**The use of PST may be required:** In the setting of severe respiratory distress or refractory dyspnoea, not responsive to titration of opioids or benzodiazepines When rapid sedation is needed to control distress (e.g. delivering a bolus of levomepromazine) When withdrawal of therapy (including oxygen, where life-sustaining) is being performed

NB: *non-pharmacological management strategies should continue to be used if effective*

Use of oxygen, non-invasive ventilation & high flow nasal cannula

High flow nasal therapy

This consists of warmed and humidified oxygen delivered via soft fitting nasal canulae at flow rates of up to 60L/min. FiO_2 can be adjusted from 0.21 to 1.0, depending on the device[4].

Advantages of HFNT:

- Maintenance of mucociliary function through delivery of heated, humidified gas
- High flow rate reduces entrainment of room air (compared with standard oxygen delivery devices)
- Increased end expiratory pressure (1cm H_2O for every 10L/min gas flow with mouth closed)
- Reduces dead space
- Lowers respiratory rate
- Generally well tolerated when compared to conventional oxygen masks

All of the above, result in reduction in work of breathing, improved oxygenation and reduced respiratory rate in patients with respiratory failure[4,19]. Data is limited, but emerging, in the use of HFNT for the symptomatic management of respiratory failure at end of life[20]. In addition, it may have an opioid-sparing effect[19,20]. Ruangsomboon et al.[21] undertook a randomised cross-over trial comparing HFNT and conventional oxygen therapy for management of respiratory distress in the emergency department (palliative cohort with DNI orders). HFNT reduced dyspnoea and was well tolerated.

HFNT does not required piped oxygen to function and can be used in the home setting via oxygen concentrators; acknowledging that the deliverable FiO2 will be limited to that produced by the concentrator. MyAirvo2TM produced by Fisher and Paykel is available in New Zealand https://www.fphcare.com/nz/homecare/home-respiratory/humidified-high-flow/myairvo-2/.

Disadvantages of the home device are the short length of the HFNT tubing and the requirement for the device to undergo a cleaning cycle daily, during which an alternative oxygen source will be needed. The MyAirvo2 does not come with a battery, and cannot be used for patient transport when discharging a patient home from inpatient settings

Application of HFNT in palliative care setting[4]:

• Explain the procedure to the patient (if patient's
• competence is not impaired).
• Choose correct nasal cannula (small, medium, large).
• Set temperature as tolerated (generally 34°C or 37°C).
• Set flow rate (usual flow rates start at 45-50 L/min but may increase gradually up to 60 L/min, depending on level of patient's comfort).
• Set Fioz as required (from 21% to 100%) to maintain desired Saoz.
• Monitor dyspnea, comfort, respiratory rate, Saoz, and patient's response. Provide support and make necessary adjustments to nasal prongs or device setup.

Non-invasive ventilation

NIV can reduce the sensation of dyspnoea by improving oxygenation and ventilation, in addition to reducing work of breathing and resistive load on respiratory muscles[19]. The use of NIV in the management of dyspnoea in the palliative setting requires further investigation and the recommendation for routine use cannot yet be made, however a trial of NIV in individual patients is not unreasonable.

In the critical care medicine workforce the use of NIV for symptomatic management of dyspnoea has been discussed[4,22] with two clear patient cohorts identified:

- Those for whom intubation is medically inappropriate (or declined by the patient), but the treatment remains active with the goal of survival.
- Symptom management in the setting of EOL – survival is not the goal
  - Clear conversations regarding ceiling of treatment and indications for NIV withdrawal need to be had and documented prior to initiation of therapy.

NIV initiation – context and communication

NIV can be used in a variety of clinical scenarios, commonly seen in the management of type 2 respiratory failure (e.g. acute exacerbation of COPD) involving the use of Bi-level NIV (BIPAP) or type 1 respiratory failure (e.g. cardiogenic pulmonary oedema) involving use of CPAP.

Initiation, monitoring and maintenance of BIPAP should be done in consultation with a respiratory physician. The details of machine settings and titration are beyond the scope of this guideline, however, some general principles include;

- Ensuring patient is upright and comfortable
- Ensure intact mask seal
- Initial IPAP of 10cm2 and EPAP of 4cm^2 is reasonable
- Titration of IPAP 2-5cm^2 every 30 minutes as tolerated usually to a target of 18-20cm^2 (maximum 26cm^2) or until desired physiological parameters are met.
- Oxygen, if required, added to circuit to achieve target $Sp0_2$ (e.g. 88-92%)

NB: *protocols for initiation and titration of BIPAP will vary between centres. The above is a guide only.*

Communication regarding use of NIV in the palliative context[22]

	Primary Goals of Care	Potentially Helpful Phrases to Clarify Goals with Family and/or Patient[a]
Category 1	Goal is to restore health; will use intubation if necessary and indicated	MD: "I recommend we use the mask (NPPV) to try to get him over this without having to put the breathing tube in his throat. If this doesn't improve things or is too uncomfortable for him, we'll use the breathing tube. Does this plan fit with your understanding of what he'd want?"
Category 2	Goal is to restore health without using endotracheal intubation and without causing unacceptable discomfort	MD: "I recommend we use the mask (NPPV) to try to get him over this. He has been very clear that he doesn't want the breathing tube, so, if the mask doesn't improve things or is too uncomfortable for him, we will plan to stop using it and focus all of our efforts on keeping him comfortable. In this situation, it would mean that he would likely die, although we would make it as comfortable as possible for him. Does this plan fit with your understanding of what he'd want?"
Category 3	Goal is to maximize comfort while minimizing adverse effects of opiates	MD: "I think it may be reasonable to try the mask (NPPV) to see if it makes him more comfortable. We know that it won't fix the underling problem, but it might make his breathing a little easier temporarily. If it doesn't make him more comfortable, we will stop it and try something else so his death will be as comfortable as possible. Does this plan fit with your understanding of what he'd want?"

[a]Note: These are example phrases developed by the authors and do not represent actual quotes from qualitative research.

Key factors which need to be considered in the use NIV for the management of dyspnoea at EO[4]

- Careful patient selection
- Staff must be skilled and experienced in the initiation, maintenance, and discontinuation of NIV
- Ability to clear/manage oropharyngeal secretions at EOL
- Fluctuating level of consciousness at EOL

Other considerations

- Ensure symptom control medications are available alongside active therapy and there is a clear understanding of how and when to use these
- A clear plan outlining indicators of treatment failure and/or the point at which the active component of treatment would be discontinued should be discussed and documented in the clinical notes.

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APPENDIX

Midazolam nasal spray 15mg/3mL (15mg total)[23]
Preparation instructions:

- Using 15mg/3mL midazolam ampules for injection
- Place 5 ampules into a 15mL nasal spray bottle
- This gives a total of 75mg in 15mL and provides 150 x 0.1mL doses of 0.5mg midazolam

Dosing:

- Initial dose is 1 spray in one or both nostrils, wait 15 minutes to assess the effect.

NB: *if the intranasal route is not accessible, can be sprayed directly onto buccal mucosa.*

Typical prescription example:
"midazolam 15mg/3mL nasal spray (15ml total). Administer 1-2 doses (0.5mg per spray) into one or both nostrils up to every hour as required for shortness of breath or anxiety"

Fentanyl nasal spray 50mcg/ml (20ml total)[23]
Preparation instructions:

- Using 100mcg/2mL or 500mcg/10mL fentanyl ampoules for injection
- Place 10 ampoules of 100mcg/2mL or 2 ampoules of 500mcg/10mL fentanyl into a 20mL nasal spray bottle
- This gives total 1000 micrograms in 20mL and provides 200 x 0.1mL doses of 5mcg fentanyl

Dosing:

- Initial dose is 1 spray in both nostrils (total 2 sprays = 10mcg) for an opioid-naïve patient, or up to 5 sprays (25mcg) in a patient on background opioid, up to hourly as required.
- Dose may be titrated to effect, though generally doses in excess of 50mcg are difficult to effectively achieve via the intranasal route due to volume and absorption.
  NB: *if the intranasal route is not accessible, can be sprayed directly onto buccal mucosa.*
- A maximum number of doses per 24 hours should be stated on the prescription

Typical prescription example:
"Fentanyl 50mcg/mL nasal spray (20mL total). Administer 1 dose (5mcg per spray) into each nostril (total 10mcg) up to every hour as required for shortness of breath. Do not use more than 10 doses in 24 hours"

ASCO dyspnoea guideline for advanced cancer 2022[5]

Management of Dyspnea in Advanced Cancer: ASCO Guideline		
Clinical Question	**Recommendation**	**Evidence Rating**
How should dyspnea be assessed in patients with advanced cancer?	**1.1.** Clinicians should perform systematic assessment of dyspnea at every inpatient and outpatient encounter in patients with advanced cancer using validated patient-reported outcome measures.	Good practice statement
	1.2. For patients who are unable to self-report, clinicians should use a validated observation measure.	Good practice statement
	1.3. Whenever possible, patients with dyspnea should undergo a comprehensive evaluation for the severity, chronicity, potential causes, triggers, and associated symptoms, as well as emotional and functional impact.	Good practice statement
What underlying conditions cause or contribute to dyspnea and warrant specific management?	**2.1.** Patients with potentially reversible, common etiologies of dyspnea such as pleural effusion, pneumonia, airway obstruction, anemia, asthma, chronic obstructive pulmonary disease (COPD) exacerbation, pulmonary embolism, or treatment-induced pneumonitis should be given goal-concordant treatment(s) consistent with their wishes, prognosis, and overall health status.	Good practice statement
	2.2. Patients with dyspnea due to underlying malignancy (e.g. lymphangitic carcinomatosis, atelectasis due to large pulmonary mass, malignant pleural effusion) may benefit from cancer-directed treatments if consistent with their wishes, prognosis, and overall health status.	Good practice statement
	2.3. Patients with underlying co-morbidities such as COPD or heart failure should have the management of these conditions optimized.	Good practice statement
What is the role of palliative care in the management of dyspnea?	**3.** Patients with advanced cancer and dyspnea should be referred to an interprofessional palliative care team where available.	Type: Evidence based Evidence quality: Intermediate Strength of recommendation: Strong
What non-pharmacologic interventions provide palliation of dyspnea?	**4.1.** Airflow interventions such as directing a fan at the cheek (trigeminal nerve distribution) should be offered.	Type: Evidence based Evidence quality: Intermediate Strength of recommendation: Moderate
	4.2. Standard supplemental oxygen should be available for patients with hypoxemia who are experiencing dyspnea (i.e. SpO_2 ≤90% on room air)	Type: Evidence based Evidence quality: Intermediate Strength of recommendation: Moderate

Management of Dyspnea in Advanced Cancer: ASCO Guideline		
Clinical Question	**Recommendation**	**Evidence Rating**
	4.3. Supplemental oxygen is not recommended when SpO_2 >90%.	Type: Evidence based Evidence quality: Intermediate Strength of recommendation: Moderate
	4.4. A time-limited therapeutic trial of high flow nasal cannula oxygen therapy, if available, may be offered to patients who have significant dyspnea and hypoxemia despite standard supplemental oxygen.	Type: Evidence based Evidence quality: Low Strength of recommendation: Moderate
	4.5. A time-limited therapeutic trial of non-invasive ventilation, if available, may be offered to patients who have significant dyspnea despite standard measures and do not have contraindications.	Type: Evidence based Evidence quality: Low Strength of recommendation: Moderate
	4.6. Other non-pharmacologic measures such as breathing techniques, posture, relaxation, distraction, meditation, self-management, physical therapy, and music therapy may be offered.	Type: Evidence based Evidence quality: Low Strength of recommendation: Weak
	4.7. Acupressure/reflexology, if available, may be offered.	Type: Evidence based Evidence quality: Low Strength of recommendation: Weak
	4.8. Evidence remains insufficient for a recommendation for or against pulmonary rehabilitation in patients with advanced cancer and dyspnea.	
What pharmacologic interventions provide palliation of dyspnea?	**5.1.** Systemic opioids should be offered to patients with dyspnea when non-pharmacologic interventions are insufficient to provide dyspnea relief.	Type: Evidence based Evidence quality: Low Strength of recommendation: Moderate
	5.2. Short-acting benzodiazepines may be offered to patients who experience dyspnea-related anxiety and continue to experience dyspnea despite opioids and other non-pharmacologic measures.	Type: Evidence based Evidence quality: Low Strength of recommendation: Weak
	5.3. Systemic corticosteroids may be offered to select patients with airway obstruction or when inflammation is likely a key contributor of dyspnea.	Type: Evidence based Evidence quality: Low Strength of recommendation: Weak
	5.4. Bronchodilators should be used for palliation of dyspnea when patients have established obstructive pulmonary disorders or evidence of bronchospasm.	Type: Evidence based Evidence quality: Low Strength of recommendation: Weak
	5.5. Evidence remains insufficient for a recommendation for or against the use of anti-depressants, neuroleptics, or inhaled furosemide for dyspnea.	
	5.6. Continuous palliative sedation should be offered to patients with dyspnea that is refractory to all standard treatment options and all applicable palliative options, and who have an expected life expectancy of days	Type: Informal consensus Evidence quality: low Strength of recommendation: moderate

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Management of End Stage Parkinson's Disease

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References

For any comments and feedback, please email us: Email

Aotearoa Specialist Adult Palliative Care Guidelines.
Guideline: Management of End Stage Parkinson's Disease.
Version 1.0. July 2023

OVERVIEW

End stage Parkinson's disease and Parkinson plus syndromes are associated with a range of symptoms that contribute to significant symptom burden, requiring palliative care input to ensure adequate control particularly in the setting of EOL.

PURPOSE

To provide guidance in the management of palliative patients with Parkinson's disease, with a focus on end of life care.

SCOPE

Palliative care specialists/palliative medicine physicians, nurse practitioners, hospice medical officers, palliative care pharmacists.

PATIENT GROUP

Patients with Parkinson's disease at end of life.

ABBREVIATIONS

CSCI	continuous subcutaneous infusion
EOL	end of life
GOC	goals of care
MAOI	mono-amine oxidase inhibitors
NG	nasogastric
NSAIDs	non-steroidal anti-inflammatory drugs
PD	Parkinson's disease
PEG	percutaneous endoscopic gastrostomy
PR	per rectal
SC	subcutaneous
SLT	speech language therapy
SSRI	selective serotonin reuptake inhibitor
SNRI	serotonin noradrenaline reuptake inhibitor

CLINICAL MANAGEMENT

Management of impaired swallow

Careful pharmacological management:

- Correct medications at the correct time
- Use of liquid preparations if tablet administration is problematic
- Consider alternate routes e.g. sub-lingual, buccal, intranasal, transdermal
- Liaison with treating neurologist to ensure optimal pharmacological management.

Feeding considerations:

- Speech language therapy referral
- Dietician referral
- Altered food consistency as appropriate
- Assistance with feeding
- Awareness of silent aspiration as common
- Nasogastric feeding is unlikely to reduce mortality (While there is no evidence specific to PD that NG feeding reduces mortality, it can be extrapolated from research related to NG feeding in patients with end stage dementia)[1].

Symptoms to address when oral route is lost:

- Motor symptoms
  - Rigidity, loss of motor function
  - Consider CSCI apomorphine infusion (liaise with treating neurologist).
  - Consider regular benzodiazepine to help with rigidity/spasticity
  - If dopaminergic medication is stopped at EOL due to loss of swallow, CSCI midazolam 5-10mg over 24 hours may help relieve rigidity.
- Dopamine agonist withdrawal symptoms (non-motor symptoms)
  - Acute dopamine depletion syndrome
  - May present as psychiatric symptoms (anxiety, panic attacks, depression, agitation, irritability, craving dopamine agonists), nausea, vomiting, flushing, orthostasis, pain, insomnia.
  - Treat with re-introduction of dopamine agonists at usual doses if possible
- Amantadine withdrawal syndrome
  - May present as agitation, anxiety delirium, delusions, depression, parkinsonian crisis, slurred speech or stupor.
  - Amantadine should not be abruptly stopped; discontinuation should be gradual to prevent withdrawal syndrome occurring in the first instance.
  - There is no specific treatment (other than reintroduction of amantadine), management is supportive[2].
- Parkinson's hyperpyrexia syndrome
  - Rare but potentially fatal
  - Presents with fever and rigidity, similar to neuroleptic malignant syndrome.
  - Treatment consists of dopaminergic drug replacement and supportive management of complications.
  - Seek advice from neurology.

Management of pain
Pain occurs in 70-90% of patients and may occasionally occur prior to motor symptom onset[1,3]. Optimal use of anti-Parkinson's medication reduces pain indirectly, through adequate control of motor symptoms.

Musculoskeletal pain

- *Non-pharmacological management:* anecdotal evidence for massage, warmth, distraction, music, TENS (transcutaneous electrical nerve stimulation) and meditation. Low grade positive evidence for yoga and acupuncture[1].
- *NSAIDs;* good evidence for efficacy if tolerated and other comorbidities allow. Liquid formulations available if impaired swallow, gastrostomy administration. PR formulations also available.
- *Paracetamol;* monitor efficacy, cease if ineffective.

Peripheral neuropathic pain

- Consider trialling pregabalin or gabapentin (available as liquid preparation).
- Trial of low dose tricyclic medication (e.g. nortriptyline 10mg nocte), monitoring closely for anti-cholinergic side effects.

Central neuropathic pain

- Typically described as poorly localised burning pain with spontaneous onset and periods of exacerbation. Central pain is often difficult to treat with standard analgesic or neuropathic agents consider[3]:
  - Trial of low dose opioids or anti-neuropathic agents
  - Cannabinoids (observational study evidence)[3]
  - Amantadine, rotigotine
  - Acupuncture if available (low grade evidence)

Restless legs syndrome

- Ensure adequate iron stores – consider replacement if ferritin <75microgm/l.
- Low dose dopamine agonists prior to bed
- Trial of gabapentinoids

Psychological/cognitive disorders
The majority of patients with end stage Parkinson's disease will develop a degree of cognitive impairment.

Depression

- Psychological support if available and appropriate
- Most evidence for SSRIs and SNRIs[4]
- Trial of rasagiline (MAOI- B)

Sleep Disorders

- Non-pharmacological measures; nocturnal routine, avoiding daytime naps, avoiding stimulants
- Melatonin
- Low dose tricyclic anti-depressant (e.g. nortriptyline 10mg nocte) or low dose mirtazapine. (e.g. 15-30mg)

Delirium/psychosis

- Non pharmacological measures; presence of whānau or familiar caregivers, use of hearing aids, low stimulus environment, avoid room or environment changes
- Discontinue or decrease medications that may contribute (e.g. MOA-B inhibitors). Note both apomorphine and rotigotine can cause delirium and/or agitation.
- Assess for and treat reversible causes; sepsis, electrolyte disturbances (e.g. hyponatraemia, hypercalcaemia), endocrine disorders (e.g. hypothyroidism), withdrawal syndromes.
- Pharmacological management:
  - Consider a benzodiazepine (however, can sometimes exacerbate delirium).
  - Antipsychotics:
    > Avoid haloperidol
    > Trial quetiapine 12.5-25mg/24 hours in divided doses if PO route available
    > Levomepromazine is less likely than haloperidol to exacerbate Parkinson's disease symptoms.
    > Clozapine (possibly the most effective, but requires a clinician familiar in the use to support prescribing). Weekly neutrophil counts are recommended for the first 18 weeks and 4 weekly following[1,4-7], however this needs to be considered alongside patient GOC and clinical context.

Nausea and vomiting

- Treat reversible causes of nausea
  (e.g. hyponatraemia, hypercalcaemia, constipation)
- Avoid centrally acting dopamine antagonist anti-emetics
  (metoclopramide, haloperidol, prochlorperazine)
- Empiric antiemetic options include:
  - Domperidone (10mg TDS or QID) if able to swallow
  - Ondansetron 4mg SL, SC, IV TDS (contra-indicated with apopmorphine)
  - Dexamethasone trial of 4mg PO/IV/SC daily for 3-5 days,
    if malignant comorbidity is present
- For refractory nausea:
  - Levomepromazine 3.125-6.25 TDS PO/SC QID
  - Mirtazapine 15mg nocte may be useful for nausea associated with anxiety
  - Olanzapine oro-dispersible 2.5mg BD
  - Hyoscine hydrobromide (Scopaderm patch being the most commonly used route of administration) – monitor orthostatic hypotension, delirium, constipation.

Dysautonomia
Impairment of the autonomic nervous system can result in constipation, orthostatic hypotension or urinary symptoms. (e.g. nocturia, urinary retention)[1,8]

Treatment of constipation:

- Dietary management, adequate fluid intake, exercise as able
- Osmotic laxatives
- Sparing use of stimulant laxatives (1-2 per week)

Treatment of orthostatic hypotension:

- Adequate hydration, compression stockings, raising the head of the bed, education on safe standing or change of position.
- Reducing antihypertensive medication
- Discuss with patient's neurologist, a gradual tapering of dopamine may improve symptoms.
- Consider fludrocortisone 100-400mcg mane (monitor electrolytes) or midodrine 2.5mg TDS

Treatment of urinary symptoms:

- Bladder training, pelvic floor exercises, restriction of evening fluid intake
- Tamsulosin 500microgram daily if prostatic enlargement is a contributor[9]
- Oxybutinin 2.5mg TDS or solifenacin 5mg daily for detrusor over-activity
  NB: *When using anticholinergic medication, monitor for constipation and orthostatic hypotension. Avoid use if retention is the predominant urinary symptom.*
- Mirabegron or Botox injections may also be considered

Excess secretions/sialorrhea

- Withdraw medications that could exacerbate symptom (e.g. clozapine[7], quetiapine)
- Atropine eye drops (0.5-1%) administered sublingual, may need to be administered frequently[10]. Patient may find the taste unpleasant.
- Hyoscine hydrobromide (Scopoderm patch) – monitor for delirium and hypotension
- Botox or radiation therapy to salivary glands for longer term control.
- See **Management Of Respiratory Secretions Guideline** for further detailed information

GUIDELINE
Management of Respiratory Secretions

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OVERVIEW

Bowel obstruction is a common complication of advanced abdominal or pelvic malignancy, in particular colorectal (incidence 25-40%) and ovarian (incidence 16-22%)[1]. There may be a number of factors contributing to obstruction. Obstruction can occur at multiple levels in the bowel, particularly in the setting of peritoneal or omental disease.

Obstruction may be partial or complete. Partial may transition to complete obstruction.

Medical management of obstruction is indicated once it has been decided that surgical options are either inappropriate or not beneficial[2,3]. The aim of medical management is to reduce symptoms of abdominal colic and pain, nausea and vomiting. If obstruction is partial, management will also be aimed at relieving obstruction and resuming normal bowel function.

PURPOSE

To provide guidance in the medical management of malignant bowel obstruction.

SCOPE

Palliative care specialists/palliative medicine physicians, nurse practitioners, hospice medical officers, palliative care pharmacists.

PATIENT GROUP

Patients with MBO for whom surgical management is not appropriate.

ABBREVIATIONS

CSCI	continuous subcutaneous infusion
GOC	goals of care
IV	intravenous
MBO	malignant bowel obstruction
SC	subcutaneous

CAUSES OF MBO

Tumour mass	Single or multiple tumours Invasion into bowel lumen Extrinsic compression of bowel
Constipation	Faecal loading, impacted faeces
Adhesions	Post-operative, malignant, post-radiation
Volvulus	Around tumour, adhesions or fistula
Ileus	Infiltrative disease affecting enteric nervous system Autonomic nerve impairment (retroperitoneal disease) Drug effect (opioids, anticholinergics) Infection/peritonitis Ascites

CLINICAL MANAGEMENT

General principles of Non-Pharmacological Management of MBO
Initial management may follow usual surgical management; bowel rest, nil by mouth, parenteral fluids and nasogastric tube (NGT) drainage of gastric contents[4]. This should only be a temporary measure while decisions are being made regarding surgical options versus medical management.

Parenteral fluids:

- Maintenance fluids should not be routinely continued as part of MBO management. Excess fluid can worsen gut oedema, increase gut secretions and overall slow the resolution of obstruction.
- Temporary parenteral hydration may be appropriate where dehydration precipitates delirium or renal failure potentiating opioid metabolite accumulation.

NGT drainage:
Obstruction can usually be managed without NGT drainage, but there may be some situations where the symptoms of nausea and vomiting are best managed via NGT drainage, providing the tube is tolerated by the patient. Situations where vomitus volume is high, such as pathology causing gastric stasis or in gastric outlet obstruction, may benefit from NGT placement to allow drainage of vomitus. The NGT can be maintained on free drainage, and may be aspirated at regular intervals or when the patient feels nauseated.

Regular mouth care and ice chips should be used to manage a dry mouth and thirst.

If nausea and vomiting is controlled it may be appropriate to cautiously restart oral intake.

Meals should be small, low residue.
Dietary supplements may be appropriate or better tolerated.

General Principles of Pharmacological Management of MBO
Medical management of MBO should include antisecretory, antiemetic, analgesia and antimotility agent (in the context of complete or irreversible bowel obstruction).

Medication should always be parenteral (SC or IV) due to variable and/or unreliable gut absorption in MBO.

Corticosteroids are traditionally used in MBO to reduce gut/peritumoral oedema indirectly contributing to analgesia and antiemesis; evidence on dosing and duration of corticosteroid use is limited. As a general rule gastric protection should be given (proton-pump inhibitor) alongside corticosteroid use. See table below for more information.

Antisecretory agents (listed below) are used to reduce gastric and small bowel secretions, thereby reducing nausea, vomiting and indirectly minimising visceral pain[2,5].

Antiemetic choice is based on degree of obstruction; prokinetics should be trialled in the first instance in partial/incomplete obstruction as prokinetic action may assist in resolution of obstruction. Prokinetics should not be used in complete obstruction or if use causes the patient to develop colicky abdominal pain.

Dopamine receptor antagonists are a reasonable empiric first-line choice for antiemesis in MBO.

In the context of MBO with intractable nausea and vomiting, trial of 5-HT3 receptor antagonist (e.g. ondansetron) should be considered. The atypical antipsychotic, olanzapine, has been demonstrated to improve nausea in the setting of advanced cancer, particularly in peritoneal carcinomatosis and incomplete bowel obstruction[6-9].

Analgesia should be given to control abdominal pain associated with obstruction.

- In the setting of complete bowel obstruction, hyoscine butylbromide (Buscopan®), may be helpful to control pain due to colic BUT it should not be used in a partial bowel obstruction.
- Hyoscine butylbromide slows gut motility and will impede resolution of partial bowel obstruction.

If faecal loading or impaction is present; per rectal/stomal treatments should be given to clear bowel. See section on the next page.

Overview of Medications Used to Manage Symptoms of MBO

DRUG	DOSING	ACTION
Corticosteroids		
Dexamethasone	4 -16 mg SC/IV mane *Daily dosing mane, there is no indication to split steroid dosing throughout day.*	For use in partial or incomplete obstruction. Reduces gut oedema, or peri-tumoural oedema/ inflammation. May have antiemetic benefit. If no improvement in symptoms after 5 days, steroid should be stopped.
Prokinetics		
*Metoclopramide**	10-20 mg SC TDS OR 30-60 mg CSCI over 24 hours	Only use in partial or incomplete obstruction. Promote peristalsis. Antiemesis. Contra-indicated in a complete bowel obstruction. Stop if causes colic – can give a trial dose of 10mg SC. If this does not cause colic then it is reasonable to give as a regular medication or via CSCI.
Anti-secretories		
Hyoscine butylbromide (Buscopan®)	20 mg SC TDS OR 60-120 mg CSCI over 24 hours	Hyoscine butylbromide may have an anti-motility/ antisecretory role in a complete obstruction but should NOT be used in partial obstruction.
Famotidine	20mg SC bolus BD OR 20-40mg CSCI over 24 hours	Famotidine reduces gastric secretions; can be useful in setting of gastric outlet obstruction or high-level obstruction.
Octreotide	300-900 microg CSCI (can be given in divided dose e.g. 100microg SC TDS)	Octreotide can be effective (although robust evidence for this is limited[10]) in relieving gastrointestinal symptoms and reducing gastric secretions. Prokinesis at level of duodenum. Reduces splanchnic blood flow. May be useful in the setting of gastric outlet obstruction or MBO with high volume vomitus.
Glycopyrrolate	200-400microg QID OR 800-1600microg CSCI over 24 hours	Antisecretory agent useful in complete obstruction, should NOT be used in partial or incomplete obstruction.

Overview of Medications Used to Manage Symptoms of MBO (continued)

DRUG	DOSING	ACTION
Antiemetics		
*Metoclopramide**	10-20 mg SC TDS OR 30-60 mg CSCI over 24 hours	Only in partial or incomplete obstruction. Promotes peristalsis and antiemesis. *Contraindicated* in complete obstruction. Stop if causes colic.
*Haloperidol**	1-2 mg CSCI (or 0.5-1 mg SC BD) 0.5 mg SC Q4H PRN Max 5 mg total / 24hrs	1st line in complete bowel obstruction. No prokinetic effect.
Cyclizine	25-50mg SC TDS OR 75-150mg CSCI over 24 hours	Can consider 2nd line or in addition to dopamine receptor antagonist.
*Levomepromazine**	5-15mg CSCI	Consider as alternate 2nd line agent. Low dose should not cause excess sedation.
*Ondansetron**	4-8mg SC TDS OR 12-24 mg CSCI over 24 hours **NB:** *oro-dispersible tablet can be used if SC route not available)*	Consider in intractable nausea/vomiting (complete obstruction only)[11].
*Olanzapine**	2.5-5mg PO/SL BD (wafer or oro-dispersible tablet)	Consider in intractable nausea/vomiting.

* QT-prolongation risk, caution when used in combination with other QT prolonging medications. Ideally avoid dopamine antagonists in patients with Parkinson's disease.

Interventional options

Gastrostomy

In the setting of obstruction with intractable nausea/vomiting or high volume emesis, placement of a gastrostomy tube to allow "venting" of gastric contents should be considered (in the context of prognosis)[12,13]. Trialling NGT decompression in the first instance is a sensible option[14]. Depending on location, gastrostomy placement can be done radiologically via interventional radiology services or endoscopically via surgical or gastroenterology services. Palliative venting gastrostomy should be considered early, as risk profile and ability for the patient to tolerate the procedure become more challenging towards end of life[2,12].

Stenting

Surgical opinion may be sought into the usefulness of stenting. This is only a consideration in the setting of a single point of obstruction. Prognosis and the patient's overall performance status must be taken into consideration. Endoscopic procedures may be a better tolerate and less invasive alternative to surgical intervention[15].

A note on use of Gastrograffin

There is limited robust data on the use on Gastrograffin for therapeutic management of malignant bowel obstruction, however anecdotally it has been used with success[16]. A 2018 Cochrane review concluded there was insufficient evidence available to determine therapeutic benefits or safety of Gastrograffin (or similar) in MBO[17]. Subsequently a recent small feasibility study has shown benefit of a single 100mL dose of oral Gastrograffin, with no significant side effects[18]. Further work is clearly needed, however consideration of the use of Gastrograffin in individuals with MBO is not unreasonable, after careful review of risk/benefit profile.

Use of laxatives and per rectal treatments in MBO

Partial bowel obstruction:

In patients with partial bowel obstruction and reduced or absent bowel movements, oral osmotic laxatives should be

trialled and titrated to tolerance and/or effect[14]. The osmotic action causing water to be drawn into the bowel lumen, softening stool and promoting peristalsis and bowel clearance. Stool softeners, e.g. Docusate, can be safely used in MBO. The use of bulk-forming laxatives (e.g. those containing psyllium like Metamucil) should not be used as these can worsen MBO by increasing stool consistency[14]. Generally stimulating laxatives (e.g. those containing senna) should be avoided if their use worsens symptoms of colic.

Laxatives are not recommended in complete bowel obstruction.

If PR examination demonstrates the presence of stool, use of suppositories or enemas may be of benefit to clear the lower bowel and facilitate overall bowel clearance.

AUDIT INDICATORS

Antiemetics are prescribed appropriately according to complete or incomplete MBO.

Corticosteroids are routinely used for medical management of MBO.

Anti-secretory medication are used in the setting of high gastric output MBO.

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OVERVIEW

Nausea and/or vomiting are common symptoms which can cause significant distress and impact on quality of life. The symptom may be treatment or non-treatment related and is frequently multifactorial in aetiology[1,2]. Associated symptoms of reflux, hiccups and early satiety are also prevalent and need to be considered in the overall assessment and management of this symptom. Chronic nausea can be associated with anorexia, fatigue, reduced quality of life and impaired performance status[2]. Unfortunately, the evidence for management of nausea and vomiting in this patient population (with the exception of chemotherapy associated nausea) is generally low[3].

PURPOSE

To provide guidance in the symptomatic management of nausea and vomiting.

SCOPE

Palliative care specialists/palliative medicine physicians, nurse practitioners, hospice medical officer, palliative care pharmacists.

PATIENT GROUP

Patients with a life-threatening or life-limiting illness who experience nausea and vomiting.

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ABBREVIATIONS

CNS	central nervous system
CSCI	continuous subcutaneous infusion
CTZ	chemoreceptor trigger zone
GI	gastro intestinal
GU	genitourinary
GOC	goals of care
ICP	intracranial pressure
IV	intravenous
NGT	naso-gastric tube
NSAIDs	non-steroidal anti-inflammatory drug
PPI	proton pump inhibitor
PO	per oral
SC	subcutaneous
TDS	three times daily

DEFINITIONS

Nausea	An unpleasant subjective sensation caused by stimulation of the gastrointestinal tract, chemoreceptor trigger zone (CTZ), the vestibular apparatus or the cerebral cortex. Nausea does not always lead to vomiting[4].
Vomiting	A neuromuscular reflex which results when one or more of the above are stimulated. Vomiting can occur without nausea[4].

CLINICAL MANAGEMENT

Determining the cause of nausea and vomiting

Management of nausea and vomiting should take into account the underlying cause of the symptom, often multifactorial in this patient cohort[4-6]. Understanding the underlying pathophysiology can help to guide antiemetic prescribing[6].

Pharmacological management targeting the relevant central emetogenic pathways and their corresponding neurotransmitter receptors (See figure 1), i.e. a mechanism based approach, is pragmatic, however many clinicians opt for an empiric approach to nausea management. Either approach is acceptable, the evidence for a mechanism-based approach is weak, with only one randomised control trial comparing methods which showed no difference between techniques[7,1,8].

Management should also include identification and treatment of reversible causes (if appropriate within the patients GOC)[4,5,9].

Key emetogenic pathways.[4,8] Ach = Acetylcholine receptor; CTZ = chemoreceptor trigger zone; D2 = dopamine type 2 receptor; GABA = gamma-aminobutyric acid receptor; H1 = histamine type 1 receptor; ICP = intracranial pressure; NK1 = neurokinin 1 receptor; 5HT2 = serotonin type 2 receptor; 5HT3 = serotonin type 3 receptor; 5HT4 = serotonin type 4 receptor.

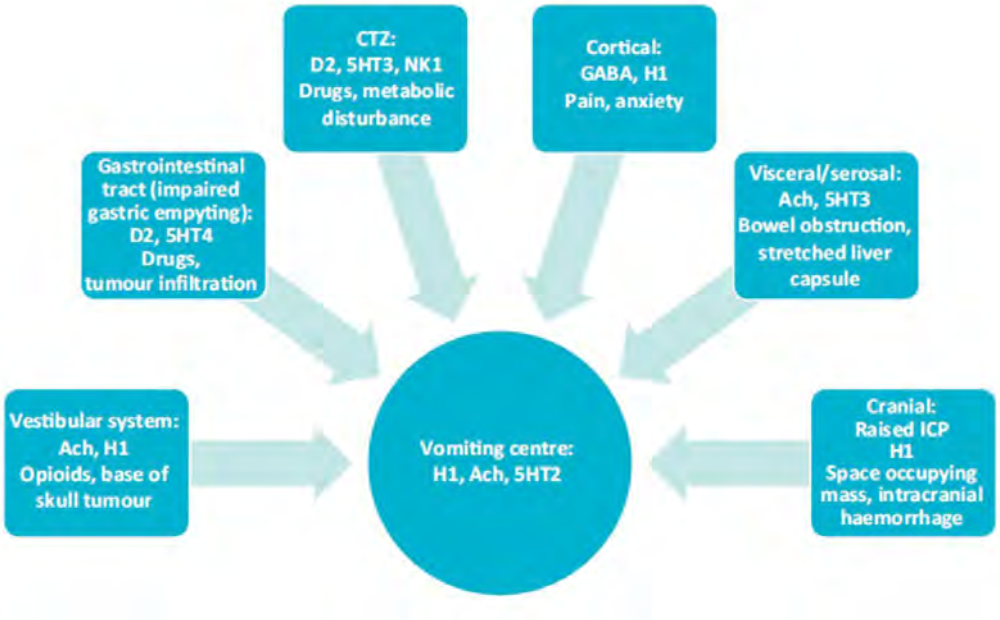

Figure 1: Emetogenic pathways[4]

Clinical scenarios and emetogenic pathways

COMMON CAUSES	CLINICAL PICTURE	MAIN SITE OF ACTION
CHEMICAL		
Drugs (opioids, antibiotics, anticonvulsants, cytotoxics etc) ***Biochemical*** (hypercalcaemia, uraemia, hyponatraemia, organ failure, hyperglycaemia, adrenal insufficiency) ***Toxins*** (tumour factors, infection, drug metabolites, radiation)	Symptoms of drug toxicity or underlying disease with nausea as the predominant symptom. Vomiting does not usually relieve nausea.	Chemoreceptor trigger zone (CTZ) Dopamine (D_2) antagonist Serotonin (5-HT_3) antagonist
GASTROINTESTINAL TRACT – VAGAL		
Gastric irritation (NSAIDs, steroids, antibiotics, blood, radiation) ***Obstruction*** (partial or complete) ***Constipation*** Gastric stasis ***Mass effect*** (GI, GU, hepatomegaly, carcinomatosis) ***Anatomic/structural***	Epigastric pain, fullness, early satiety, reflux, hiccups, flatulence. Intermittent nausea relieved by vomiting. Altered bowel habit. May have pain with oral intake. Vomitus may be large volume and/or feculent.	Vagal and sympathetic afferent nerve pathways D_2 and 5-$HT_{3\&4}$ antagonists H_2 receptor antagonists Acetylcholine antagonists
CENTRAL NERVOUS SYSTEM		
Increased ICP (brain metastases, cerebral oedema, bleeding)	Headache and/or cranial nerve signs. Early morning symptoms. Vomiting often without nausea.	Histamine (H_1) receptor antagonists Corticosteroids **NB:** *Acetazolamide can be used in addition to steroids for management of raised ICP.*
PSYCHOLOGICAL		
Fear, anxiety, pain	Anticipatory nausea/vomiting to triggers (sights, smells etc). Often low volume vomitus.	Benzodiazepines (anticipatory nausea only).
PSYCHOLOGICAL		
Vestibular dysfunction (motion sickness) ***Cerebellar tumour***	Nausea and vomiting with movement	H_1 receptor antagonists

Table 1: Causes of nausea and vomiting[2,4-6]

Pharmacological management options based on cause of nausea and vomiting
Nausea is mediated by several neurotransmitters as described above. Selection of antiemetic should take into consideration the aetiology of nausea/vomiting and site of action of the medication.

General principles:

- Metoclopramide or other dopamine antagonist is the usual first choice as it targets common causes of nausea in advanced malignant disease[1].
- Titrate antiemetics to their maximum (as tolerated) dose before adding a second drug.
- If nausea has improved but is not fully controlled with the initial drug add a second antiemetic from a DIFFERENT group, but do not stop the initial drug.
- Use regular dosing (or CSCI) of antiemetics and ensure breakthrough doses are charted.
- Avoid the oral route (where possible), give parenterally (SC or IV) until nausea is controlled or cause of nausea has been reversed.
- If opioid-induced, consider opioid rotation

Antiemetics, mechanism of action and dosing options

DRUG	MOA	ROUTE	DOSE RANGE	FREQUENCY
Metoclopramide	Dopamine (GI and CNS), prokinetic 5-HT4 (upper GI at higher doses)	PO, SC, IV	10-20mg *Max. 60mg/24 hours*	Q8H
Domperidone	Dopamine (GI), prokinetic. Does not cross blood-brain barrier	PO	10mg	Q6H
Cyclizine	Histamine	PO, SC, IV	12.5-50 mg *Max. 150mg/24 hours* *Oral: parenteral ratio 2:1*	Q8H
Ondansetron	Serotonin (CNS and GI)	PO, SC, IV	4-8 mg *Max. 24mg/24 hours*	Q8H
Haloperidol	D2 CTZ	PO, SC, IV	0.5 -1 mg *Max. 5mg/24 hours*	BD
Dexamethasone	Multiple	PO, SC, IV	2-4 mg	Daily (mane)
Levomepromazine	5-HT2, dopamine, histamine & acetylcholine	PO, SC, IV	3.125-6.25 mg *Anti-emetic ceiling approx. 25 mg/day* *Oral:parenteral ratio 2:1*	Q4H
Olanzapine	D2, 5-HT2, acetylcholine	PO (wafer)	1.25-5 mg *Max. 10mg/day*	OD-BD
Prochlorperazine	Dopamine	PO, Buccal, SC	5-10 mg PO 3-6 mg Buccal	BD – TDS depending on route
Scopolamine/hyoscine (Scopoderm patch)	Acetylcholine, muscarinic	Transdermal	TTS topical	Change every 3 days

Table 2: Antiemetics, mechanism of action and dosing options[7]

NB: *Many antiemetic drugs increase risk of QT prolongation, use with caution especially in combination with other QT prolonging drugs. Dopamine antagonists can cause extrapyramidal effects; akathisia (more common with metoclopramide), abnormal movements, tardive dyskinesia (long-term use).*

Management of nausea caused by gastric stasis/delayed gastric emptying:
This may occur in the following scenarios:

- Constipation
- Malignant bowel obstruction (partial or complete)
- Mechanical/"squashed stomach" e.g. due to hepato-splenomegaly, intra-abdominal tumour burden, ascites
- Use of medications that slow gut peristalsis or delay gastric emptying
- Diabetic gastroparesis

Management of nausea should focus on reduction of gastric contents. This can be achieved by the following:

- Use of prokinetic antiemetic (not in complete bowel obstruction)
- Consider drainage of gastric contents via NGT or gastrostomy tube (dependent of patient GOC); free drainage and regular aspiration when patient becomes nauseated
- Oral intake should be focused on comfort; eating/drinking small amounts as tolerated
  - Consider fluids only initially
  - Small volumes (sips) frequently throughout the day rather than large volumes.
  - Consider ice chips/ice blocks
- Use of antisecretory agents to reduce volume of gastric secretions:
  - Famotidine 20mg SC BD or CSCI 20-40mg per 24 hours
  - Octreotide 300-900microg SC (split TDS or via CSCI per 24 hours)

Non-pharmacological management of nausea:

- Avoid triggering smells
- Use of ice-chips for thirst
- Oral intake should be small amounts/small volume intermittently throughout the day rather than large boluses.
- Attention to oral hygiene

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OVERVIEW

Respiratory secretions can occur at end of life (EOL), this is a normal part of the dying process and represents pooling of a small volume of secretions in the hypopharynx usually in the last hours to days of life[1].

Secretions from the lower respiratory tract can be multifactorial and depending on underlying pathology, can occur at any point in the patient's disease trajectory. Symptomatic management of these secretions differs from the management of "terminal" or EOL secretions. Increased mucus production and/or inability to adequately clear mucus, can occur in head and neck cancers, lung cancers, neurodegenerative disorders (e.g. motor neuron disease) or end-stage cardiorespiratory disease.

PURPOSE

To provide guidance in the management of respiratory secretions.

SCOPE

Palliative care specialists/palliative medicine physicians, nurse practitioners, hospice medical officers, palliative care pharmacists.

PATIENT GROUP

Patients with a life-threatening or life-limiting illness associated with respiratory secretions as part of their underlying illness or in the context of EOL.

ABBREVIATIONS

COX	cyclo-oxygenase
CSCI	continuous subcutaneous infusion
EGFR	epidermal growth factor receptor
GI	gastrointestinal
GOC	goals of care
LOC	level of consciousness
LRT	lower respiratory tract
MDT	multidisciplinary team
MOA	mechanism of action
OT	occupational therapy
PT	physiotherapy
SC	subcutaneous
SLT	speech-language
URT	upper respiratory tract

DEFINITIONS

Respiratory secretions	Excess secretion/mucus production at any point along the respiratory tract.
Bronchorrhea	Excess watery endobronchial fluid (>100mL/day in the setting of lung tumours and other non-malignant respiratory conditions[2].
Sialorrhea	Excess drooling/salivation, often associated with neurodegenerative disease.
Terminal secretions ("noisy breathing", "death rattle")	Pooling of oropharyngeal and/or upper respiratory (URT) secretions due to impaired clearance (reduced LOC and impaired swallow).

CAUSES OF RESPIRATORY SECRETIONS

Upper respiratory tract and/or oropharyngeal secretions at the EOL are generally due to the inability to clear saliva/secretions (e.g. impaired swallow from fluctuating or lowered level of consciousness). The presence of secretions can produce noisy breathing which family/whānau may find distressing. Lower respiratory tract secretions can occur alone or in addition to upper respiratory tract/oropharyngeal secretions and can be multifactorial. See table below:

	CAUSES	CLINICAL PICTURE	MANAGEMENT OPTIONS
Increased mucus/ secretion production	Head and neck cancer Lung cancer Cardiorespiratory disease (COPD, bronchiectasis, heart failure, interstitial lung disease)	Cough Dyspnoea	Anticholinergic drugs Treatment of infection Optimisation of medical management in the context of cardiorespiratory disease Physiotherapy Mucolytics
Impaired clearance of mucus/sections	Reduced level of consciousness (impaired swallow) Neurological conditions Stroke Motor neurone disease Parkinson's disease Parkinson's plus syndromes Neurogenic pulmonary oedema (e.g. following steroid cessation at EOL)	Weak/ineffective cough Aspiration risk Pneumonia	Physiotherapy assistance Cough assist device and/or techniques Anticholinergic drugs (**NB:** *may thicken secretions leading to increased difficulty with clearance*) Mucolytics Suction as tolerated

CHANGES TO BREATHING PATTERNS AT EOL

See **Management of Dyspnoea Guideline**.

GUIDELINE
Management of Dyspnoea and Respiratory Distress

CLINICAL MANAGEMENT

Management of Respiratory Secretions at EOL

Non-pharmacological management options:
Although anticholinergic agents are often used for the management of secretions, current evidence does not support their routine use[3]. The interventions below should be first-line in the management of respiratory secretions, although it is important to note, there is also no evidence for these non-pharmacological interventions either, however the potential harm is less than the potential drug side effects associated with anticholinergic use[4].

Education and Reassurance:

- Consider a pre-emptive discussion with whānau/family regarding the changes that can occur at the EOL, including change in breathing patterns and noise.
  - The noise associated with secretions can be distressing for whānau/family; there may be concern that their loved one is struggling to breathe, "drowning" with fluid etc[4]. It is important to reassure and explain that this is not the case.
  - Terminal secretions do not generally represent fluid in the lungs, rather pooling of oropharyngeal secretions.
  - Respiratory secretions are a normal part of dying.
  - A small amount of fluid in the oropharynx can produce significant noise.
    > It may be helpful to use the analogy of the noise made when drinking the final few millilitres of water from a glass with a straw – a loud noise is made despite a very small amount of fluid.
  - If noisy breathing is a source of distress to the family/whānau, consider distraction with music, television or radio at low level in the background.

Patient positioning:
Patient positioning to allow drainage of secretions is frequently described in the literature, again there is no evidence to suggest this is beneficial, but clinically remains a tool used to assist in management of excess secretions. The aim being to try and keep the oropharyngeal airway patient and allow secretions to drain out the mouth. The frequency of positional changes also takes into account the prevention of pressure area injuries. For the individual patient, note should be taken of positions in which the intensity of noisy breathing is less and use of these positions, within reason, maximised.

Frequent mouth care:
Attendance to regular mouth care is very important, this may be something family/whānau are willing to assist with.

Suctioning:
This is generally not recommended at the EOL due to risk of causing distress to the patient and trauma to mucous membranes, which can inadvertently increase oral secretions. However, it is not unreasonable to gently suction secretions that are visible at the front of the mouth as tolerated.

Avoid parenteral fluids (IV or SC):

- The role of supplementary fluids at EOL is controversial, particularly in some cultures and/or religions. It is not common practice in Aotearoa to provide parenteral fluids at EOL. There is currently no evidence that parenteral fluids reduce thirst sensation and there is concern that artificial hydration at EOL may increase the likelihood of respiratory secretion accumulation as the patient deteriorates and is physiologically unable to manage the additional fluid load.

- Internationally, it is practice in some centres to provide low volume SC hydration (0.5-1L per 24 hours) to patients at EOL, the rationale being that provision of very low volume fluid may allay family/staff/patient concerns regarding hydration, but is unlikely to cause significant harm[5,6]. This further highlights the complexity of this scenario.
- Further robust research is needed around artificial hydration at EOL to determine benefits/harms and the effect it may or may not have on respiratory secretions. Kingdon et al. undertook a systematic review of the clinical impact of artificial hydration at EOL. Their findings support the need for further research in this domain, highlight the paucity of evidence to guide clinical decision making and emphasise the crucial role of expert communication around this complex topic[7].

Pharmacological management options:
The evidence for efficacy of anticholinergic agents in the management of respiratory secretions at EOL is limited, however, they have traditionally been used to manage this symptom[4,8]. In New Zealand EOL guidelines (Te Ara Whakapiri), hyoscine butylbromide (Buscopan) is listed in the symptom management algorithm for respiratory secretions.

There is evolving evidence that anticholinergics may reduce the amount of fluid produced and prevent further secretions accumulating, however they will not "dry up" existing fluid[9]. A recent RCT comparing hyoscine butylbromide 20mg QID with placebo, given prophylactically at the onset of the dying phase, showed it to be an effective means of reducing the incidence of respiratory secretions at EOL[10,11]. Further work is needed to assess the efficacy of prophylactic anticholinergics, as well as determining the risk/benefit profile.

If anticholinergic agents are trialled in the management of respiratory secretions, it is important to document efficacy of bolus doses, this can then guide decision making regarding commence of CSCI dosing. It is also important to discuss use with family/whānau, in particular, highlighting that the medication may not be effective.

Drugs that have been used to manage respiratory secretions at EOL include:

DRUG	DOSE
Hyoscine butylbromide (Buscopan)	20mg Q4H SC OR 60-120mg via CSCI over 24 hours *max. 120mg/24 hours*
Glycopyrronium bromide	200-400mcg Q4H SC OR 400-1600mg via CSCI over 24 hours *max. 1600mg/24 hours*
Atropine (1% ophthalmic solution)	1-2 drops sublingual Q2-4H

NB: *anticholinergics often cause dry mouth (in addition to effect of other anticholinergic medications the patient may have prescribed) which can be distressing.*
* Avoid hyoscine hydrobromide, this crosses blood-brain barrier and can cause delirium

Management of respiratory secretions EOL due to cardiorespiratory disease
In the context of excess LRT secretions due to pulmonary oedema, e.g. secondary to end stage heart failure or renal failure, use of diuretics (provided effective diuresis ensues) may be appropriate at EOL.

The use of antibiotics in the context of purulent LRT secretions at EOL may be considered if significant symptomatic distress is occurring. The goal being reduction of secretion volume and viscosity.

Furosemide
Can be use administered undiluted via SC bolus or CSCI without diluent (due to volume). SC bolus should be given slowly over a few minutes due to volume being injected. If using bolus doses higher than 20mg, these need to be divided, by administration time (e.g., mane and midi dosing) or split between SC sites. Diuresis takes place approximately 30 minutes after administration of SC furosemide. Furosemide can be given via CSCI and should not be combined with other medications.

Antibiotics
Ceftriaxone is a broad-spectrum cephalosporin which can be administered via SC injection and would be reasonable to trial in the context of purulent LRT secretions causing distress at EOL. To avoid painful injection, diluent should be lidocaine 1%. Data on this is limited but it is used successfully in aged care, palliative care settings or situations when IV access is poor[12].

- Dilute ceftriaxone 1 gram with 2.2ml of lidocaine 1% and administer SC slowly over a few minutes (if a 2 gram dose is needed, split dose over two SC sites).

Management of sialorrhea
Sialorrhea can be associated with a number of different clinical conditions. In the palliative care context it is often seen with neurodegenerative diseases (such as motor neuron disease, Parkinson's disease and Parkinson's plus syndromes) as well as some head and neck cancers. This is usually as a result of impaired swallowing ability, however excess saliva production can also be a feature contributing to the overall clinical picture[13]. Sialorrhea can be socially debilitating, cause skin excoriation, affect oral intake and place a patient at increased risk of aspiration and respiratory complications, overall creating significant burden and an impact on QOL[14,15].

Management involves behavioural and non-pharmacological intervention initially, which can then be followed by pharmacotherapy. In general, management is a delicate balance between reducing the volume of secretion produced, but avoiding increasing secretion viscosity such that clearance becomes an added challenge. A multi-disciplinary approach to both assessment and management of sialorrhea is important.

Non-pharmacological management options

- Involvement of allied health professionals including SLT, PT and OT as appropriate.
- Skin care/management of excoriation secondary to sialorrhea.
- Suctioning (potentially self-administrated for some patients).
- Positioning to allow drainage/prevent pooling.

Pharmacological management options

Anticholinergic medications are used for their "drying" effect, however the dose of medication required to control symptoms may cause intolerable side effects, particularly in frail patients. Some patients may also continue to experience unmanageable sialorrhea despite maximal pharmacotherapy[13]. There is no robust evidence for the use of anticholinergics, however the medications outlined below[16,17] are often trialled in the management of sialorrhea.

DRUG	DOSING OPTIONS	COMMENTS
Tricyclic antidepressants (nortriptyline)	10-50mg nocte	Sedating at higher doses, risk of confusion and other anticholinergic side effects.
Hyoscine butylbromide (Buscopan)	As per above table	PO generally ineffective due to bioavailability
Glycopyrronium bromide	As per above table	Can be given sub-lingually using injectable formulation
Atropine (1% ophthalmic solution)	1-2 drops sublingual Q2-4H	Short duration of action
Scopolamine (Scopoderm patch)	TTS Q72 hours	Can cause sedation

Interventional management options

Consider when medical management options are ineffective or cause intolerable side effects. A recent systematic review, demonstrated both botulinum and radiation therapies to be effective treatments for sialorrhea in the context of motor neuron disease[14,18]. Radiotherapy may have a longer duration of action than botulinum therapy. Xerostomia is a risk post radiation and botulinum toxin therapy, careful and ongoing assessment for this should occur. In those with poor dentition, risk of xerostomia and dental infections may be higher post treatment.

Botulinum toxin therapy

This is an effective, well tolerated intervention shown to reduce sialorrhea. Duration of effect is around 2 to 4 months, and patients generally benefit from repeat treatment[19,20]. Botulinum toxin therapy is usually undertaken by neurology and/or interventional radiology services, this will differ between sites within New Zealand.

Radiation therapy

Radiation treatment to the parotid and submandibular glands as a means of controlling sialorrhea was first proposed, after radiation treatment to head and neck tumours caused hyposalivation post-treatment[21]. Various treatment options have be explored, in general doses of 20 Gy over 5 fractions, or 8 Gy in a single fraction is used[21,22]. More intensive treatment regimens were found to increase risk of xerostomia, swelling and pain[14].

Management of Bronchorrhea

Bronchorrhea is defined as excess watery fluid (>100mL per day) associated prominently with lung tumours (primary or metastatic disease). However, it can also be associated with non-cancer diagnoses such as tuberculosis, bronchiectasis, chronic asthma or bronchitis[2]. Bronchorrhea can be very distressing for patients, it may also worsen symptoms of cough and dyspnoea. In extreme cases, electrolyte and fluid imbalance can occur. There is limited data available on the management of bronchorrhea in the palliative care setting. Internationally, various pharmacotherapy has been trialled including; indomethacin, corticosteroids, octreotide, tyrosine-kinase inhibitors (gefitinib). The various promised mechanisms of action for these agents are listed in the table below[2, 24,25].

DRUG	PROPOSED MOA
Indomethacin	Inhibition of COX-2 – block prostaglandin production Reduced chloride and glandular secretion – increased sodium absorption through airway mucosa
Corticosteroids	Block glycoprotein & chloride excretion. COX inhibition
Octreotide	Inhibition of pituitary and GI hormones – decrease secretin induced chloride excretion from bronchial epithelial cells
Gefitinib	Inhibition of mucin production in lung tumour cells (may be independent of EGFR status)
Erythromycin	Decreased chloride excretion

When considering pharmacotherapy for bronchorrhea, in the Aotearoa context, a practical application of the limited data available to date, would suggest trial of corticosteroids and/or octreotide is reasonable.

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Appendix

For any comments and feedback, please email us: Email

OVERVIEW

Pruritus is not a common symptom but it can be extremely distressing with an extensive impact on quality of life. The severity of distress caused by failure to recognise the impact of this symptom and appropriately manage it, is significant[1-3]. Pruritus can be very challenging to manage and understanding the underlying causative pathophysiology can be helpful in navigating management options.

PURPOSE

To guide the management of patients experiencing pruritus.

SCOPE

Palliative care specialists/palliative medicine physicians, nurse practitioners, hospice medical officers, palliative care pharmacists.

PATIENT GROUP

Patients with a life-threatening or life-limiting illness.

ABBREVIATIONS

CSCI	continuous subcutaneous infusion
EGF	epidermal growth factor
ERCP	endoscopic retrograde cholangiopancreatography
ESRD	end stage renal disease
GOC	goals of care
HD	haemodialysis
PD	peritoneal dialysis
SC	subcutaneous
PO	per oral
SC	subcutaneous

DEFINITIONS

Pruritus or itch, is an unpleasant sensation which causes the person experiencing it to scratch or rub at the affected area to relieve the sensation[4].

Pathophysiology of pruritus
Understanding the underlying cause for pruritus is a useful starting point for ongoing management. The aetiology of pruritus can be cutaneous, centrally mediated or a mix, depending on the underlying condition.

Useful definitions and examples

Prurioreceptive	Cutaneous origin e.g. reaction to insect bite – histamine-mediated.
Neurogenic	Centrally mediated, effects central inhibitory pathways e.g. pruritus associated with liver or renal failure.
Neuropathic	Damage to the afferent pathway e.g. shingles/post-herpetic, post-stroke, often associated with tingling/burning sensation.

Non-pharmacological options[2,7,8]:

- Avoidance of potential triggers (e.g. cold air, smoke etc)
- Positioning
- Assessment by speech language therapy
- Fan therapy
- Appropriate oral care
- Over the counter "cough drops"/hard boiled sweets etc. (there is no evidence to support this, however a therapeutic trial is unlikely to cause any harm provided there is not a significant financial burden associated with their use).

CLINICAL MANAGEMENT

Understanding the underlying cause(s) can guide management. There are multiple causes for pruritis (and in the individual patient the symptom may be multifactorial). Some common causes found in the palliative care context are listed below:

- Uraemia secondary to ESRD
- Hyperbilirubinaemia
- Cancer-related:
  - Paraneoplastic syndrome; paraneoplastic dermatoses, secondary to paraneoplastic neuropathy
  - Skin involvement; cutaneous tumours
  - Side effect of systemic anti-cancer treatment (particularly EGF inhibitor biologics), post-radiation therapy
- Opioid-induced

Non-drug treatment and topical options:

- Keep skin hydrated with moisturisers and emollients (BD-TDS application)
- Use products that are fragrance and lanolin free, or formulated for sensitive skin
- Avoid soap
- Avoid heat, stay in cool environment
- Wear loose, non-irritating clothing
- Trim fingernails/wear cotton gloves to minimise damage from scratching
- Apply cold compress
- Topical applications e.g. Aqueous cream or Cetomacrogol with menthol (0.5-2%) or phenol 2%)
- Acupuncture may be of benefit

Systemic treatment options

CLINICAL CONTEXT	DRUG	MECHANISM OF ACTION
Hyperbilirubinaemia/cholestasis • Consider ERCP/stenting if appropriate • Consider corticosteroids if intra-hepatic tumours causing ductal compression. • Stop drugs that worsen cholestasis, e.g. flucloxacillin, Augmentin	Paroxetine 5-20 mg mane Sertraline 50-100mg mane Mirtazapine 7.5-15mg nocte Rifampicin 75-150 mg daily Cholestyramine is NOT recommended. *It is generally unpalatable and may cause diarrhoea and malabsorption.*	5-HT_3 reuptake inhibition 5-HT_3 reuptake inhibition 5-HT_2, 5-HT_3, H_1 antagonist Bile acid uptake inhibitor
Uraemia • Uraemic pruritus is essentially neuropathic pain. • May improve with dialysis; but over 50% of dialysed patients report pruritus, prevalence between PD versus HD is variable[5-7]. • Secondary and tertiary hyperparathyroidism associated with ESRD may contribute to pruritus[5]. • Gabapentinoids are effective in relieving itch, no difference in efficacy[8]. • Antidepressants listed, may be useful in management of refractory pruritus[9-12].	Gabapentin 100 mg nocte* (100-300mg after dialysis 3 times weekly) Pregabalin 25 mg nocte* Paroxetine 5-10mg mane Sertraline 50-100mg mane Mirtazapine 7.5-30mg nocte	Impedes c-fibre transmission Impedes c-fibre transmission 5-HT_3 reuptake inhibition 5-HT_3 reuptake inhibition 5-HT_2, 5-HT_3, H_1 antagonist
Opioid-induced • Uncommon outside epidural/intrathecal route[5]. – Opioids may activate serotonin pathways causing itch. • May resolve with opioid rotation. • 5-HT_3 receptor antagonist may reduce severity of opioid induced pruritus (**NB:** *constipation risk*).	Low dose naloxone Ondansetron 4 mg SC/PO TDS	20-40 micrograms SC PRN 5-HT_3 receptor antagonist
Malignancy (solid tumours and haematologic) Antidepressant medications used for pruritus may take up to 2-3 weeks to show clinical benefit[5].	Sertraline 50-100 mg mane Paroxetine 5-10 mg mane Mirtazapine 7.5-30mg nocte[13] Ondansetron 4 mg IV/SC/PO TDS Granisetron 3mg IV/SC over 24 hours[5] *Not funded*	5-HT_3 reuptake inhibition 5-HT_3 reuptake inhibition 5-HT_2, 5-HT_3, H_1 antagonist 5-HT_3 antagonist 5-HT_3 antagonist
Allergy	Antihistamine	H_1 antagonist

* Adjust to eGFR – refer to monograph for detail on dosing and haemodialysis

NB: *Palliative Care Formulary PCF 8 outlines specific guidance on the management of pruritis based on likely aetiology. Guidance is specific to the United Kingdom, therefore some medications or preparations are not available in NZ. This table is included in the appendix for completeness[14].*

Intractable pruritus

In severe cases anxiolytics may be helpful as anxiety and agitation may precipitate or exacerbate perception of pruritus.

Nocte sedation may be helpful if sleep affected;

- Consider sedating antihistamine (if histamine mediated)
- Levomepromazine (Nozinan) 6.25-12.5mg PO/SC nocte

Midazolam may be useful in the context of centrally mediated pruritus.

PROTOCOL
Lidocaine

Consider lidocaine infusion 0.5-1mg/kg/hr subcutaneously[15,16]. See **Subcutaneous Lidocaine Infusion Protocol** for further information on administration.

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APPENDIX

Table 1 Suggested treatment for specific causes of pruritus (UK)[a,b,14]

Condition	*Step 1*	*Step 2*	*Step 3*
Cholestasis[c]	Sertraline 25–100mg once daily **A**[d,15,55]	Rifampicin 150mg once daily–300mg b.d. **A**[55–57]	Naltrexone 12.5–250mg once daily **A**[e,57,58]
Uraemia	If localized, capsaicin cream 0.025–0.075% once daily–q.d.s. **A**[42]	Gabapentin 100–400mg or pregabalin 25–75mg after haemodialysis **A**[f,42]	Doxepin 10mg once daily–b.d. **A**[49–51] *or* Nalfurafine (not UK) 5microgram IV after haemodialysis **A**[42]
Systemic opioids (for spinal opioids, see Chapter 32, p.908)	Stat dose of H_1-antihistamine, e.g. chlorphenamine 4–12mg; if after 2–3h there is definite benefit, prescribe 4mg t.d.s. (for alternatives, see main text below) *or* a less sedative second generation H_1-antihistamine, e.g. cetirizine 10mg once daily/at bedtime[59]	Switch opioid, e.g. morphine → oxycodone[32,60]	Ondansetron 8mg b.d.
Hodgkin's lymphoma	Prednisolone 30–60mg once daily	Cimetidine 800mg/24h[g,61]	Carbamazepine 200mg b.d.[62]
Paraneoplastic, other causes, idiopathic	Sertraline 50–100mg once daily *or* Paroxetine 5–20mg once daily **A**[16]	Mirtazapine 15–30mg at bedtime[63]	Thalidomide (see When all else fails, below)

a. strength of recommendations: grade **A** is based on evidence from ≥1 RCTs, and grade **B** on well-designed non-randomized studies; where no grade is given, the recommendation is based on case reports and/or expert opinion
b. given PO unless stated otherwise
c. in biliary obstruction due to cancer, where bile duct stenting is impossible or unwanted
d. compared with **rifampicin** there are less RCT data for **sertraline**, but efficacy appears similar (see Commentary below); given its tolerability, familiarity and fewer interactions, *PCF* recommends **sertraline** is generally tried first
e. unsuitable for patients who need opioids for pain relief (see Opioid antagonists (therapeutic target within CNS), p.492); for the use of **methylnaltrexone** in cholestasis, see Other options below.
f. although some studies started at the upper end of these dose ranges, to reduce the risk of CNS undesirable effects, it is generally advisable to start at the lower end
g. in various haematological cancers, there are anecdotal reports of enhanced benefit when an H_1 antagonist and an H_2 antagonist are used in combination.

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Version 1.0. July 2023. Review date July 2025

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OVERVIEW

Palliative sedation therapy (PST) is used in the context of refractory or intractable symptom management at the end of life, when all usual means of symptom control have been trialled, are ineffective, not tolerated by the patient (e.g. due to side effects) or are not available in the treating centre[1-3].

NOTE: Sedation is used in palliative care for a variety of reasons:

- Transient sedation for painful or distressing procedures
- Sedation at end of life (EOL) when weaning from ventilatory support
- Sedation in the management of refractory symptoms at the end of life
- Respite sedation
- Crisis sedation in response to an acute EOL event

This guideline will focus primarily on the use sedation for refractory symptoms at EOL.

This guideline is designed to reflect best practice, while the authors appreciate some settings in Aotearoa to not have a palliative care specialist on site, the advice remains to discuss all cases being considered for PST with a palliative care specialist (this may include telephone discussion with specialists at the nearest tertiary centre).

For any comments and feedback, please email us: Email

PURPOSE

To provide guidance on PST in the context of refractory symptom management in palliative care patients.

SCOPE

Palliative care specialists/palliative medicine physicians, nurse practitioners, hospice medical officers, palliative care pharmacists.

PST should be considered an extraordinary measure, utilised by skilled and experienced palliative specialists[4]. It must NOT be initiated without consultation with a palliative specialist (this may require telephone conversation with a palliative specialist at another site). Prescribing for palliative sedation must be done by the palliative specialist OR under direct guidance of a palliative specialist.

PATIENT GROUP

Patients with a life-threatening or life-limiting illness for whom symptoms are refractory to usual standard of care options.

NOTE: *This guideline does not include or suggest any support for the practice of physician assisted dying or euthanasia. Palliative sedation therapy is distinct from euthanasia and assisted dying through intent (control of symptoms) and in the individualised, proportional use of sedating medication[4].*

This guideline does not include crisis sedation for emergency end of life scenarios such as exsanguination or respiratory distress.

ABBREVIATIONS

CSCI	continuous subcutaneous infusion
EOL	end of life
GOC	goals of care
IV	intravenous
MDT	multi-disciplinary team
NFR	not for resuscitation
PST	palliative sedation therapy
RASS-Pal	Richmond agitation-sedation scale (palliative version)
SC	subcutaneous

DEFINITIONS

The following table provides important definitions regarding PST.

Refractory symptoms	(Also "intractable") are symptoms (physical or emotional) for which all other possible treatments have been unsuccessful or are unavailable for symptom management[1,3]. Geography and relative availability of interventions may influence or determine refractoriness .
Existential suffering	Relates to patients facing terminal illness who may or may not have physical symptoms but report distress associated with facing one's own mortality. May present as a sense of meaningless, hopelessness, feeling of being a burden and/or a grief response. Existential suffering is unrelated to a psychiatric or mood disorde[5].
Natural sedation	("drowsiness") that occurs as part of the dying process. Progressive drowsiness/ reduced level of consciousness is an expected part of the normal dying process and is related to hepatic/renal/neurological and other physiological changes leading to coma and death.
Consequential sedation	The unintended but predictable side effect of some medications used for symptom control. May be transient and/or resolved through dose adjustment and/or tolerance. **NB:** *Brief periods (hours) may be used in general management of pain, delirium or dyspnoea. This is not palliative sedation therapy.*
Respite sedation	(Intermittent) the intent is temporary sedation for an agreed time period (usually 24-48 hours) whereby the patient is then awakened. Rationale is two-fold; recognition that patient's ability to tolerate the symptom may improve after a period of rest and that a period of sedation may allow for "resetting" of symptom severity (usually in the context of pain). Consideration of hydration therapy needs to be given.
Palliative Sedation Therapy	(also "terminal sedation" "continuous deep sedation") the intentional lowering of a patients level of consciousness to an agreed level in the final hours or days of a patient's life. The practise involves proportional, titrated and monitored use of sedating medications to relieve suffering related to refractory symptoms. The goal being relief of symptoms until natural death occurs by the underlying disease process[3]. *NB: Palliative sedation therapy does not alter the timing or mechanism of a patient's death. In euthanasia or physician assisted death there is no proportional use of medication as the primary intent is the death of the patient.*
Crisis sedation	Sedation used to rapidly lower a patients level of consciousness in response to an extremely distressing terminal event; haemorrhage, airway obstruction, extreme respiratory distress etc.

CLINICAL MANAGEMENT

Determine Symptoms are Refractory

"A symptom is determined as being refractory (as opposed to difficult to treat) when the clinician perceives that further invasive or non-invasive interventions are either; incapable of providing further relief or associated with excessive or intolerable acute or chronic morbidity and/or unlikely to provide relief within an acceptable timeframe[6]."

Refractory symptoms include (but are not limited to):

- Pain
- Nausea
- Dyspnoea/respiratory distress
- Agitated delirium

Refractory symptoms effect not only the patient but can have significant impact (both short and long term) on family/whānau who are caring for and witnessing their loved one in distress. Inadequate control of distressing symptoms at the end of life is associated with prolonged and complex grief[7,8]. When practicing holistic care, we have a duty of care to both our patients and those most important to them.

Considerations Prior to Implementing PST

Determine if the following criteria are met:

- The patient has refractory symptoms (ideally 2 palliative care specialists should be involved in this decision; at some sites this may require telephone conversation with a palliative specialist at another site, this collaboration is advised to ensure all other management options have been considered.
- An MDT approach is recommend as part of the decision-making and planning process to ensure all health professionals caring for the patient are aware of the rational for and intent of PST
- The patient is terminally ill and near death with no realistic hope of recovery; death is usually anticipated within hours to short days
- The patient has minimal or no oral intake
- A Not for Resuscitation (NFR) order is in place (especially if patient is in a hospital setting)
- The clinicians intent is to relieve refractory symptoms
- The planned degree of sedation is proportionate to the severity of the refractory symptoms
- The patient is fully informed and involved in the decision making (where able). If the patient does not have capacity, consent is gained from an activated enduring power of attorney (EPOA) who is acting in accordance with the patient's values and beliefs. If there is no EPOA, next of kin and immediate family will be included in decision making process.

Key considerations:

- Involve all members of the team caring for the patient:
  - Agree on goals of care, symptom(s) for which PST is being implemented, proportionality of PST
  - Discuss any ethical/moral concerns staff may have
  - All other viable therapeutic options have been discussed, including potential risks/benefits
  - Place of care; PST is usually (but not exclusively) best undertaken in an inpatient environment due to the level of monitoring and nursing care required.

- Ensure the following are addressed/planned for:
  - Timing of sedation initiation
  - Proportionality of sedation; document level of sedation that is being targeted (the Palliative Richmond Agitation-Sedation Score (RASS-Pal) is a useful tool to guide this[6,9]). See appendix of copy of this document.
  - State duration of sedation (if not continuous); state if sedation will be discontinued or reversed at any point and what factors will influence this.
  - Hydration and nutrition; in almost all PST situations artificial hydration and nutrition are inappropriate (and may be harmful), however their use/relevance may be questioned by whānau/family; it is important to explore any concerns the patient or whānau/family may have regarding absence of hydration and nutrition.
  - Elimination; indwelling catheter (IDC) and bowel care is planned for
  - Pressure area monitoring and care is attended to
  - Mouth care/oral hygiene is monitored and attended to
  - Plan for ongoing management of other symptoms (discontinue any medication not needed for symptom control and comfort)
  - Consider how to support family and staff if patient does not die in the expected time frame
  - Address any cultural and/or spiritual needs of patient and whānau/family

Documentation of Decision Making

Ensure the following is documented in the clinical records:

- GOC established and documented (including NFR form signed and in place)
- Rationale used to determine that the symptom is refractory
- Summary of discussion:
  - People involved in decision-making
  - Information provided to aide decision making
  - Record patient's expressed wishes
  - Informed consent given by the patient or activated EPOA
- Summary of the plan:
  - Timing of initiation
  - Target level of sedation (RASS-Pal, if this tool is being used)
  - Medication regime being prescribed for sedation including loading dose (if any) and bolus doses available to assist in maintenance of sedation.
  - Plan for other symptom management
  - Any acute/crisis events that may occur and plan for managing these (including bolus crisis sedation dosing etc).

See appendix – PST checklist

Initiating, Assessment and Ongoing care

- Initiating sedation can be an emotional event for family and staff, particularly if level of consciousness is lowered rapidly.
  - Ensure conversations regarding what to expect are had with patient (if appropriate) whānau/family and staff and document these conversations in the clinical notes.
- Continue regular assessment and management of other symptoms, ensure clear documentation of this in the clinical notes.
- Monitor sedation on a regular basis to ensure goal of symptom relief and sedation level remains appropriate.

Pharmacological Options for Initiation and Maintenance of PST[6,10-12]

Note: In addition to PST, the ongoing management of pain and other symptoms must continue as part of the overall management plan.

DRUG	INITIATION	MAINTENANCE	CONSIDERATIONS
Midazolam	5-10mg SC Q30 minutes	CSCI 30-100mg over 24 hours Make PRN doses available	Tachyphylaxis Paradoxical response (older adults)
Levomepromazine	12.5-25mg SC Q30 minutes	CSCI 25-300mg over 24 hours Make PRN doses available	Risk of extrapyramidal effects at higher doses may limit dosing Can reduce seizure threshold
Phenobarbitone	Loading dose 200mg SC* or IM	CSCI 400-2000mg over 24 hours	Multiple drug interactions Skin irritation
Dexmedetomidine	See specific **Dexmedetomidine Protocol** **NB:** *patients are generally rousable when using dexmedetomidine, if deep sedation required, use alternate drug.*		
Propofol	See specific **Propofol Protocol**		

PROTOCOL
Dexmedetomidine

NB: *more than one sedative agent may be required*
** phenobarbitone can cause irritation and skin necrosis; 1:1 dilution with WFI or sodium chloride 0.9% is recommended for SC bolus injection[10].*

What to do if patients wakes or is not adequately sedated?

- Are indications for PST still present?
- Ensure delivery device is working correctly
- Check SC line sites for extravasation and signs of inflammation which could impact drug delivery
- Titrate bolus doses and background sedation to desired sedation level

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APPENDIX

Palliative Sedation Therapy Documentation Checklist

Purpose

- To be completed by the Palliative Specialist initiating PST
- Palliative Specialist initiating PST should, ideally, have discussed the case with a second Palliative Specialist (both agreeing the symptoms are refractory)
- To ensure the safe and effective delivery of PST for the management of refractory symptoms.

Checklist

The following should be clearly documented in the patients clinical notes:

- ☐ The Palliative Specialist responsible and the 2nd Palliative Specialist, with whom the case has been discussed
- ☐ Clinical indication for PST (i.e.. the refractory symptom(s) being managed)
- ☐ Brief description of the attempts made to control symptoms prior to the decision to initiate PST
- ☐ Likely prognosis (e.g. hours, days)
- ☐ The presence of a Not For Resuscitation order
- ☐ Details of the discussion had with family/whānau and/or patient
- ☐ Details of the PST:
  - ☐ Timing – when PST is to be initiated
  - ☐ Medication(s) being used for PST including use of loading dose (if used)
  - ☐ The target level of sedation. (RASS-Pal level if using this system)
  - ☐ Frequency of medical assessment until level of sedation is achieved
  - ☐ Clear plan for inadequate sedation (role of bolus medication and/or infusion titration). Specifically state drug, dose, frequency etc.
  - ☐ Role of crisis medications – documentation of medications and indication for use
  - ☐ Clear instructions on medical staff contact and phone number (e.g. SMO on call)
  - ☐ Management of elimination (e.g. presence of indwelling urinary catheter)
  - ☐ Management of hydration. This may just be stating “artificial hydration is not appropriate”
  - ☐ Other symptoms (current or potential) requiring management and how this will be managed

Richmond Agitation Sedation Scale – Palliative Version (RASS-PAL)

SCORE	TERM	DESCRIPTION
+4	Combative	Overtly combative, violent, immediate danger to staff, (e.g., throwing items): + / - attempting to get out of bed or chair
+3	Very Agitated	Pulls or removes lines (e.g. IV / SC / Oxygen tubing) or catheter(s); aggressive, + / - attempting to get out of bed or chair
+2	Agitated	Frequent non-purposeful movement, + / - attempting to get out of bed or chair
+1	Restless	Occasional non-purposeful movement, but movements are not aggressive or vigorous
0	Alert and Calm	
-1	Drowsy	Not fully alert but has sustained awakening (eye-opening / eye contact) to voice for 10 seconds or longer.
-2	Light Sedation	Briefly awakens with eye contact to voice for less than 10 seconds
-3	Moderate Sedation (common goal)	Any movement (eye of body) or eye opening to voice, but no eye contact
-4	Deep Sedation	No response to voice but any movement (eye or body) or eye opening to stimulation by light touch
-5	Not rousable	No response to voice or stimulation by light touch

TOOL NOTES
• The Richmond Agitation-Sedation Scale – Palliative Version (RASS-PAL) is a valid and reliable assessment tool to assess the person's level of sedation during Palliative Sedation Therapy (PST)[i].
• Unlike the original RASS, the RASS-PAL does not require eliciting a response using painful or startling stimuli;
• The aim of palliative sedation is to provide symptom relief with the lightest possible level of sedation necessary and / or as per the identified goals.
• Use of a standardized tool to assess level of sedation improves monitoring, communication and documentation in PST, see procedure on reverse."

SCORE	PROCEDURE FOR RASS-PAL
0 to +4	1. Observe patient for 20 seconds a. Patient is alert, restless or agitated for more than 10 seconds. Note if the patient is alert, restless or agitated for less than 10 seconds and is otherwise drowsy, then score patient according to your assessment for the majority of the observation period.
-1 **-2** **-3**	2. If not alert, greet patient, call by name and say "open your eyes and look at me". a. Patient awakens with sustained eye opening and eye contact **(10 seconds or longer)**. b. Patient awakens with eye opening and eye contact, but not sustained **(less than 10 seconds)**. c. Patient has any eye or body movement in response to voice but no eye contact
-4 **-5**	3. When no response to verbal stimulation, physically stimulate patient by light touch, e.g., gently shake shoulder a. Patient has any eye or body movement to gentle physical stimulation b. Patient has no response to any stimulation

i Bush SH, Grassau, PA, Yarmo MN, Zhang T, Xinkie SJ, Pereira JL (2014). *The Richmond Agitation-Sedation Scale modified for palliative care inpatients (RASS- PAL): a pilot study exploring validity and feasibility in clinical practice*. BMC Palliative Care,13:17 1186/1472-684X-13-17.

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Aotearoa Specialist Adult Palliative Care Guidelines.
Guideline: Seizure Management in Palliative Care.
Version 1.0. July 2023

OVERVIEW

Seizures occur in 10-15% of people with a palliative diagnosis and seizure activity at the end of life can be distressing for patients and family/whānau.

This guideline is designed to provide advice on the management of patients who have a known seizure disorder in addition to their life-limiting illness, or who develop seizure activity as a result of their underlying disease process.

PURPOSE

To provide guidance in the management of seizure activity for those with palliative care needs.

SCOPE

Palliative care specialists/palliative medicine physicians, nurse practitioners, hospice medical officers, palliative care pharmacists.

PATIENT GROUP

Patients with a life-threatening or life-limiting illness who experience seizure activity as a feature of their underlying disease or who have a history of seizure disorder in addition to their palliative diagnosis.

ABBREVIATIONS

AED	anti-epileptic drugs
CNS	central nervous system
CSCI	continuous subcutaneous infusion
GOC	goals of care
ICP	intracranial pressure
PPI	proton pump inhibitor
SC	subcutaneous
SSRI	selective serotonin reuptake inhibitors

CLINICAL MANAGEMENT

Common causes of seizure activity:

Central nervous system	• Raised ICP due to primary or secondary disease • Encephalopathy • Hypoxia • Radiation induced oedema
Metabolic	• Hypoglycaemia • Uraemia • Electrolyte abnormalities
Drugs	• Medication that lowers seizure threshold e.g. – Tramadol – SSRI's – Antipsychotics e.g. levomepromazine, haloperidol • Toxicity – opioid-induced neurotoxicity – Withdrawal e.g. alcohol, benzodiazepines
Known seizure disorder	• Abrupt cessation of AED's e.g. loss of oral route.

Pharmacological management options:
Management of seizure activity should focus on identifying and treating the underlying cause, as appropriate (as per patient's GOC). A plan should be in place for seizure prevention and for treatment of acute seizure activity[1,2].

In the setting where treatment or reversal of the underlying cause of seizure activity is not possible, or is inappropriate within the patients GOC, management and prevention of seizures is important. If the patient is already taking an oral AED this should be continued for as long as the oral route remains viable.

A plan should be made for seizure prevention if and when the patient is unable to swallow oral AED's. Traditionally an infusion of midazolam (or BD clonazepam) has been used for seizure prophylaxis in patients who are no longer able to take AED's[3]. While this generally provides good seizure control, the dose required is often sedating which (if the patient is not in the final hours to days of life) may not be acceptable to the patient or whānau/family[4].

Seizure prophylaxis and maintenance:
It is important to note that AEDs do not need to be commenced in patients with intracranial disease who have not had any seizure activity. Seizure prophylaxis refers to the prevention of further seizure activity after initial seizure.

Corticosteroids
If seizure activity is due to peritumoral oedema or raised intracranial pressure, reduction in swelling may help to prevent seizures. Corticosteroids should be maintained at the lowest dose needed to control symptoms and a plan for weaning/monitoring for side effects is recommended on initiation of any corticosteroid therapy (Corticosteroid use in palliative care guideline to follow). However, some patients may require maintenance steroid therapy. Initiation of regular AEDs is also usually required in addition to steroid therapy. Corticosteroids should be prescribed with a PPI for gastric protection in patients at increased risk of gastric irritation/bleeding.

PROTOCOL
Levetiracetam

Levetiracetam
This is a commonly used AED in the palliative setting[5] due to its tolerability and rapid titratability. There is evidence for the use of subcutaneous levetiracetam in the palliative setting via CSCI when the oral route is lost[3]. The conversion ratio between PO:SC is 1:1 and doses of 500 – 3000mg mg CSCI over 24 hours have been used safely in the palliative care setting[5-8]. (See **Levetiracetam Protocol**).

NB: *Depending on dose, two syringe drivers may need to be used to account for solution volume.*

There is limited compatibility data available[3].

Sodium valproate
Less commonly used in the palliative care setting due to pharmacokinetics, drug interactions and side effect profile. The most likely scenario for the use of SC sodium valproate is in the context of a patient already maintained on it orally, who suddenly loses their oral route. Sodium valproate can be safely administered via CSCI, with a dosing range of 400-2500mg over 24 hours[3,9,10]. A conversion ratio PO:SC of 1:1 is used. There is no known compatibility data, therefore a separate syringe should be used[3]. Depending on dose, two syringe drivers may need to be used to account for solution volume and it is recommended that two syringe drivers be used with higher doses (>2000mg) to allow for more dilution[3].

Use sodium chloride 0.9% or water for injection to volume in 30mL syringe.

Benzodiazepines
Benzodiazepines have been traditionally used in the context of seizure prophylaxis in patients who are no longer able to take oral AEDs, however, the doses required may cause sedation.

Midazolam 20-30 mg via CSCI over 24 hours is a usual starting dose for seizure prophylaxis but may need titration to control seizure activity over time[3].

NB: *consider lower starting dose for frail elderly.*

Clonazepam 0.5-1 mg SL BD is a reasonable starting dose for seizure prophylaxis (injectable clonazepam is no longer available in New Zealand).

Phenobarbital
Phenobarbital depresses CNS activity and can be used to control seizure activity unresponsive to other AEDs. It is a CYP3A4, CYP2C9, CYP2C19 inducer and can reduce the plasma concentration of multiple drugs (see appendix). Enzyme induction takes 3-5 days to be clinically meaningful. Phenobarbital can be given orally (tablet and liquid preparations available), SC or IV (can be administered IM as a last resort, generally avoid due to pain). A loading dose of 10-15mg/kg (up to 1g) IV (if IV access is available) is recommended prior to initiating infusion.

SC bolus administration; 200mg (1mL injectable 200mg/mL solution) diluted with sodium chloride 0.9% or WFI to 4mL and injected via SC line slowly over 2-5 minutes. Can use >1 site to administer multiple boluses.

NB: *Martindale brand phenobarbital can be administered via SC bolus undiluted (see:* https://www.medicines.org.uk/emc/product/3607/smpc#gref*)*

CSCI of phenobarbital (100-400mg over 24 hours) can be initiated following loading dose.

Termination of acute seizure:
Midazolam 5-10mg SC every 10 minutes as required to terminate seizure.
If seizure persists after 3 doses consider use of phenobarbital bolus (200mg)

In the home setting the use of buccal midazolam (use injectable solution) 10mg buccally may be preferable to subcutaneous midazolam (easier for family to administer). Rectal diazepam (Stesolid) 10-20mg is another alternative.

For patients at risk of seizure activity, midazolam should be prescribed pre-emptively and available in the care setting should seizure activity occur.

Medications that lower seizure threshold:
There are multiple medications which can lower seizure threshold and their use in patients with known seizure disorders should be used after weighing up the risk-benefit profile to the individual patient.

Antipsychotic medications are known to be epileptogenic, with second generation anti-psychotics (olanzapine, clozapine, quetiapine) holding a higher epileptogenic risk that first generation antipsychotics (levomepromazine and haloperidol)[11,12].

Drugs which have a serotonergic effect can also lower seizure threshold (e.g. tramadol, SSRIs).

Polypharmacy is a common feature in the management of patients with palliative diagnoses. As such, the cumulative effect of medications on seizure threshold should also be taken into consideration when prescribing in patients with known seizure disorders.

AUDIT INDICATORS

1. Appropriate cessation of medications that may lower seizure thresholds
2. Documented review of correctable factors e.g. electrolyte disturbance, opioid or local anaesthetic toxicity
3. Documentation of recent alcohol or benzodiazepine showing awareness of withdrawal syndromes
4. Appropriate seizure prophylaxis if oral route is unavailable for usual medications
5. Appropriate prn medications charted or available to treat seizures

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APPENDIX

The table below shows common inhibitors and inducers by CYP450 enzyme, so doses can be adjusted in the presence of these drugs. It is not an exhaustive list.

	CYP3A4	CYP2D6	CYP2C8/9	CYP2C19	CYP1A2
Strong inhibitor	Aprepitant Clarithromycin Erythromycin Grapefruit juice* Itraconazole Ketoconazole Voriconazole	Buproprion Fluoxetine Paroxetine Perhexiline	Fluconazole	Fluconazole	Ciprofloxacin
Moderate inhibitor	Amiodarone Ciclosporin Ciprofloxacin Diltiazem Fluconazole Verapamil	Haloperidol Levomepromazine	Amiodarone Ketoconazole Voriconazole	Clarithromycin Fluoxetine Ketoconazole Lansoprazole Omeprazole Pantoprazole	Amiodarone Ketoconazole
Strong inducer	Carbamazepine Phenytoin Rifampicin St John's wort	There no CYP2D6 inducers	Phenobarbitone Phenytoin Rifampicin	Carbamazepine Phenytoin Rifampicin St John's wort	Phenobarbitone Phenytoin Rifampicin Smoking

*only affects intestinal CYP3A4; can increase bioavailability of oral CYP3A4 substrates but does not affect clearance or drugs given SC/IV.

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Monographs

Definitions & Abbreviations

ADR	Adverse drug reaction
AKPS	Australian Karnofsky Performance Status
BD	Twice daily
BSA	Body surface area
Caution	There is additional risk of harm, consideration should be given to additional monitoring or dose-adjustment or an alternative used.
Contraindication	There is a very high risk of harm, use is justifiable only in exceptional circumstances.
CSCI	Continuous subcutaneous infusion
CYP	Cytochrome P450
IM	Intramuscular
IV	Intravenous
NZ	New Zealand (Aotearoa)
PRN	As required
q1h, q2h, etc.	Every 1 hour, every 2 hours, etc.
SC	Subcutaneous
TDS	Three times daily
QTc	Corrected QT-interval on ECG

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Monographs

Amitriptyline

PHARMACOLOGY	
Mechanism of action:	Poorly understood. The antidepressant effects are likely to be mainly through inhibition of noradrenaline and serotonin reuptake (increasing their synaptic effects). The analgesic effects may be also be through noradrenaline and serotonin pathways but also the opioid agonism, α-adrenoceptor blockade, and ion channel blockade to reduce neurotransmission. A significant proportion of the effect is through the metabolite **Nortriptyline**.
Oral bioavailability:	50%.
Half-life:	15 hours (**Nortriptyline** is 30 hours).
Clearance:	Main pathway is metabolism to **Nortriptyline** by CYP2C19 and CYP2C8/9. Negligible renal clearance.
CLINICAL USE	
Indications:	Neuropathic pain; depression.
Cautions / contraindications:	Recent MI or current heart block (contraindication); urinary retention without urinary catheter *in situ* (contraindication); angle-closure glaucoma (contraindication); epilepsy (caution); bipolar disorder (caution, cease in manic phase); suicidal ideation (high mortality in overdose).
ADRs:	Anticholinergic (constipation, dry mouth, blurred vision, photophobia, urinary retention, tachycardia, confusion, delirium); sedation; postural hypotension; weight gain (even over weeks); sweating (rare); QT-prolongation; reduced seizure threshold.
Interactions:	Serotonin syndrome with other serotonergic drugs; QT-prolonging drugs; monoamine oxidase inhibitors (contraindicated).
Available routes:	Oral (may be able to be crushed, see notes).
Dosing:	*Pain:* 10mg at night, titrated to 25-50mg daily. 10mg is usually ineffective and used to test tolerability. Maximum for pain is 75-100mg daily but this is rarely tolerated in palliative patients.
Funding:	Fully funded.
Notes:	• Higher doses are used for depression, but are not usually tolerated in palliative patients. The analgesic doses are unlikely to confer any benefit on mood. • **Nortriptyline** is often preferred to amitriptyline due to less anticholinergic effect in vitro, although the clinical difference in studies appears small, and reduced mortality in overdose. • Amitriptyline and **Nortriptyline** plasma levels can be measured, but there is no therapeutic range established for analgesia. They may be useful in confirming concordance or toxicity. • Arrow-Amitriptyline brands tablets are film coated. There are no data on crushing available but they may be able to be crushed.

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Monographs

Cannabidiol (CBD)

PHARMACOLOGY	
Mechanism of action:	Not well understood. Antagonist of cannabinoid receptors CB1 and CB2 but interacts with multiple other systems.
Oral bioavailability:	5-10%. Inhaled bioavailability is 10-30%, sublingual is 10-15%.
Half-life:	24 hours.
Clearance:	Metabolism by CYP2C19 and CYP2C9 (major) and CYP3A4 (minor). One active metabolite which is metabolised by unknown mechanism. Negligible renal clearance.
CLINICAL USE	
Indications:	Adjunct antiepileptic; spasms in MS (combined with THC); anxiety (experimental, not definitive phase III trials).
Cautions / contraindications:	No specific cautions/contraindications.
ADRs:	Sedation; diarrhoea; anorexia; hepatotoxicity; rash; pyrexia.
Interactions:	Not well understood; likely inhibits CYP2C19, potentially several other enzymes but probably does not inhibit CYP3A4. Does **not** block the "high" from **THC** and increased driving impairment when combined with **THC**.
Available routes:	Oral, sublingual.
Dosing:	*MS spasms:* Approved indication in NZ when combined with THC as Sativex. Dose starts at 1 spray per day, titrated to 6 sprays twice daily. *Epilepsy:* No adult dosing regimen has been established. Trials for paediatric epilepsy syndromes used 2.5mg/kg/day to 30mg/kg/day (given once or twice daily) and some trials included some adult patients. Specialists often use lower doses clinically.
Funding:	Unfunded (hospital or community).
Notes:	• CBD does not require ministerial approval under the NZ Medicinal Cannabis Scheme provided the prescribed product meets Ministry of Health quality standards. • The Ministry of Health recommends CBD should be prescribed by both brand and generic name and include the amount of **THC** (if any). • There is no evidence for CBD for pain, despite widespread marketing claims. • CBD does not appear to be addictive or cause a withdrawal phenomenon.

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Monographs

Celecoxib

PHARMACOLOGY	
Mechanism of action:	COX-2 selective non-steroidal anti-inflammatory drug (NSAID). COX-2 selective NSAIDs have similar analgesic effect to traditional NSAIDs without affecting platelet function.
Oral bioavailability:	Unknown. Absorption is slow, with a peak effect after 3 hours.
Half-life:	11 hours.
Clearance:	Metabolised to inactive metabolites by CYP2C9. Negligible renal clearance.
CLINICAL USE	
Indications:	Pain - particularly visceral, inflammatory, pleuritic.
Cautions / contraindications:	Severe heart failure (contraindication); active peptic ulcer disease (contraindication); severe renal impairment and not on dialysis (contraindication); NSAID-induced asthma (contraindication). Mild or moderate renal impairment (caution); previous peptic ulceration (caution); cardiovascular disease (caution, see notes).
ADRs:	Acute kidney injury; nausea, vomiting; oedema; dyspepsia; peptic ulceration (but not intestinal); myocardial infarction (very rare). Does not impair clotting.
Interactions:	Glucocorticoids (increases risk of peptic ulceration); antiplatelets/anticoagulants (increased bleeding from peptic ulceration although non-GI bleeding rates not affected); nephrotoxics, particularly loop diuretics (increases risk of acute kidney injury). Celecoxib is a weak inhibitor of CYP2D6.
Available routes:	Oral (if needed, Celecoxib Teva brand capsules may be opened and contents sprinkled on food or administered down a PEG/NG tube).
Dosing:	100-200mg twice daily. Maximum of 400mg per day. Can take 3 hours to reach peak effect so less effective PRN.
Funding:	Fully funded.
Notes:	• COX-2 inhibitors are associated with higher rates of cardiovascular events than traditional NSAIDs, especially naproxen. However, the absolute rate is around 3 myocardial infarctions per 1000 patients per year and usually not a significant contraindication or caution in palliative care. • Gastroprotection with a proton-pump inhibitor or H2 antagonist should be considered for patients taking COX-2 selective NSAIDs and with additional risk factors for peptic ulceration. The risk of peptic ulceration is lower than traditional NSAIDs and similar to that of glucocorticoids. • Celecoxib is the only community funded COX-2 selective NSAID in Aotearoa/New Zealand.

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Monographs

Clonidine

PHARMACOLOGY	
Mechanism of action:	Partial agonist of α2-adrenoceptors. Clonidine affects central α2 receptors more than peripheral at lower doses. The analgesic effect is thought to be from inhibition of α2 receptors in the dorsal horn.
Oral bioavailability:	90-100%.
Half-life:	12 hours.
Clearance:	Renal (60%), 20-30% metabolised by CYP2D6 to inactive metabolites.
CLINICAL USE	
Indications:	Adjuvant analgesic for refractory pain; secondary anxiolysis when used as an analgesic.
Cautions / contraindications:	2nd or 3rd degree AV block without pacemaker *in situ* (contraindication); Raynaud's syndrome or peripheral vascular disease (caution, may reduce peripheral perfusion); MRI (remove patches prior to MRI).
ADRs:	Constipation; dry mouth; confusion, hallucinations; sedation; postural hypotension; depression; poor sleep; AV block (rare, particularly at analgesic doses).
Interactions:	
Available routes:	Oral, subcutaneous, intravenous, transdermal, intrathecal.
Dosing:	Initially 50mcg day given as 25mcg BD, but alternatively a 100mcg/24h patch can be used in patients with less concern over adverse reactions. TDS dosing is not necessary due to the long half-life and slow absorption (peak concentrations reached after 2-3 hours). Maximum dose is 300mcg per day.
Funding:	Fully funded (including oral tablets, patches and solution for injection).
Notes:	• Adverse reactions are common and often prohibitive in palliative care. Use the lowest possible starting dose and monitor carefully. • Withdrawal reactions are possible; consider a taper over several days if ceasing higher doses.

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Monographs

Dexmedetomidine

PHARMACOLOGY	
Mechanism of action:	Full α-2 adrenoceptor agonist, affecting the α-2B subtype at lower doses (causing tachycardia and hypertension) and α-2A and α-2C at higher doses (causing net bradycardia and hypotension).
Oral bioavailability:	15%. Buccal bioavailability is 70-90%; intranasal is 35-90%.
Half-life:	2-3 hours.
Clearance:	Mainly through CYP2A6, with minor contributions from non-CYP enzyme UGT2B10 and UGT1A4. No active metabolites and negligible renal clearance.
CLINICAL USE	
Indications:	Complex pain; sedation.
Cautions / contraindications:	2nd or 3rd degree heart block (unless pacemaker fitted); significant hypotension; unstable cardiovascular or cerebrovascular disease.
ADRs:	Dry mouth; nausea, vomiting; tachycardia, hypertension (low doses, usually transient at start of infusion); bradycardia, hypotension (dominant cardiovascular effect, attenuated by SC dosing).
Interactions:	Drugs which can cause AV block (diltiazem, beta blockers). When effective, can cause opioid narcosis when used for pain in patients taking opioids.
Available routes:	Intravenous, subcutaneous, buccal, intranasal.
Dosing:	Starting dose is 0.2 mcg/kg/hr, titrated to a maximum dose of 1.4 mcg/kg/hr. Dexmedetomidine has a ceiling effect, with doses above that unlikely to be beneficial.
Funding:	Only funded for hospital use.
Notes:	• Dexmedetomidine is usually used in palliative care as a SC infusion (see **Dexmedetomidine Protocol**). • Studies have used boluses of dexmedetomidine IV, intranasally and buccally. • Dexmedetomidine is associated with tolerance with prolonged use. • Withdrawal is possible with abrupt cessation; wean if ceasing after prolonged use.

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Monographs

Fentanyl

PHARMACOLOGY	
Mechanism of action:	Potent μ-opioid receptor agonist, more selective for μ than other opioids.
Oral bioavailability:	<30%, not used orally due to poor bioavailability. Nasal bioavailability 80-90%.
Half-life:	3 hours.
Clearance:	CYP3A4 to inactive metabolites. Negligible renal clearance.
CLINICAL USE	
Indications:	Moderate to severe pain in patients with moderate/severe renal impairment; opioid-sensitive pain as second- or third-line opioid; breathlessness in patients with severe renal impairment (limited evidence).
Cautions / contraindications:	Substance misuse disorder (caution). Pyrexia (caution, see notes).
ADRs:	See opioid section under **Morphine**. May be less constipating, in part because it is given parenterally.
Interactions:	Subcutaneous, transdermal, intravenous, sublingual, nasal. Oromucosal formulations are used extensively overseas but not available in NZ/Aotearoa.
Available routes:	Intravenous, subcutaneous, buccal, intranasal.
Dosing:	*Pain:* Starting doses for moderate pain are 12.5-25mcg q1-2h SC/IV PRN. Higher doses may be needed for acute pain. Fentanyl patches are not usually used at doses over 6.25mcg/hr in opioid naïve patients, and not in acute pain. There is no agreed maximum dose, but total daily doses over 3000mcg are uncommon and may be an indication to rotate opioid. *Breathless:* Data are limited. Starting doses are similar to pain, but doses beyond 300-500mcg per day are unlikely to confer additional benefit.
Funding:	Fully funded.

Notes:	• Fentanyl patches take 24-48 hours to reach peak effect, and so are only used in stable pain. For acute titration, a syringe driver is preferred. • After removal of a fentanyl patch it can take 2-3 days for fentanyl to be cleared from the body due to reservoirs under the skin. • When switching from modified-release morphine or oxycodone to a fentanyl patch, the last dose of morphine/oxycodone should be given at the same time as the patch is applied. When switching from a subcutaneous infusion of morphine, oxycodone or fentanyl to a fentanyl patch the infusion should be continued for 6-9 hours after patch application. • Patch manufacturers state that patches should not be occluded or cut. However, dose is directly proportional to the patch area for matrix patches (which are the only currently available patches in Aotearoa/New Zealand). Studies have shown it is safe to half 12.5mcg/hr patches to achieve a lower dose of 6.25mcg/hr. This can be done by cutting the patch in half diagonally, or occluding half and applying a transparent dressing e.g. Opsite™ or Tegaderm™. • Fentanyl patch absorption may be increased by heat. Caution when bathing; do not place heat packs over patches; assess febrile patients for toxicity.

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Monographs

Gabapentin

PHARMACOLOGY	
Mechanism of action:	Reversible blockage of voltage-gated calcium channels which reduces neuronal excitability (sensory nerves which used for analgesia, central when used as an antiepileptic).
Oral bioavailability:	25- 70%. Absorption is via an active transporter, LAT1, which is saturable – bioavailability is 70% for single doses up to 300mg, but then falls to around 25% with doses of 1600mg. This means doses increases have smaller increases in effect than with most drugs.
Half-life:	6 hours.
Clearance:	Renal (>90%).
CLINICAL USE	
Indications:	Neuropathic pain; systemic itch, especially uraemic; restless leg syndrome in renal impairment; antiepileptic.
Cautions / contraindications:	Elderly patients (caution, increased cognitive adverse effects); end-stage renal failure (caution, increased risk of myoclonus), consider dose reduction even after correcting for renal function; substance misuse disorders (caution).
ADRs:	Sedation; cognitive impairment and delirium; dizziness and ataxia; nausea; myoclonus and tremor; dry mouth; very rarely it has been associated with risk of suicidal thoughts and behaviours.
Interactions:	Drugs which slow gastric transit can increase bioavailability (e.g. morphine increases bioavailability by 50%).
Available routes:	Oral (capsules can be opened – see notes).
Dosing:	*Pain:* Starting doses are typically 100-300mg per day, with a maximum of 3600mg per day. Doses are usually given q12h initially, but then q8h from 900mg per day to maximise bioavailability. Evidence of efficacy is limited to doses over 900mg per day. *Restless legs / itch:* When used for itch or restless legs in renal impairment, starting doses are 100mg daily if eGFR is 15-30 ml/min, and 100mg alternate days for eGFR 0-15 ml/min. Maximum dose is 100-200mg per day and this can be once daily. When used for restless legs or itch outside of renal impairment there is limited data, similar dosing to pain is reasonable.
Funding:	Fully funded.

GABAPENTIN CONTINUED

Notes:	• Gabapentin is a weak antiepileptic and rarely used in this context now. • Can cause withdrawal with abrupt cessation, wean over at least one week after prolonged, high dose use. • Haemodialysis reduces plasma concentrations by 50%. • The conversion between gabapentin and **Pregabalin** depends on the dose because of the inconsistent bioavailability of gabapentin. See **Neuropathic Pain Guideline**. • Nupentin brand capsules can be opened and contents added to food if needed. The contents have an unpleasant taste, and hydrolyse rapidly so should be administered immediately.

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Monographs

Glycopyrronium
(also known as glycopyrrolate)

PHARMACOLOGY	
Mechanism of action:	Antagonist of M2 and M3 muscarinic acetylcholine receptors. Relaxes smooth muscle in the gut, and reduces gastrointestinal tract secretions.
Oral bioavailability:	<10%, due to poor absorption rather than first-pass metabolism.
Half-life:	6 hours.
Clearance:	65% renal, 20% metabolised (variety of enzymes, inactive metabolites) and 15% unchanged in bile.
CLINICAL USE	
Indications:	Oropharyngeal secretions at end of life.
Cautions / contraindications:	Myasthenia gravis (contraindication); urinary retention without urinary catheter *in situ* (contraindication); angle-closure glaucoma (contraindication); tachycardia, coronary artery disease (caution, has very rarely caused acute myocardial infarction in these settings – no risk if oral).
ADRs:	Typical anticholinergic ADRs (constipation, dry mouth, blurred vision, photophobia, urinary retention, tachycardia); very rarely, tachycardia can lead to arrythmia and or acute myocardial infarction.
Interactions:	Anticholinergics (additive effect); may decrease the effectiveness of metoclopramide or domperidone.
Available routes:	Subcutaneous, intravenous, sublingual.
Dosing:	200-400mcg PRN up to hourly. Can also be 400-1600mcg via CSCI. Maximum of 1600mcg per day.
Funding:	Fully funded.
Notes:	• Oral and inhaled formulations available overseas. • Injectable formulation can be given sublingually. Systemic absorption is not expected to occur.

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Monographs

Haloperidol

PHARMACOLOGY	
Mechanism of action:	Antipsychotic which works mainly by antagonising central dopamine receptors.
Oral bioavailability:	70%.
Half-life:	20 hours.
Clearance:	Almost completely metabolised to inactive metabolites, mainly by the non-P450 enzymes UGT2B7 and cytosolic carbonyl reductase but with CYP3A4 as a minor pathway. CYP2D6 is not a clinically significant pathway.
CLINICAL USE	
Indications:	Antiemetic; hiccups; to alleviate symptoms of delirium (with limited evidence).
Cautions / contraindications:	Parkinsonism (contraindication); history of neuroleptic malignant syndrome (contraindication); seizures (caution); QTc >500ms (caution).
ADRs:	Extrapyramidal symptoms (e.g. parkinsonism, dystonia, akathisia); QT prolongation; postural hypotension; reduced seizure threshold; sedation (mainly at doses > 5mg daily).
Interactions:	Drugs which prolong QT (e.g. metoclopramide, ondansetron, levomepromazine, methadone) and reduce seizure threshold (e.g. levomepromazine).
Available routes:	Oral, subcutaneous, intravenous, sublingual.
Dosing:	*Nausea:* Usual starting doses are 0.5-1mg daily, given either BD or once daily. Increasing doses above 3mg is not usually effective for nausea and other agents should be considered. If used PRN, frequency is usually q2-3h. *Hiccups:* Similar doses to nausea are used. *Delirium:* Evidence suggests that low-dose haloperidol is not effective at controlling symptoms of delirium. Doses of over 5mg daily, or in 2mg PRN doses, have been used in some studies. Maximum of 15mg per day.
Funding:	Fully funded.
Notes:	• Use of haloperidol for delirium is contentious. It remains common clinical practice although there is a lack of evidence.

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Monographs

Hyoscine Butylbromide
(also known as scopolamine butylbromide)

PHARMACOLOGY	
Mechanism of action:	Antagonist of M2 and M3 muscarinic acetylcholine receptors. Relaxes smooth muscle in the gut, and reduces gastrointestinal tract secretions.
Oral bioavailability:	<10%, due to poor absorption rather than first-pass metabolism.
Half-life:	5 hours.
Clearance:	50% renal, and 50% metabolised by esters (a family of non-CYP enzymes) to inactive metabolites.
CLINICAL USE	
Indications:	Abdominal spasms; diarrhoea; bowel obstruction; oropharyngeal secretions at end of life (parenteral only); sialorrhoea; bladder spasms (parenteral only).
Cautions / contraindications:	Myasthenia gravis (contraindication); urinary retention without urinary catheter *in situ* (contraindication unless oral only); angle-closure glaucoma (contraindication unless oral only); tachycardia, coronary artery disease (caution, has very rarely caused acute myocardial infarction in these settings – no risk if oral).
ADRs:	Constipation; other typical anticholinergic ADRs (dry mouth, blurred vision, photophobia, urinary retention, tachycardia) are only present with parenteral use; very rarely, tachycardia can lead to arrythmia and or acute myocardial infarction. Sedation, confusion, dizziness, nausea, and delirium are minimal even with parenteral use as hyoscine butylbromide does not cross the blood brain barrier.
Interactions:	Anticholinergics (parenteral use only); may decrease the effectiveness of metoclopramide or domperidone.
Available routes:	Oral, subcutaneous, intravenous.
Dosing:	*All indications:* 10-20mg 2-4 times daily is a usual starting dose. Oral dose reductions are rarely needed as there is minimal systemic absorption. Maximum of 120mg per day (although much higher oral doses have been tolerated in studies, additional benefit is unlikely).
Funding:	Fully funded.
Notes:	• Hyoscine butylbromide and hyoscine hydrobromide sound similar but are different medications. They share the same central structure and anticholinergic activity at a receptor level, but distribute differently in the body. Hyoscine butylbromide has very poor ability to cross gut membrane and the blood-brain-barrier which mitigates central effects; hyoscine hydrobromide crosses skin, gut membrane, and the blood-brain-barrier and causes central anticholinergic effects (sedation, confusion, delirium) but also gains antiemetic properties. • Oral hyoscine butylbromide is negligibly absorbed from the gut. However, it retains full activity in the gut and is a safe way to effectively treat abdominal symptoms and reduce adverse effects. For the same reasons, parenteral use is necessary to treat oropharyngeal or bladder symptoms.

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Monographs

Ketamine

PHARMACOLOGY	
Mechanism of action:	Analgesia is mainly through NMDA receptor antagonism, but ketamine acts on multiple other receptors (opioid, GABA, dopamine, serotonin, sodium channels) but this is of uncertain clinical significance.
Oral bioavailability:	10-30% (ratios of oral:SC conversion are probably between 3:1 and 1:1 due to the active metabolite). Intranasal bioavailability is 40-50%; sublingual is 30-40%; rectal is 30%.
Half-life:	2-4 hours.
Clearance:	Metabolised by CYP3A4 and CYP2B6 to norketamine, which is active. Negligible renal clearance of either active moiety.
CLINICAL USE	
Indications:	Opioid-refractory pain; neuropathic pain; central sensitisation; opioid-induced hyperalgesia; depression (experimental).
Cautions / contraindications:	Substance misuse disorder (caution); history of psychosis (contraindication). Raised ICP is unlikely to be of significance at analgesic doses. Seizures are not a contraindication.
ADRs:	Nausea, vomiting; hallucinations, nightmares, delirium; diplopia, nystagmus; bronchial secretions, bronchospasm; ketamine uropathy (dysuria, frequency, incontinence, haematuria) with prolonged, high dose use; raised ICP (clinical significance uncertain, minimal effect with analgesic doses); deranged LFTs (very rare).
Interactions:	Serotonin syndrome with other serotonergic drugs. When effective, can cause opioid narcosis when used for pain in patients taking opioids.
Available routes:	Oral, subcutaneous, sublingual, intranasal, rectal.
Dosing:	For PRN use, doses of 10-30mg subcutaneously are typically used every 3 hours. Starting dose is 50-100mg per 24 hours via CSCI, titrated to a maximum of 500mg. For 'burst' regimens, a test dose of 10mg is used subcutaneously and then 100-500mg per 24 hours for 3-5 days.
Funding:	Only funded for hospital use.
Notes:	• Benzodiazepines and haloperidol at doses of up to 5mg have been used to treat hallucinations from ketamine. Some protocols recommend prophylactic benzodiazepines or haloperidol; there is only evidence to support the use of benzodiazepines. • Ketamine induced uropathy occurs frequently in people using ketamine recreationally. It can be persistent after cessation in up to half of patients with the syndrome. • The only formulation available in Aotearoa / NZ is liquid for injection. This can be administered orally, sublingually, or intranasally. If administering this orally it should be diluted in juice to mask the taste. • Withdrawal can be problematic after prolonged use; wean slowly if used longer than 3 weeks. • See **Ketamine Protocol** for further dosing and administration advice.

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Monographs

Lidocaine
(previousy known as lignocaine)

PHARMACOLOGY	
Mechanism of action:	Reversibly blocks fast voltage-gated sodium channels, increasing the threshold for action potentials in nerves. It affects sensory nerves at lower concentrations than other nerves, allowing for its systemic use as an analgesic without cardiac arrhythmia.
Oral bioavailability:	35%. Topical 3% (5% lidocaine patch on normal skin).
Half-life:	1-2 hours.
Clearance:	Predominantly CYP1A2, with a minor (30%) contribution from CYP3A4. It is extensively metabolised to active metabolites monoethylglycylxylidide (MEGX) and glycylxylidide (GX) which are also metabolised by CYP1A2. There is negligible renal clearance of lidocaine or its active metabolites.
CLINICAL USE	
Indications:	Opioid refractory pain, neuropathic pain, oropharyngeal pain (oral gel), topically to cutaneous ulcers/fungating tumours.
Cautions / contraindications:	Central and peripheral neuropathies (caution); methaemoglobinaemia or G6PD deficiency (contraindication).
ADRs:	Paraesthesia, tinnitus and dizziness are early sign of toxicity; sedation, nausea and vomiting are later signs of toxicity; bradycardia, hypotension and cardiac arrest occur at higher exposures than used for analgesia.
Interactions:	Smoking induces CYP1A2 (reducing lidocaine exposure). When lidocaine is effective, can cause opioid narcosis when used for pain in patients taking opioids.
Available routes:	Subcutaneous, intravenous, intrathecal, topical.
Dosing:	*Systemic analgesia:* 0.5 to 2 mg/kg/hr over 24 hours via syringe driver. Lower doses are used initially and titrated to response. *Oropharyngeal pain:* 10-15ml of 2% oral gel every 2-3 hours, maximum of 120ml per day. *Cutaneous ulcers/fungating tumours:* 1-2g of EMLA (25mg/g lidocaine and prilocaine) per 10cm^2 has been used for ulcers up to 50cm^2, or 10g for any ulcer under 50cm^2. Systemic absorption is detectable but subclinical. A similar regimen is reasonable for fungating tumours, but systemic exposure has not been measured.
Funding:	1% and 2% lidocaine for injection are fully funded. 2% lidocaine is recommended due to the high volumes needed. 2% oral gel is fully funded.
Notes:	• See **Lidocaine Protocol** for details on systemic administration.

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Monographs

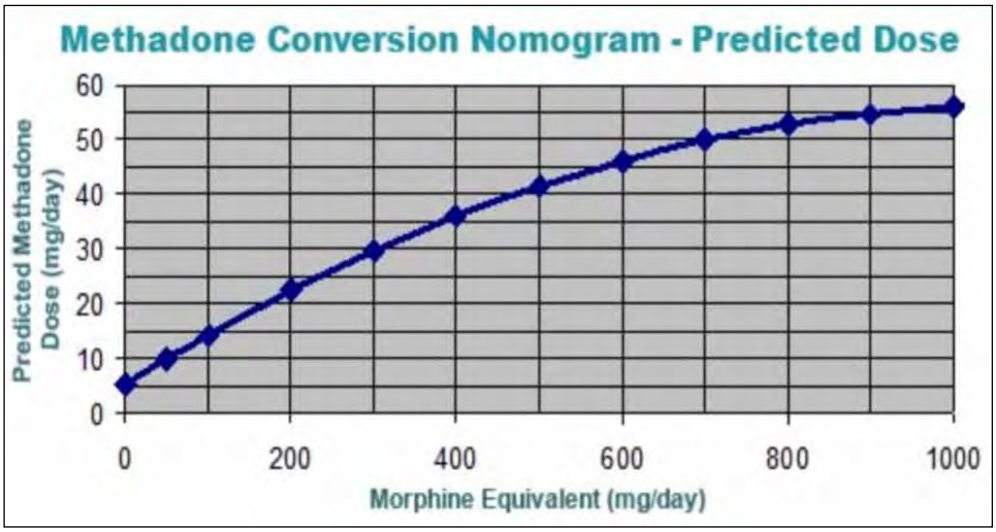
Methadone

PHARMACOLOGY	
Mechanism of action:	Primarily a μ-opioid receptor agonist but with more δ-opioid receptor agonism than other opioids, some NMDA-receptor antagonism at higher doses, and weak serotonin reuptake inhibition.
Oral bioavailability:	85%.
Half-life:	24-36 hours, with significant variability. Methadone distributes widely in tissues but takes hours to do this; 2-6 hours after oral doses there is clinically significantly higher methadone exposure (increasing analgesia and potential for ADRs) not reflected in the half-life which reflects the background concentration (see typical methadone PK profile in 'notes').
Clearance:	Metabolised by CYP3A4 to inactive metabolites.
CLINICAL USE	
Indications:	Complex opioid-sensitive pain refractory to other opioids; neuropathic pain; moderate to severe pain with severe renal impairment; opioid substitution therapy (OST); can be used 'adjuvantly', at a low dose with a primary opioid
Cautions / contraindications:	Substance misuse disorders (caution); QTc > 500ms (caution).
ADRs:	See opioid section under **Morphine**: slightly less constipating than morphine but laxatives should still be routinely co-prescribed; QT prolongation; local irritation can occur with subcutaneous boluses.
Interactions:	Serotonin syndrome with other serotonergic drugs; QT-prolonging drugs. When effective, can cause opioid narcosis when used for pain in patients taking other opioids.
Available routes:	Oral, subcutaneous, intravenous, sublingual.
Dosing:	Regular doses are usually given twice daily, and 2.5mg BD is a typical starting dose. Titrate no more frequently than 3 days in inpatient settings, or 7 days in outpatient settings. No specific maximum dose but doses over 100mg per day are uncommon for pain (higher doses are more common when used for OST). Methadone can be used PRN but with caution due to the long half-life: peak effect is 2-3 hours after oral administration and should be taken no more frequently than q4h and usually only 2-3 doses per day.
Funding:	Fully funded.

METHADONE CONTINUED

Notes:

- The long half-life means steady state is not achieved for 1-2 weeks in many patients; avoid rapid titration.
- ECG monitoring may be appropriate, see **Neuropathic Pain Guideline**.
- Opioid conversion is complex, see **Neuropathic Pain Guideline** and methadone-morphine conversion nomogram below.

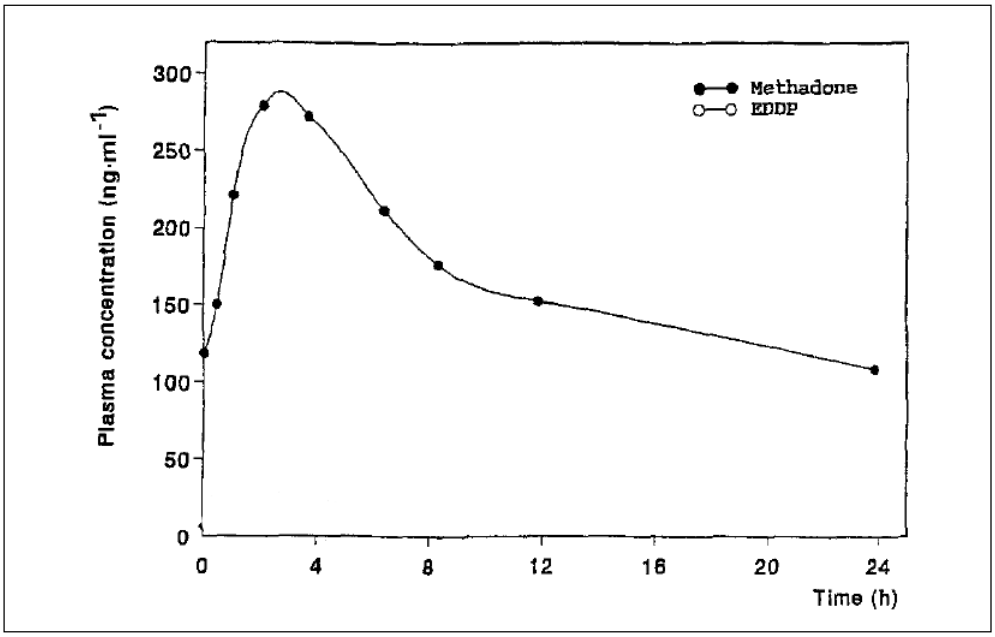


- Toombs JD. Oral methadone dosing for chronic pain. A practitioner's guide. Pain treatment topics 2008. Available from: http://pain-topics.org/ (accessed April 2022).

METHADONE CONTINUED

Notes Continued:

- The half-life quoted assumes methadone has redistributed evenly to peripheral tissues and does not apply to the first few hours (see methadone PK profile image below) when the half-life is much faster. For this reason, methadone can sometimes be used as a PRN analgesic, but with a maximum of 2-3 times daily reflecting the longer half-life after re-distribution.



A typical concentration-time profile for methadone showing the difference between the 'redistribution' phase in the first 8 hours and the later phase after oral administration. Adapted from: de Vos *et al.* Pharmacokinetics of methadone and its primary metabolite in 20 opiate addicts. Eur J Clin Pharmacol. (1995) 48:361-366.

Methadone is most commonly used as background analgesia, when the period after redistribution is most relevant. Historically, methadone has been often been used TDS. However, the long half-life allows once or twice daily administration which has advantages of reducing patient/carer burden, simplifying dosing, adding precision to dosing, and improving concordance.

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Monographs

Mexiletine

PHARMACOLOGY	
Mechanism of action:	Mexiletine is an oral analogue of lidocaine. It reversibly blocks fast voltage-gated sodium channels, decreasing neuronal excitation. It affects sensory nerves at lower concentrations than other nerves, allowing for its systemic use as an analgesic without cardiac arrhythmia.
Oral bioavailability:	90%.
Half-life:	10 hours.
Clearance:	Metabolised by CYP2D6, with some contribution from CYP1A2. Metabolites are inactive.
CLINICAL USE	
Indications:	Opioid refractory pain and neuropathic pain, especially if responsive to lidocaine.
Cautions / contraindications:	Central and peripheral neuropathies (caution); 2nd or 3rd degree heart block unless pacemaker *in situ* (caution); recent seizures (caution).
ADRs:	Nausea and vomiting; abdominal pain; tremor; dizziness and ataxia; fatigue; constipation; taste disturbance, paraesthesia and tinnitus. Haemodynamic effects (hypotension or bradycardia) are rare with oral dosing and analgesic dosing.
Interactions:	Smoking reduces mexiletine exposure.
Available routes:	Oral (Mexiletine Teva brand cannot be crushed or chewed).
Dosing:	150mg BD increasing to a maximum of 900mg per day.
Funding:	Fully funded.
Notes:	• There is limited evidence for mexiletine in palliative care compared to lidocaine. Where possible, lidocaine is preferred initially and mexiletine used in lidocaine-responders (see **Neuropathic Pain Guideline**). Mexiletine may be useful initially in patients with a barrier to inpatient admission.

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Monographs

Morphine

PHARMACOLOGY	
Mechanism of action:	μ-opioid receptor agonist with weak δ-opioid receptor agonism
Oral bioavailability:	30% (despite this an oral:parenteral conversion of 2:1 is usually used in Aotearoa/NZ because the active metabolite morphine-6-glucuronide has analgesia properties).
Half-life:	2-3 hours.
Clearance:	Metabolised by non-CYP450 enzyme UGT2B7 to M-3-G and M-6-G which are both active (both cause toxicity, only M-6-G is analgesic) and renally cleared.
CLINICAL USE	
Indications:	Moderate to severe pain; breathlessness; cough.
Cautions / contraindications:	Substance misuse disorder (caution); moderate renal impairment (GFR 30-50ml/min), use lower doses (caution); severe renal impairment (GFR < 30ml/min, contraindication).
ADRs:	(Common to all opioids) Constipation (around 90% of patients require regular laxatives, weak correlation with dose); nausea; sedation/dizziness; myoclonus; delirium; respiratory depression; pruritis (most common with morphine); urinary retention.
Interactions:	
Available routes:	Oral (unmodified and slow-release preparations available, see notes for crushing slow-release capsules), subcutaneous, intravenous, sublingual, intrathecal, topical (on cutaneous ulcers).
Dosing:	*Pain:* Starting doses for moderate pain are 2.5-5mg q2-4h orally PRN. Subcutaneous or IV doses 50% of the oral dose and usually given q1-2h. Regular morphine can be started at 20-40mg per day for opioid naïve patients with more severe pain and can be given either q4h or BD with a slow-release preparation. For patients on regular opioids the PRN dose is usually 1/5th to 1/6th of the total daily dose. There is no agreed maximum dose, but total daily doses over 500mg are uncommon and may be an indication to rotate opioid. *Breathlessness:* Starting doses are 2.5-5mg q2-4h, but morphine SR 10mg BD can also be started in opioid naïve patients.
Funding:	Fully funded.
Notes:	• Usually considered the first-line opioid in patients with normal renal function. • The m-Eslon brand of slow-release morphine capsules cannot be crushed or chewed. However, they can be opened and the microcapsules sprinkled on food or administered down an NG/PEG tube. The microcapsules can stick to NG/PEG tubes; anecdotally, suspending them in water for injection and twisting the plunger as it is pressed creates a whirlpool which reduces adherence to the tube.

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Nortriptyline

PHARMACOLOGY	
Mechanism of action:	Poorly understood. The antidepressant effects are likely to be mainly through inhibition of noradrenaline and serotonin reuptake (increasing their synaptic effects). The analgesic effects may be also be through noradrenaline and serotonin pathways but also the opioid agonism, α-adrenoceptor blockade, and ion channel blockade to reduce neurotransmission.
Oral bioavailability:	50%.
Half-life:	30 hours.
Clearance:	Metabolism by CYP2D6 to inactive metabolites.
CLINICAL USE	
Indications:	Neuropathic pain; depression.
Cautions / contraindications:	Recent MI or current heart block (contraindication); urinary retention without urinary catheter *in situ* (contraindication); angle-closure glaucoma (contraindication); epilepsy (caution); bipolar disorder (caution, cease in manic phase).
ADRs:	Anticholinergic (constipation, dry mouth, blurred vision, photophobia, urinary retention, tachycardia, confusion, delirium); sedation; postural hypotension; weight gain (even over weeks); sweating (rare); QT-prolongation; reduced seizure threshold.
Interactions:	Serotonin syndrome with other serotonergic drugs; QT-prolonging drugs; monoamine oxidase inhibitors (contraindicated).
Available routes:	Oral (may be able to be crushed, see notes).
Dosing:	*Pain:* 10mg at night, titrated to 25-50mg daily. 10mg is usually ineffective and used to test tolerability. Maximum for pain is 75-100mg daily but this is rarely tolerated in palliative patients.
Funding:	Fully funded.
Notes:	• Higher doses are used for depression, but are not usually tolerated in palliative patients. The analgesic doses are unlikely to confer any benefit on mood. • Nortriptyline plasma levels can be measured, but there is no therapeutic range established for analgesia. They may be useful in confirming concordance or toxicity. • Norpress-Nortriptyline brand tablets are film coated. There are no data on crushing available but they may be able to be crushed.

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Monographs

Octreotide

PHARMACOLOGY	
Mechanism of action:	Synthetic analogue of somatostatin (or growth hormone-inhibiting hormone) with identical mechanism of action. Reduces gastrointestinal secretions.
Oral bioavailability:	<5%.
Half-life:	90 minutes (the indirect mechanism of action means that duration of effect is often longer than would expected from half-life alone).
Clearance:	Mainly metabolised by unknown mechanisms to inactive metabolites. Only 20-30% renal clearance.
CLINICAL USE	
Indications:	Malignant bowel obstruction; neuroendocrine tumours (oncological use only).
Cautions / contraindications:	Diabetes (caution, reduction of hyoglycaemic agents may be required).
ADRs:	Nausea, vomiting; bloating, abdominal pain; diarrhoea; headache; dizziness; hypoglycaemia (rare).
Interactions:	Hypoglycaemic drugs and insulin (reduction may be required).
Available routes:	Subcutaneous, intravenous.
Dosing:	*Bowel obstruction:* 250 – 500 micrograms per day initially, usually by CSCI. SC boluses TDS are also sometimes used. Maximum of 900 micrograms per day.
Funding:	Fully funded.
Notes:	• The standard injectable formulation is used for palliative care; do not confuse with the depot preparation for IM use by oncology or endocrinology. • There are multiple ADRs of octreotide that only appear with persistent use (e.g. hyperglycaemia, thyroid dysfunction, gallstones) which are not relevant with short-term use in palliative care.

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Monographs

Oxycodone

PHARMACOLOGY	
Mechanism of action:	μ-opioid receptor agonist with weak δ-opioid receptor agonism.
Oral bioavailability:	60-70%.
Half-life:	3 hours.
Clearance:	CYP3A4 (approx. 50%) and CYP2D6 (minor, approx. 20%, usually of little clinical significance). Multiple active metabolites which are renally cleared. Renal clearance only 10%, not of clinical significance.
CLINICAL USE	
Indications:	Moderate to severe pain in patients intolerant of morphine or with moderate renal impairment; breathlessness (limited evidence); cough (limited evidence).
Cautions / contraindications:	Substance misuse disorder (caution); severe renal impairment (GFR < 30ml/min, contraindication).
ADRs:	See opioid section under **Morphine**.
Interactions:	
Available routes:	Oral (unmodified and modified-release preparations available), subcutaneous, intravenous, sublingual.
Dosing:	*Pain:* Starting doses for moderate pain are 1-2.5mg q2-4h orally PRN. Subcutaneous or IV doses 60-70% of the oral dose and usually given q1-2h. Regular oxycodone can be started at 5-10mg per day for opioid naïve patients with more severe pain and can be given either q4h (immediate release formulation) or BD (slow-release formulation). For patients on regular opioids the PRN dose is usually 1/5th to 1/6th of the total daily dose. There is no agreed maximum dose, but total daily doses over 500mg are uncommon and may be an indication to rotate opioid. *Breathless / cough:* Data are limited. Starting doses are similar to pain, but there is usually limited benefit from dose escalation beyond 20mg per day.
Funding:	Fully funded.
Notes:	• Oxycodone Sandoz brand modified-release tablets cannot be crushed or chewed. If not able to be swallowed, a CSCI should be considered.

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Monographs

Parecoxib

PHARMACOLOGY	
Mechanism of action:	It is a prodrug for the COX-2 selective non-steroidal anti-inflammatory drug (NSAID) valdecoxib. Valdecoxib has one active metabolite, but it is less potent and quantitatively less than valdecoxib so unlikely to contribute strongly to the drug effect. COX-2 selective NSAIDs have similar analgesic effect to traditional NSAIDs without affecting platelet function.
Oral bioavailability:	Unknown.
Half-life:	20 minutes (valecoxib 7 hours).
Clearance:	Metabolised by hepatic hydrolysis (non-CYP pathway) to valdecoxib. Valdecoxib is mainly metabolised by unknown UGTs (non-CYP enzyme family) to inactive metabolites, with a minor metabolic pathway to an active metabolite (M1) via CYP2C9 and CYP3A4. M1 is metabolised by non-CYP pathways. None of parecoxib, valdecoxib or metabolite M1 have meaningful renal elimination.
CLINICAL USE	
Indications:	Pain – particularly visceral, inflammatory, pleuritic.
Cautions / contraindications:	Severe heart failure (contraindication); active peptic ulcer disease (contraindication); severe renal impairment and not on dialysis (contraindication); NSAID-induced asthma (contraindication). Mild or moderate renal impairment (caution); previous peptic ulceration (caution); cardiovascular disease (caution, see notes).
ADRs:	Acute kidney injury; nausea, vomiting; oedema; dyspepsia; peptic ulceration (but not intestinal); myocardial infarction (very rare). Does not impair clotting.
Interactions:	Glucocorticoids (increases risk of peptic ulceration); antiplatelets/anticoagulants (increased bleeding from peptic ulceration although non-GI bleeding rates not affected); nephrotoxics, particularly loop diuretics (increases risk of acute kidney injury).
Available routes:	Subcutaneous, intravenous, intramuscular.
Dosing:	20-40mg twice daily. Maximum of 80mg per day.
Funding:	Hospital only.
Notes:	• COX-2 inhibitors are associated with higher rates of cardiovascular events than traditional NSAIDs, especially naproxen. However, the absolute rate is around 3 myocardial infarctions per 1000 patients per year and usually not a significant contraindication or caution in palliative care. • Gastroprotection with a proton-pump inhibitor or H2 antagonist should be considered for patients taking COX-2 selective NSAIDs and with additional risk factors for peptic ulceration. The risk of peptic ulceration is lower than traditional NSAIDs and similar to that of glucocorticoids. • Parecoxib is the only subcutaneous NSAID available in Aotearoa/New Zealand. • Valdecoxib is available as a separate drug overseas, but not currently in Aotearoa/New Zealand.

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Monographs

Pregabalin

PHARMACOLOGY	
Mechanism of action:	Reversible blockage of voltage-gated calcium channels which reduces neuronal excitability (sensory nerves which used for analgesia, central when used as an antiepileptic).
Oral bioavailability:	>90%.
Half-life:	6 hours.
Clearance:	Renal (>90%).
CLINICAL USE	
Indications:	Neuropathic pain; systemic itch, especially uraemic; restless leg syndrome in renal impairment; antiepileptic.
Cautions / contraindications:	Elderly patients (caution, increased cognitive adverse effects); end-stage renal failure (caution, increased risk of myoclonus), consider dose reduction even after correcting for renal function; substance misuse disorders (caution).
ADRs:	Sedation; cognitive impairment and delirium; dizziness and ataxia; nausea; myoclonus and tremor; dry mouth; very rarely it has been associated with risk of suicidal thoughts and behaviours.
Interactions:	
Available routes:	Oral (Pregabalin Pfizer brand capsules cannot be opened or crushed – if unable to swallow whole **Gabapentin** could be considered).
Dosing:	*Pain:* Starting doses are typically 25-50mg BD, with a maximum of 300mg BD. Evidence of efficacy is limited to doses over 75-150mg BD (with normal renal function). *Restless legs / itch:* When used for itch or restless legs in renal impairment, starting doses are 25mg once daily (eGFR 15-30 ml/min) or 25mg alternate days (eGFR 0-15 ml/min). Titrate to a maximum of 50-75mg per day. When used for restless legs or itch outside of renal impairment there is limited data, similar dosing to pain is reasonable.
Funding:	Fully funded.
Notes:	• Pregabalin is a weak antiepileptic and rarely used in this context now. • Can cause withdrawal with abrupt cessation, wean over at least one week after prolonged, high dose use. For some patients, weaning can takes weeks or months. • Haemodialysis reduces plasma concentrations by 50%. • The conversion between **Gabapentin** and pregabalin depends on the dose because of the inconsistent bioavailability of gabapentin. See **Neuropathic Pain Guideline**.

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Monographs

Tetrahydrocannabidol (THC, also known as dronabinol)

PHARMACOLOGY	
Mechanism of action:	Presumed to be through partial agonism of cannabinoid receptors CB1 and CB2. However, THC interacts with multiple other systems including dopamine, opioid, and immune systems – the clinical significance of these interactions is not known.
Oral bioavailability:	5-10%. Inhaled bioavailability 10-30%; sublingual and oromucosal expected to be around 5-20% but no studies have accurately quantified it.
Half-life:	24 hours.
Clearance:	Metabolised by CYP2C9, CYP2C19, and CYP3A4 to one active metabolite (11-OH-THC) which is metabolised by glucuronidation (non-CYP pathway) to inactive metabolites. Negligible renal clearance.
CLINICAL USE	
Indications:	Refractory spasms in multiple sclerosis (MS), usually combined with **CBD**; chronic non-cancer pain; chemotherapy-induced nausea and vomiting.
Cautions / contraindications:	Active psychotic, mood or anxiety disorder (contraindication); substance misuse disorder (caution); currently driving (caution).
ADRs:	CNS (hallucinations, "high", dizziness, sedation); mood (anxiety, depression); gastrointestinal (nausea and vomiting (paradoxical as also antiemetic, nausea more at higher doses), cyclical vomiting syndrome, diarrhoea, increased appetite, dry mouth); cardiovascular (tachycardia, hypotension, platelet inhibition); fatigue.
Interactions:	Smoking cannabis inhibits CYP1A2.
Available routes:	Oral, oromucosal spray (combined with **CBD**), sublingual, inhaled (not in pharmaceutical form in NZ).
Dosing:	*MS spasms:* Approved indication in NZ when combined with **CBD** as Sativex. Dose starts at 1 spray per day, titrated to 6 sprays twice daily. *Pain:* There is insufficient efficacy demonstrated in trials to firmly recommend a dose. Trials have used 2.5mg twice daily, titrated to doses of up to 15mg twice daily. *Nausea:* Starting dose is 2.5 twice daily, titrated up to 20mg per day in trials. Trials have used regimens of 3-4 times daily but there is no evidence to support more than twice daily dosing.
Funding:	Unfunded (both in hospital and community).

TETRAHYDROCANNABIDOL CONTINUED

Notes:	• THC is a controlled drug, but does not require ministerial approval under the NZ Medicinal Cannabis Scheme provided the prescribed product meets Ministry of Health quality standards. • The Ministry of Health recommends THC should be prescribed by both brand and generic name and include the amount of CBD (if any). • THC has very poor evidence of efficacy for pain, whether neuropathic or not, with a number needed to treat for a 30% reduction in pain of around 24, and a number needed to harm of 6. • Withdrawal phenomenon can occur with prolonged THC use.

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Protocol

Dexmedetomidine

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OVERVIEW

Dexmedetomidine is a selective alpha-2 adrenoceptor agonist with sedative, anxiolytic and analgesic properties. It is commonly used in anaesthesia and ICU settings for sedation and increasingly in pain medicine as an analgesic adjuvant. Dexmedetomidine's use in palliative medicine is increasing internationally and it appears to be a promising drug in the context of delirium and also in complex pain.

> *For further information on the management of complex pain please see ANZSPM* **Management of Complex Pain** *guideline.*

PURPOSE

To provide guidance in the use of dexmedetomdine in people with palliative care needs.

SCOPE

Palliative care specialists/palliative medicine physicians, palliative care pharmacists.

PATIENT GROUP

Patients with a life-threatening or life-limiting illness associated with pain that is complex (such as neuropathic pain or poorly opioid-responsive pain), management of refractory symptoms and/or agitated delirium.

ABBREVIATIONS

CSCI	continuous subcutaneous infusion
ICU	intensive care unit
OME	oral morphine equivalent
RASS	Richmond Agitation-Sedation Score
SC	subcutaneous

For any comments and feedback, please email us:

Email

PROTOCOL

Drug action	• Dexmedetomidine is a selective alpha-2 adrenoceptor agonist with sedative, anxiolytic and analgesic properties [1-3]. • For further information see **Dexmedetomidine Monograph**.
Indications [4-9]	• Opioid refractory pain or intolerable opioid side effects. • Pain refractory to analgesic adjuvants (ketamine, lidocaine, methadone), or adjuvant use has resulted in intolerable side effects or adjuvants are contra-indicated. • Bridge to therapy while considering other interventional analgesic options. • Option for rousable sedation in clinical scenarios where traditional palliative sedation methods are not appropriate. • Agitated delirium.
Presentation	Dexmedetomidine 200 micrograms in 2 mL vial [10]. *The preparation contains dexmedetomidine as the hydrochloride but strengths always refer to the dexmedetomidine component alone.* pH of dexmedetomidine is 4.5 to 7.
Route	Subcutaneous ONLY.
Dose	Dexmedetomidine 0.1-1.4 microgram/kg/hr. Lower doses are required in patients with hepatic or severe renal impairment. • Consider reducing background opioid dose (20-30%) if: » Receiving methadone concurrently » OME (oral morphine equivalent) > 300mg/24h • If concurrent ketamine or lidocaine infusion – consider reducing dose or stopping. • If concurrent benzodiazepine, consider weaning and/or stopping.
Duration	At the discretion of palliative medicine specialist. *NB: abrupt cessation can result in rebound tachycardia and hypertension, recommend slow wean [11].*
Drug/drug and interactions incompatibilities	Do not mix with other medications.

Adverse effects

Adverse effects are dose-related.

Infusion via subcutaneous route generally results in attenuated cardiovascular effects compared with intravenous administration [12].

- Bradycardia
- Hypotension
- Dry mouth
- Nausea

Relative opioid narcosis:

- Reduced RR (≤ 8)
- Other features of opioid excess

Contact on-call palliative medicine specialist (or lead clinician for the patient) if any of the above occur. (See Rescue Medication section below for management options).

- Make an infusion concentration of **0.4 microgram/kg/mL**, using sodium chloride 0.9% as the diluent.
- To calculate the total micrograms of dexmedetomidine required use the following formula:
  0.4 x patient weight in kg x infusion volume in mL
- Administer via either *Alaris GH syringe driver* (using 50mL syringe) or *CADD-solis* device (using 50mL or 100mL bag)

  e.g. for a 70kg patient, preparing a 50mL syringe. The amount of dexmedetomidine required is 0.4 x 70 x 50 = 1400 micrograms. Draw up 14 mL of dexmedetomidine (100 micrograms/mL) and make up to a final volume of 50 mL with sodium chloride 0.9%.

  e.g. for a 70kg patient, preparing a 100mL infusion bag. The amount of dexmedetomidine required is 0.4 x 70 x 100 = 2800 micrograms. Draw up 28mL of dexmedetomidine. Take a 100mL bag of 0.9% sodium chloride and remove the same volume (28mL) from this bag. Then add the required amount of dexmedetomidine into the bag (28mL).

Preparation

Dexmedetomidine	
microgram/kg/hr	mL/hr
0.1	0.25
0.2	0.5
0.3	0.75
0.4	1.0
0.5	1.25
0.6	1.5
0.7	1.75
0.8	2.0
0.9	2.25
1.0	2.5
1.1	2.75
1.2	3.0
1.3	3.25
1.4	3.5

Start infusion at 0.5 ml/hr (0.2 microgram/kg/hr) and increase by 0.25-0.5ml/hr (depending on delivery device capability) every 30 minutes until:

- Acceptable improvement

OR

- Infusion rate of 1.4 microgram/kg/hr reached.

Monitoring

Note: monitoring can be omitted depending on goals of care; palliative medicine specialist discretion.

Pre-infusion:

- Baseline BP, HR, SpO2, RR, RASS (Richmond Agitation Sedation Scale).

During infusion:

- BP, HR, SpO2, RR, RASS every 1 hour for 4 hours, then every 4 hours for 24 hours.
- Check for signs of opioid narcosis (and pain level, if appropriate).
- If RR ≤ 8, please speak with palliative medicine specialist on call before administering routine opioids.
- *Minimum monitoring requirement is RR to monitor for relative opioid narcosis.*

Special considerations

Dexmedetomidine is not licensed in New Zealand for subcutaneous administration or sedation in the palliative care setting.

Rescue medications	In the event of bradycardia or hypotension a) Notify palliative specialist (or lead clinician) – advice below is dependent on the clinical context. b) Decrease infusion rate by 0.1 microgram/kg/hr if: i) HR less than 40 beats per minute ii) OR systolic BP less than 80mmHg iii) OR if there is a greater than 30% drop in HR or systolic BP from pre-infusion baseline observations. c) If no improvement stop infusion and reassess in 30 minutes. d) If HR remains low give atropine 0.6 mg OR glycopyrronium 400 micrograms intravenously or subcutaneously. e) If BP remains low position patient head down/legs elevated and give 500mL IV fluid bolus, if available, give ephedrine 30mg subcutaneously (dose range 10-50mg) if hypotension is unresponsive to fluid bolus. *NB: The above management of bradycardia and hypotension must be considered in the context of the patients goals of care. Management remains at the discretion of the treating palliative medicine specialist or lead clinician.*

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Ketamine

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OVERVIEW

Ketamine has been used for the management of complex pain for a number of years in both cancer and non-cancer pain. This guideline has been developed to advice on the use of ketamine in palliative care settings (hospital, hospice/inpatient unit and community).

> *For further information on the management of complex pain please see ANZSPM* **Management of Complex Pain** *guideline.*

PURPOSE

To provide guidance in the management of complex pain in people with palliative care needs.

SCOPE

Palliative care specialists/palliative medicine physicians, nurse practitioners, hospice medical officers.

PATIENT GROUP

Patients with a life-threatening or life-limiting illness associated with pain that is complex such as neuropathic pain or poorly opioid-responsive pain.

ABBREVIATIONS

CSCI	continuous subcutaneous infusion
GOC	goals of care
ICP	intracranial pressure
NMDA	N-methyl D-aspartate
SC	subcutaneous

PROTOCOL

Drug action	• Ketamine is a non-competitive inhibitor of the NMDA receptor. • It has some opioid receptor activity and psychomimetic properties. • Its analgesic effect has only been studied in a few trials. • For further information please see **Ketamine Monograph**.
Indications	• Neuropathic pain poorly responsive to increasing opioid doses and oral adjuvant analgesics [1-7] • Pain due to ischaemia (e.g. critical limb ischaemia, ischaemic bowel) • Complex abdominal or visceral pain with neuropathic component • "Bridging" e.g. during methadone rotation while titrating and allowing methadone to reach steady state (inpatient only) [8] • Presence of allodynia or hyperalgesia [5] • Opioid-induced hyperalgesia [2, 3, 9] • Features of central sensitisation
Presentation	200mg/2ml vials
Route	Subcutaneous Oral – use solution for injection, which may be diluted with juice to minimise taste. (Alternatively, it can be made into tablets by a compounding pharmacy).
Dose	**Analgesic regime:** *** Via NikiT34 syringe driver:** • Start 50-100 mg / 24 hours via continuous subcutaneous infusion (CSCI). • Review daily and increase in 50-100 mg increments/24 hours. • Doses greater than 500 mg / 24 hours are unlikely to provide further analgesic benefit and may cause burdensome side effects. • Ketamine can be given on a PRN basis 10-25 mg SC in addition to infusion. • If patient has been on ketamine for > 3 weeks and a decision is made to stop; discontinue gradually, do not stop abruptly. ***Via CADD-Solis infusion pump:** *Preparation:* This is a standard or high concentration infusion – prescriber needs to specify which infusion they want when prescribing. • **Standard concentration infusion (2mg/ml):** » Make up a concentration of 2mg/ml using 100ml 0.9% saline bag » Remove 2ml of saline and add 2ml of ketamine (200mg/2ml ampoules) to give solution of 200mg ketamine in 100ml = 2mg/ml • **High concentration (infusion (4mg/ml):** » Make up concentration of 4mg/ml using 100ml 0.9% saline bag » Remove 4ml of saline and add 4ml of ketamine (200mg/2ml ampoules) to give solution of 400mg ketamine in 100ml = 4mg/ml

Prescription:
e.g. Ketamine infusion standard concentration 2mg/ml in 100ml 0.9% saline bag, SC

OR ketamine infusion high concentration 4mg/ml in 100ml 0.9% saline bag, SC

Start at _____mg/hr

Titrate _____ to _____mg/hr

Ketamine (2mg/ml)		
mg/hr	mL/hr	24-hour dose (mg)
2	1	48
3	1.5	72
4	2	96
5	2.5	120
6	3	144
7	3.5	168
8	4	192
9	4.5	216
10	5	240
11	5.5	264
12	6	288
13	6.5	312
14	7	336
15	7.5	360
16	8	384
17	8.5	408
18	9	432
19	9.5	456
20	10	480

Ketamine (4mg/ml)		
mg/hr	mL/hr	24-hour dose (mg)
4	1	96
6	1.5	144
8	2	192
10	2.5	240
12	3	288
14	3.5	336
16	4	384
18	4.5	432
20	5	480
22	5.5	528
24	6	576
26	6.5	624
28	7	672
30	7.5	720
32	8	768
34	8.5	816
36	9	864
38	9.5	912
40	10	960

Converting 24-hour subcutaneous ketamine to oral ketamine for maintenance therapy:

- Conversion is complex due to low oral bioavailability and an active metabolite, there is no international consensus on a ratio. “starting at 1:1 is reasonable but some patients may need a higher oral dose” [10].
- Oral ketamine should be given in divided doses 3-4 times per day.
- Oral ketamine should be increased in 5–10 mg increments.
- There are no firm guidelines on how to switch between parenteral and oral ketamine. Options include:
  - » Stopping infusion at the time the first oral dose is administered OR
  - » Gradual reduction in infusion as oral dose is increased.

"Burst" regime (3-5 days) [4, 11]:

- Ketamine is used short term only (3-5 days) then discontinued, usually in higher doses with a more rapid up-titration than with analgesic regime.
- Can be effective in increasing opioid sensitivity (thereby improving pain control) and allow for reduction of background opioids.
  - » Monitor closely for opioid toxicity or narcosis and adjust opioids accordingly.
- Allows for "re-setting/re-booting" of pain pathways.
- Ketamine dosing (add haloperidol 1mg / 24 hours – see note below):
  - » Start with 100mg daily
  - » If not effective after 24 hours increase to 300mg daily
  - » If not effective after 24 hours increase to 500mg daily
  - » Stop 3 days after last effective dose
  - » If intolerable side effects following dose increase, reduce down to the last effective dose and maintain for 3 days then stop.

Note: Ketamine can cause dysphoria, hallucinations or dissociation, which can be distressing for patients. For this reason, it is recommended to co-prescribe an antipsychotic medication, usually haloperidol 0.5-1mg PO/SC daily and have PRN 0.5mg Q4H available if required.

Alternately midazolam (5 -10mg/24 hours) can be used, or other benzodiazepine. [4]

Contraindications	• Hypersensitivity to ketamine or any component of the preparation • Delirium • History of psychosis
Precautions	• Use with caution in older or frail adults, potential for increased sensitivity to side effects - Consider lower starting dose and slower titration. *NB: Concern regarding ketamine use in patients with raised ICP/seizure activity has been highlighted in the literature, however this is in the context of anaesthetic dosing, acute intracranial hypertension/acute stroke/haemorrhage and may not be clinically applicable to palliative medicine patient cohort [12].*
Adverse effects	• Dysphoria, hallucinations, vivid dreams • Urinary symptoms (long-term use); frequency, urgency, incontinence, dysuria* • Nausea, vomiting • Nystagmus and diplopia • Increased bronchial secretions, bronchospasm • Hypertension, tachycardia, raised intracranial pressure • Deranged LFT's (very rare, only in prolonged use, unlikely to be relevant to palliative cohort). **For patients prescribed ketamine for > 3 weeks or for whom repeated doses are anticipated consider further monitoring (Ketamine Monitoring Chart – see appendix), provided this is consistent with the patient GOC [13].*
Preparation	• Use sodium chloride 0.9% saline as diluent • Can be mixed with other medications within same syringe driver providing compatibility information supports this (see syringe driver compatibility chart) [11] • For use in NikiT34 syringe drivers. • Ketamine subcutaneously can be an irritant. Consider adding dexamethasone 0.5 - 1mg to the solution if irritation occurs.

**This protocol is adapted from the Waikato Palliative Care Services, Waikato DHB, Ketamine for Palliative Care, with permission.*

Observations and management	• Observe for visual hallucinations, dysphoria, confusion • Observe for excess sedation • Dose reduction may be needed
Special considerations	• Ketamine is classified as a Class C4 controlled drug and therefore is required to be stored in a controlled drug safe. • Ketamine is not licensed for analgesic use in New Zealand therefore patients should be advised, and consent obtained. • pH of ketamine is 3.5 to 5.5 • Ketamine is not funded for use in the community currently. An application for funding can be made through Pharmac using the following: Named Patient Pharmaceutical Assessment (NPPA) application https://pharmac.govt.nz/medicine-funding-and-supply/make-an-application/nppa-applications/

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APPENDIX

Ketamine monitoring chart [13]
Modified from palliativedrugs.com ketamine monitoring chart.

palliativedrugs.com
Essential independent drug information for palliative and hospice care

Ketamine monitoring chart

Chronic ketamine use may cause urinary and hepatobiliary tract toxicity *(see monograph on palliativedrugs.com).*

Practitioners should:

- advise patients to promptly report any new urinary tract symptoms or abdominal pain
- monitor for these toxicities, at least monthly.

Name
Hospital no.
D.O.B.
Address

(or affix sticker)

	Baseline	*Visit 1*	*2*	*3*	*4*	*5*
Date						
Ketamine dose (mg/24h)						

Urinary symptoms*: enter score using questionnaire overleaf*						
Urgency						
Frequency >2 hourly						
Nocturia						
Dysuria						
Haematuria						

If new or worsening symptoms, dip test urine.
If dip test suggests possible infection, send MSU.
In the absence of infection, consider ketamine-related cystitis.
Consider stopping the ketamine (ideally withdraw over 2–3 weeks), and seeking the advice of a urologist.

Urinary symptom assessment

During the past month, how often have you felt the strong urge to pass urine with little or no warning?	0 Not at all 1 Less than 1 time in 5 2 Less than half the time 3 About half the time 4 More than half the time 5 Almost always
During the past month, have you had to pass urine less than 2 hours after the last time?	0 Not at all 1 Less than 1 time in 5 2 Less than half the time 3 About half the time 4 More than half the time 5 Almost always
During the past month, how often do you typically get up at night to pass urine?	0 None 1 Once 2 Twice 3 Three times 4 Four times 5 Five or more times
During the past month, have you experienced pain or burning in your bladder?	0 Not at all 1 A few times 2 Fairly often 3 Usually 4 Almost always
During the past month, have you experienced passing blood or blood clots in your urine?	0 Not at all 1 A few times 2 Fairly often 3 Usually 4 Almost always

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Version 1.0. July 2023. Review date July 2025

Protocol

Levetiracetam

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OVERVIEW

Subcutaneous use of levetiracetam in patients may be used by specialist palliative care for seizure management and/or prevention. It may be indicated when the oral route is unavailable, when intravenous (IV) access is not available or desirable, and other medication options would cause unacceptable sedation.

PURPOSE

To provide guidance on the safe and effective use and administration of subcutaneous levetiracetam in palliative care for the management or prevention of seizures.

SCOPE

Palliative care specialists/palliative medicine physicians, nurse practitioners, hospice medical officers, palliative care pharmacists.

PATIENT GROUP

Patients with a life-threatening or life-limiting illness in whom seizures have occurred or have the potential to occur.

ABBREVIATIONS

CSCI	continuous subcutaneous infusion
GOC	goals of care
IV	intravenous
SC	subcutaneous

PROTOCOL

Indication	To maintain control of seizures in a deteriorating and dying patient where minimal reduction in level of consciousness is desired, and where the patient is unable to swallow oral medication and IV access is not possible or not desired. *Whilst this medication remains unlicensed for SC administration, there is common usage in palliative care via this route.*
Pharmacology	Levetiracetam binds to synaptic vesicle protein SV2A, interfering with the release of the neurotransmitter stored within the vesicle. It gains access after the neurotransmitter release as vesicles are recycled. Thus, it selectively accumulates in and inhibits rapidly firing neurones. It also inhibits potassium and N-type voltage-gated calcium channels.
Pharmacodynamics **Pharmacokinetics**	Levetiracetam does not induce or inhibit cytochrome P450. Renal excretion. Plasma half-life 6-8 hours, duration of action 24 hours. Conversion ratio of 1:1 between oral and SC/IV routes.
Presentation	Levetiracetam: 500mg in 5ml solution for infusion.
Contraindications/ Cautions	***Absolute:*** Hypersensitivity to levetiracetam. ***Cautions:*** Renal impairment. Advise patient to report mood disturbance (if appropriate). Concurrent administration with carbamazepine, methotrexate or phenytoin (isolated reports of toxicity). Avoid abrupt withdrawal.
Dose	• 1:1 conversion from oral to subcutaneous route. • Starting dose is 100 to 1000mg over 24 hours via continuous subcutaneous infusion (CSCI) titrated to effect. • NB: Can be given SC BD for doses <1g diluted in 100mL sodium chloride 0.9% over 60 mins.
Duration	At the discretion of palliative medicine specialist. *NB: abrupt cessation can result in rebound tachycardia and hypertension, recommend slow wean [11].*
Hepatic impairment	No dose adjustment is required for mild to moderate hepatic impairment. In patients with hepato-renal syndrome, dosing should be based on renal function (see below).

Renal impairment

Reduce dose in severe renal impairment when the eGFR is less than 60ml/min.

Creatinine clearance (ml/min)	Usual maintenance dose
>80	1000-3000mg over 24 hours
50-70	1000-2000mg over 24 hours
30-49	500-1500mg over 24 hours
<30	500-1000mg over 24 hours

Peritoneal or haemodialysis
750mg/24 hours on initial day of treatment, then 500-1000mg/24 hrs.
Consider a 250-500mg supplementary dose after haemodialysis.

Additional equipment

For subcutaneous administration:

Saf-T-Intima (preferred)

- Continuous CSCI infusion pump. (Niki T; Bodyguard T, with tubing PB-G40720)

Compatibility

Sodium Chloride 0.9% or water for injection.

Limited clinical experience suggests that levetiracetam is compatible with morphine sulphate, oxycodone, haloperidol, levomepromazine, methadone, metoclopramide, midazolam, dexamethasone, hyoscine butylbromide.

Administration

Levetiracetam should be diluted as much as practical to reduce infusion site irritation.

Maximum 1500mg in 20ml syringe; 2400mg in 30ml syringe.

Consider adding dexamethasone 0.5mg over 24 hours to CSCI for site protection.

Adverse effects

Very common >10% fatigue, drowsiness, headache.

Common 1-10% naso-pharyngitis, anorexia, abdominal pain, cough, headache, tremor, dizziness, vertigo, blurred vision, cognitive changes, mood or behavioural changes, gastrointestinal symptoms, rash, myalgia, thrombocytopenia, hyponatraemia.

Uncommon: suicidal ideation.

Dexamethasone 0.5mg may be added to preserve sites if necessary.

This is not a comprehensive list, refer to Medsafe data sheet, accessible from http://medsafe.govt.nz/

Monitoring

Monitor seizure activity and titrate dose accordingly, over 3-4 days.

Monitor infusion site.

Monitor mood and other side effects.

No requirement for monitoring of plasma levels.

Practice points	Unlike other anti-epileptics, levetiracetam has a low potential for pharmacokinetic drug interactions. Clinical experience to date suggests it is best administered in an independent pump device/syringe driver and diluted maximally to avoid drug-drug interactions and/or site reactions. Ensure dosage adjustment is made for renal impairment. Use benzodiazepines for acute, or prolonged seizure.

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Lidocaine

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OVERVIEW

Lidocaine is used for the management of complex pain, usually neuropathic in nature, commonly poorly opioid responsive. This protocol has been developed to guide clinicians in the safe administration of subcutaneous lidocaine in the hospital, hospice/ inpatient unit setting.

> *For further information on the management of complex pain please see ANZSPM* **Management of Complex Pain** *guideline.*

PURPOSE

To provide guidance in the management of complex pain in palliative care patients.

SCOPE

Palliative care specialists/palliative medicine physicians, nurse practitioners, hospice medical officers palliative care pharmacist.

PATIENT GROUP

Patients with a life-threatening or life-limiting illness associated with pain that is complex such as neuropathic pain or poorly opioid-responsive pain.

ABBREVIATIONS

CSCI	continuous subcutaneous infusion
CADD	continuous ambulatory delivery device
GOC	goals of care
OME	oral morphine equivalent
SMO	specialist medical officer (consultant/lead clinician)

PROTOCOL

Drug action	Lidocaine is a sodium channel blocker typically used for local anaesthesia. The mechanism by which lidocaine relieves pain is not fully understood but presumably components of the nervous system involved in chronic pain maintenance are sensitive to the partial blockade of sodium channels caused by systemic lidocaine [1, 2]. It also has an effect on the priming of polymorphic neutrophils and as such reduces the inflammatory stress response [3]. Using subcutaneous lidocaine to provide analgesia over a few days is intended to 'reset' the pain system, allowing analgesia to persist for an extended period after the infusion ceases (weeks to months). Opioid sparing effects may allow for reduction in background opioids [3, 4]. For further information on metabolism and clearance please see **Lidocaine Monograph**.
Indications	• Opioid refractory pain or intolerable opioid side effects. • Previous response to lidocaine (lasting longer than 2 weeks). • Insufficient response to other analgesics (including adjuvants). • Neuropathic pain, allodynia, opioid-induced hyperalgesia. • History of chronic pain. • History of previous opioid misuse.
Contraindications	• Severe degree of sinoatrial, atrioventricular or intraventricular heart block (without pacemaker in-situ). • Uncontrolled seizure activity. • Known hypersensitivity to lidocaine or other anaesthetic agents of the amide group. *NB: contraindications need to be considered in the context of the individual and their GOC.*
Presentation	Lidocaine 200mg in 20mL ampoule or 50mg in 5mL (1%). Lidocaine 400mg in 20mL ampoule (2%). Lidocaine 100mg in 5mL ampoule (2%).
Route	Subcutaneous ONLY.
Preparation	Use sodium chloride 0.9% as diluent or lidocaine can be given without diluent to facilitate volume requirements [5]. Administer via NikiT34 syringe driver or CADD-solis pump.

Dose & administration

Lidocaine 0·5 – 2mg/kg/hour.

Dosing guide

- Commence at 0.5mg/kg/hr.
- Consider dose increase by 0.5mg/kg/hr every 12-24 hours, at the discretion of the treating SMO.
- Consider reducing opioid dose (20-30%) if:
  - » Receiving methadone concurrently.
  - » OME (oral morphine equivalent) > 300mg/24h.

***Via NikiT34 syringe driver (using 30ml syringe):**

Below are examples of doses that take into consideration the volume restrictions of the NikiT34 syringe drivers.

- 600mg (single pump over 24 hours).
- 1200mg (single pump, change every 12 hours).
- 1800mg (single pump, change every 8 hours).
- 2400mg (2x pumps with 600mg each, change every 12 hours).
- 3600mg (2x pumps with 600mg each, change every 8 hours).

***Via CADD-solis**

- Use of the CADD-solis device eliminates the need for frequent syringe driver changes and/or requiring more than one device attached to the patient. If available in your centre, it is advised to use CADD-solis rather than NikiT34 syringe driver.
- Add 250mL of lidocaine 2% to 250mL CADD-solis reservoir cassette, (nil diluent) to give a concentration of 20mg per mL. (Alternately pre-mix bags may be available from pharmacy).

Prescription:

e.g. Lidocaine infusion standard dose 20mg/ml, 250ml via cassette, subcutaneously.

Infuse at _____mg/hr (starting 0.5mg/kg/hr and titrate to effect).

mg/hr	mL/hr	24-hour dose (mg)
20	1	480
40	2	960
60	3	1440
80	4	1920
100	5	2400
120	6	2880
140	7	3360
160	8	3840
180	9	4320

Duration

24 – 72 hours – *or longer, at the discretion of the SMO.*

Drug/drug and interactions incompatibilities

Do not mix with other medications – infuse in separate syringe driver [5].

Adverse effects	Adverse effects are dose-related. Signs of central nervous system (CNS) toxicity usually precede those of the cardiovascular (CV) system [6]. ***CNS toxicity:*** • Perioral numbness/metallic taste • Tinnitus • Reduced level of consciousness • Paraesthesia • Myoclonus/seizures ***Relative opioid narcosis:*** • Miosis • Reduced RR (< 8) • Reduced level of consciousness ***CVS toxicity:*** • Bradycardia, ventricular arrhythmia, widened QRS complex • Hypotension • CVS collapse Pause infusion and contact on-call palliative SMO if any of the above occur.
Monitoring	*** The degree of monitoring needs to be individualised to the patient; consider prognosis, GOC, risk/benefit profile and clinical setting. See appendix.* ***Monitoring (once infusion started):*** • In the 8 hours following infusion initiation; 1 hourly for the first 4 hours then 2 hourly thereafter. » Check for signs of CNS toxicity, opioid narcosis and pain level. » BP and HR. • If drowsy or RR < 10, please speak with SMO on call before administering routine opioids. ***Re-evaluation: (at 24 hours)*** • PRN use • Reported pain experience • If effective: » Consider increasing dose by 0.5-1mg/kg and re-evaluate in 24 hours. » Discontinue at 72 hours regardless of effectiveness (unless continuation is advised by SMO).
Special considerations	• Lidocaine is not licensed in New Zealand as a subcutaneous infusion for the treatment of pain. • pH of undiluted lidocaine is 5 to 7.

APPENDIX

A note on monitoring:
In general, lidocaine infusions are well tolerated and safe in the palliative context. Historically concerns regarding cardiovascular toxicity have impacted on clinician decision-making, often resulting in a decision not to proceed with lidocaine therapy. There are multiple studies demonstrating the safety and efficacy of lidocaine infusions in the palliative setting, including assessment of the level of monitoring required.

From a practical perspective, signs of mild CNS toxicity (metallic taste, perioral numbness) are generally the first to appear and will usually be apparent (if they occur at all) 4-6 hours after commencing infusion (which corresponds to when you would expect peak plasma concentration to occur). The 4-6 hour mark is also when evidence of opioid narcosis can occur. In general, if there is no evidence of either 6 hours after commencing infusion, they are unlikely to

**This protocol is adapted from the Waikato Palliative Care Services, Waikato DHB, Ketamine for Palliative Care, with permission.*

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occur in the proceeding hours. The same applies to any dose increase, the 4-6 hour mark, is when features of toxicity +/- opioid narcosis are likely to occur.

The minimum monitoring that should occur in the patient on a lidocaine infusion at the EOL is monitoring for opioid excess as this is the most likely thing to occur in an effective lidocaine infusion; pain level is reduced due to lidocaine, therefore the amount of opioid required is less and opioids may need to be reduced or withheld.

Lidocaine has a short half-life. Stopping infusion will usually result in resolution of any mild CNS toxicity effects within 1-4 hours, the infusion can then be restarted at a lower dose. For further information on lidocaine pharmacology see drug monograph.

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Appendix

Bioavailability

Bioavailability is the percentage of drug which reaches the systemic circulation and is usually described in terms of the route of administration, e.g. oral bioavailability is the percentage of drug given orally which reaches the systemic circulation.

The clinical significance is that it defines the conversion between that route of administration and the subcutaneous (SC) or intravenous (IV) route.

For example, if the oral bioavailability of a drug is 50% then half of the oral drug is reaching the systemic circulation. Therefore, the dose should be half giving the same drug SC (assuming you want the same exposure). Therefore the oral:SC conversion is 2:1.

There are some useful clinical tips for using bioavailability:

- There is always variation between individuals. Any conversion ratio used, whether based on bioavailability or not, is only an *average* value. For *your patient*, the bioavailability is unknown. Changes of route should **always** be treated as a potential change in dose that requires follow up and retitration if needed.
- Because bioavailability varies between patients, it is usually appropriate to round conversions to a convenient dose for patients or carers rather than focusing on precision.
- Drugs with low bioavailability (<50%) have the least stable bioavailability and are the least predictable.

There are also some clinical pitfalls to consider:

- Bioavailability reflects *overall* exposure to a dose. SC and IV doses will still have higher *peak* exposures, even if you correct for bioavailability. Therefore bioavailability works best for converting regular oral medications to a syringe driver (or vice versa) than for PRN doses where the peak concentration matters more.
- For drugs that are metabolised (rather than renally cleared), low bioavailability is usually due to first-pass metabolism rather than absorption. For these patients, enzyme inhibitors and inducers can markedly alter bioavailability. Severe disease usually reduces metabolism by 30-50% and increases bioavailability.
- Bioavailability only refers to the parent drug, not metabolites. Most drugs are fully orally absorbed and so the metabolite exposure is the same by the oral or SC/IV routes. Therefore, for drugs with active metabolites (e.g. ketamine, morphine) the ratio for converting oral:SC may not reflect the bioavailability.

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Appendix

Cyp Enzyme Inhibition / Induction Table

Drugs usually inhibit or induce metabolising enzymes specifically. The effect on other drugs in predictable, if the enzyme metabolising that drug is known. The monographs give information about enzymes known to significantly metabolise each drug.

A strong inhibitor would typically increase concentrations and half-life of affected drugs by more than 5-fold; a moderate inhibitor typically increases concentrations and half-life by 2-5 fold. Inhibition is usually immediate.

A strong inducer would typically reduce concentrations and half-life of affected drugs to less than 50%. Induction takes a few days to be clinically significant and can take up to two weeks to fully manifest.

Weak inhibitors and inducers are of low clinical relevance and not included.

The table below shows common inhibitors and inducers by CYP450 enzyme, so doses can be adjusted in the presence of these drugs. It is not an exhaustive list.

	CYP3A4	CYP2D6	CYP2C8/9	CYP2C19	CYP1A2
Strong inhibitor	Aprepitant Clarithromycin Erythromycin Grapefruit juice* Itraconazole Ketoconazole Voriconazole	Buproprion Fluoxetine Paroxetine Perhexiline	Fluconazole	Fluconazole	Ciprofloxacin
Moderate inhibitor	Amiodarone Ciclosporin Ciprofloxacin Diltiazem Fluconazole Verapamil	Haloperidol Levomepromazine	Amiodarone Ketoconazole Voriconazole	Clarithromycin Fluoxetine Ketoconazole Lansoprazole Omeprazole Pantoprazole	Amiodarone Ketoconazole
Strong inducer	Carbamazepine Phenytoin Rifampicin St John's wort	There no CYP2D6 inducers	Phenobarbitone Phenytoin Rifampicin	Carbamazepine Phenytoin Rifampicin St John's wort	Phenobarbitone Phenytoin Rifampicin Smoking

*only affects intestinal CYP3A4; can increase bioavailability of oral CYP3A4 substrates but does not affect clearance or drugs given SC/IV.

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Appendix

Prodrugs

Prodrugs are biologically inactive (or weakly active) drugs which are metabolised to their active form. The significance of this is that inhibition of the metabolising enzyme (whether by drugs, disease, or genetics) will *reduce* drug effect, and induction of the enzyme will *increase* effect. This is the converse of active drugs.

It is equally relevant to understand the pharmacokinetics of the active metabolite, as it is the combination which is predictive of drug effect. For example, the half-life of the prodrug will predict the time to onset of effect, but the half-life of the metabolite will predict the duration of that effect.

Like other drugs, the active metabolite of a prodrug can still have active metabolites.

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Appendix

Dose adjustments for renal impairment

Drugs which are cleared renally will accumulate in renal impairment. Therefore doses are usually adjusted with the aim of giving the same exposure as the original dose in patients with normal renal function.

Knowing which drugs are cleared renally, and to what extent, allows clinicians to identify which drugs need adjustment in renal impairment and to calculate the adjustment.

The exposure is inversely proportional to renal function – so halving renal function will double the exposure. Normal renal function is around 100ml/min. Therefore the eGFR in ml/min can be considered the percentage of remaining renal function.

To adjust drugs for renal function:

1. ASSESS RENAL FUNCTION

Most laboratories report eGFR in ml/min/1.73m^2 alongside measured creatinine. This is the renal function for the average sized patient (1.73m^2 is an average BSA). Adjusting for BSA is not usually required for patients of typical weight (e.g. 50-100kg) unless the drug has a narrow therapeutic index and needs adjusted precisely, e.g. enoxaparin.

For patients with extremes of weight (≤ 50kg, or ≥ 100kg), you can use an online calculator to correct the eGFR for BSA or use the followng equation:

$$\text{Adjusted eGFR} = \text{unadjusted eGFR} \times \left(\frac{\text{BSA}}{1.73}\right)$$

The Cockcroft and Gault equation is no longer recommended.

2. ADJUST DOSES DEPENDING ON EXTENT OF RENAL CLEARANCE.

The methods below can be applied equally well to individual doses, the total daily dose, starting doses and maximum doses.

Drugs with high renal clearance (> 70%)

For drugs with high renal clearance, doses can be simply adjusted with the following equation:

$$\text{Adjusted dose} = \text{standard dose} \times \left(\frac{\text{eGFR}}{1.73}\right)$$

In other words, the eGFR in ml/min is the percentage of

DOSE ADJUSTMENTS FOR RENAL IMPAIRMENT CONTINUED

the standard dose for the adjusted dose.

Drugs with moderate renal clearance (30 – 70%)
For drugs with moderate renal clearance, precise dose adjustment is more complex because only the proportion of drug which is renally cleared needs to be adjusted. Thankfully, there are only a small number of drugs in this group.

To adjust these kinds of drugs, either use a table or the following equation:

$$\text{Adjusted dose} = \text{standard dose} \times \left[(1-fe)+fe\left(\frac{\text{eGFR}}{1.73}\right)\right]$$

f_e is the fraction of drug cleared renally (e.g. 60% is 0.6).

Drugs with low renal clearance (< 30%)
These drugs do not routinely require renal adjustment.

3. OTHER CONSIDERATIONS

This approach corrects doses to give the same exposure despite renal impairment. However, patients with severe renal impairment (eGFR < 30ml/min) may be more vulnerable to adverse effects even at the same exposure and need further dose reduction (e.g. renal failure increases risk of myoclonus from gabapentinoids). This concept applies to drugs not renally cleared too.

Severe uraemia associated with end-stage renal impairment also impairs hepatic metabolism, so even metabolised drugs should have a 50% dose reduction in end-stage renal failure.

Reducing drug clearance proportionally increases half-life, so a 50% reduction in clearance will double the half-life.

- This will alter time to steady state and monitoring times.
- It also provides the opportunity to reduce the dosing frequencies for patient convenience (for example, a drug usually given twice daily might be able to be given once daily).

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Appendix

Syringe Driver Compatibility Chart

PURPOSE:

To provide compatibility information when compounding syringes for use in syringe driver for administration via continuous subcutaneous infusion (CSCI) for a period of 24 hours. With regards to diluent, this 2023 update reflects the preference for sodium chloride 0.9% (NaCl 0.9%) wherever possible. This is because NaCl 0.9% is isotonic and therefore less irritating to subcutaneous tissue compared to water for injection (WFI) which is hypotonic.

DILUENT:

Sodium Chloride 0.9% is recommended for all single medication infusions with the exception of cyclizine - always use WFI for cyclizine. In combinations, check the chart overleaf and if not listed, check other compatibility sources (see references) and consider WFI as the diluent where no data is available. Your hospice and palliative care pharmacist can provide further advice.

REFERENCES:

1. Dickman A & Schneider J. The Syringe Driver: Continuous subcutaneous infusions in palliative care. 4th ed. Oxford University Press; 2016.
2. Palliative Care Formulary, PCF8. 8th ed. Edited by Wilcock A, Howard P & Charlesworth S. Pharmaceutical Press; 2022. Appendix: Compatibility Charts and individual monographs.
3. Good PD, Schneider JJ & Ravenscroft PJ. The compatibility and stability of midazolam and dexamethasone in infusion solutions. J. Pain Symptom Manag [Internet]. 2004 [cited 2023 Oct 6];27(5):471-475. Available from: https://www.jpsmjournal.com/article/S0885-3924(04)00067-3/fulltext
4. Safer Care Victoria. Syringe Driver Compatibility Guidance Document [Internet]. 2021. [cited 2023 Oct 6]. Available from: https://www.safercare.vic.gov.au/clinical-guidance/palliative/syringe-driver-compatibility
5. Observational data from clinical setting (based on observation of the medication combination on mixing and during infusion for any physical changes e.g. precipitation, discolouration or clouding) via:
    a. New Zealand hospice pharmacists,
    b. correspondence with Dr Andrew Dickman, or
    c. Drug Compatibility Checker via Medicines Complete online (formerly known as the Syringe Driver Survey Database via palliativedrugs.com)

TWO-DRUG COMBINATIONS FOR USE IN SYRINGE DRIVERS VIA CSCI OVER 24 HOURS

	cyclizine	dexamethasone*	famotidine+	fentanyl	glycopyrrolate	haloperidol	hyoscine BUTYLbromide	ketamine	levetiracetam	levomepromazine	methadone	metoclopramide	midazolam	morphine sulphate	octreotide	ondansetron	oxycodone
cyclizine		SI		SI								SI			SI	SI	SI
dexamethasone*	SI					SI				SI			SI#		SI		
famotidine+															SI		
fentanyl	SI																
glycopyrrolate																	
haloperidol		SI					SI										
hyoscine BUTYLbromide						SI											
ketamine																	
levetiracetam																	
levomepromazine		SI															
methadone																	
metoclopramide	SI																
midazolam		SI#															
morphine sulphate																	
octreotide	SI	SI	SI														
ondansetron	SI																
oxycodone	SI																

Incompatible

NaCl 0.9% as diluent

SI — Sometimes incompatible in NaCl 0.9% (usually at higher concentrations)

WFI as diluent

SI — Sometimes incompatible in WFI (usually at higher concentrations)

SI — Sometimes incompatible in both NaCl 0.9% and WFI (usually at higher concentrations)

Not usually used together (if split cell it means that there is still compatibility information available for combination)

No information available within stated references

* Dexamethasone should always be added to the syringe last (after diluting the other medications as much as possible); transient turbidity can happen initially.

Chemical incompatibility can occur between midazolam and dexamethasone in a time and temperature dependent way resulting in reduced effectiveness of midazolam. [Reference: Good et al, 2004]. However, this shouldn't be an issue for infusions stored ≤ 25°C for ≤ 24 hours or at the doses of dexamethasone used for site protection (0.5-1 mg).

\+ Famotidine is still new to practice in NZ – this data is predominantly from the clinical setting and still requires caution, especially at higher concentrations of medications.

COMMON THREE-DRUG COMBINATIONS

	DILUENT
morphine + midazolam + levomepromazine	NaCl 0.9%
morphine + metoclopramide + midazolam	NaCl 0.9%
morphine + haloperidol + midazolam	NaCl 0.9%
morphine + hyoscine BUTYLbromide + haloperidol	NaCl 0.9%
oxycodone + midazolam + levomepromazine	NaCl 0.9%
oxycodone + metoclopramide + midazolam	NaCl 0.9%
oxycodone + haloperidol + midazolam	NaCl 0.9%
oxycodone + hyoscine BUTYLbromide + haloperidol	NaCl 0.9%
fentanyl + midazolam + levomepromazine	NaCl 0.9%
fentanyl + haloperidol + midazolam	NaCl 0.9%
Fentanyl + cyclizine + midazolam	WFI

NOTES:

- Heat and light can cause medication combinations to become incompatible – **keep below 25°C and protect from sun and UV light**.
- Results from some included combinations are based on data collected in clinical settings via observing the medication combination at time of mixing and during infusion for any physical changes (discolouration, clouding or crystallisation). Hence, it is important that all CSCI syringes are observed for physical changes on compounding and at regular intervals during infusion.
- Although the combinations are based on physical and chemical compatibilities over 24 hours, many of the combinations have been observed to be physically compatible over a period of 72 hours when kept at 2-8°C. In NZ, a 72-hour expiry may be assigned to syringes compounded aseptically within pharmacies (NZ Pharmacy Service Standards 2010 – Aseptic Dispensing of Sterile Products). A watchful eye must be kept to ensure that the syringe remains colourless, clear and free from particulate matter during this extended period.
- Particular attention should be paid to those syringes containing high doses of any of the medications as they have the potential to become incompatible at higher concentrations.
- Please note that the hyoscine formulation stated in these charts is hyoscine BUTYLbromide (Buscopan®, Spazmol®) **NOT** hyoscine HYDRObromide, which although can be administered via CSCI is not included in this chart.

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