FIRST EDITION | 2024

Te Puka Manaaki Pairuri o Aotearoa – Putanga Tuatahi

The Palliative Care Handbook New Zealand

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GUIDELINES FOR CLINICAL MANAGEMENT AND SYMPTOM CONTROL

Edited for New Zealand by
Dr Warrick Jones and Clare Randall

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PUBLISHED BY

Hospice New Zealand Incorporated
93 Cuba Street, Te Aro
Wellington 6011, New Zealand

Previous editions written by Rod MacLeod, Jane Vella-Brincat and Sandy Macleod.
Ninth Edition edited by Rod MacLeod and Steve Macfarlane.
Adapted for New Zealand by Hospice New Zealand Incorporated
Edited for New Zealand by Dr Warrick Jones and Clare Randall.

Disclaimer

The Palliative Care Handbook New Zealand – First Edition includes guidance on the prescribing and administration of various medicines. In New Zealand, health practitioners prescribing medication must comply with the relevant law, their own professional obligations, the Code of Health and Disability Services Consumers' Rights and other applicable standards. Health practitioners are required to act with reasonable care and skill, to inform patients (or a patient's legal representative) about treatment options (including the expected benefits, risks, side effects and costs), and to obtain informed consent before proceeding with any treatment (or otherwise have a legal basis for proceeding with treatment). In places this Handbook refers to the prescription of medicines outside of approved use (e.g. 'off-label' use), and where this is proposed, it is especially important that this is explained to the patient, informed consent is obtained (or there is a legal basis for provision of the medication), and the patient or their representative is made aware that supply of the medicine may be notified to Medsafe.

The guidance in this handbook is provided for the general assistance of health practitioners and has not been tailored to any specific individual or circumstance. While care is taken to ensure its accuracy at the time of printing, the information and practices described within may change over time. This handbook is not a substitute for individualised medical advice, and users of the handbook must always consider current best practice and apply their own clinical judgement to each patient under their care. The prescription of any medicine remains the responsibility of the prescribing health practitioner.

Funding of pharmaceuticals should be confirmed using the Pharmaceutical Schedule online, which at the time of printing is updated monthly and can be accessed here: *https://schedule.pharmac.govt.nz/ScheduleOnline.php*

Reviewers acknowledge the references to the Palliative Care Formulary (PCF8), New Zealand Formulary (NZF) and Medsafe Datasheets in the Palliative Care Handbook monographs.

For clarity, in the Palliative Care Handbook, all controlled release and modified release are referred to as slow release.

Abbreviations

BBB	blood brain barrier
bd	twice daily
CNS	central nervous system
CR	controlled release
CSCI, SD and SCP	acronyms that refer to continuous subcutaneous infusion (CSCI) of medication using a syringe driver (SD) or subcutaneous pump (SCP)
DLB	dementia with lewy bodies
GIT	gastrointestinal tract
IR	immediate release
LFTs	liver function tests
MAOIs	monoamine oxidase inhibitors
MR	modified release
NSAIDs	nonsteroidal anti-inflammatory drugs
qid	four times daily
SR	slow release
subcut	subcutaneous
tds	three times daily

Acknowledgements

We are grateful to HammondCare (ABN 48 000 026 219) for their permission to use and adapt content from the previous Ninth Edition of The Palliative Care Handbook to develop Te Puka Manaaki Pairuri o Aotearoa – Putanga Tuatahi - The Palliative Care Handbook New Zealand – First Edition.

Thank you to previous editors Rod MacLeod and Steve Macfarlane also, for their time and contributions.

Thank you to Dr Warrick Jones, Director of Clinical Services, North Haven Hospice for being the lead editor on the clinical content of the handbook, and to Clare Randall, CE Arohanui Hospice & Palliative Care Pharmacist Prescriber for being the lead editor of the Pharmacopeia section.

We extend our appreciation to other reviewers Dr Di Murphy for reviewing a significant portion of the clinical content, Dr Richard Eagan for reviewing Te Wairuatanga – Spirituality chapter, and Dr Ann Kim for developing content for the chapter on Caring for the older person, and to Viv Young for reviewing the chapter on Grief and loss. We also express gratitude to Dr Jessica Kelly and Dr Helen Lunt for reviewing the chapter on Diabetes.

We would also like to acknowledge Emma Griffiths, Clinical Pharmacist for leading the review of the Syringe Driver Compatibility Chart and support from the Australia New Zealand Society of Palliative Medicine (ANZSPM) for permission to use the revised chart.

We acknowledge HealthPathways and the ANZSPM Aotearoa Specialist Adult Palliative Care Guidelines to enable cross referencing of the content with current best practice. The digital information on HealthPathways will continue to be periodically reviewed to reflect the most up to date practice.

Glossary of Māori Terms

The more commonly known Māori terms used in the **whānau-family and patient voices** are described below. For more translations, please refer to the app *Te Aka*.

Kaimahi	Kaimahi is a worker (used in an English context it can be singular or plural). In the context of palliative care, kaimahi refers to all health professionals (and support roles) who work and care for patients and their whānau.
Mana	Mana is a supernatural force in a person, place or object, and is interconnected with tapu and wairua. Its wider meaning includes status and prestige. “Mana comes from knowing who you are, where you come from and your connection to the land” Tame Iti
Mirimiri	Mirimiri is traditional Māori healing practice that uses touch, sound, words and song, karakia and incantations, as well as massage, stroking and pressure to calm, soothe, ease and lessen physical, spiritual, emotional and mental disease. A Mirimiri session will be unique to the receiver, the practitioner and the occasion.
Rongoā Māori	Rongoā is traditional Māori medicine and healing that was passed on experientially, and was comprised of diverse practices that placed emphasis not only physical health, but also on spiritual dimension of wellbeing. Rongoā includes natural remedies such as bush/herbal medicine; locations, such as mountains, rivers and land; physical therapies such as touch, massage and manipulation; and spiritual healing, such as karakia, waiata, incantations, whakapapa and whakatauki.
Taonga	Taonga can be anything that is considered socially or culturally valuable, including objects, resources, phenomenon, ideas, abilities and techniques.
Tapu	Tapu is a state of restriction or prohibition. – a supernatural condition. It is untouchable, no longer to be put to common use.
Tinana	Tinana is the actual and real part of anything, such as a body or tree, as opposed to an apparition. Tinana is commonly used to refer to the human body.

Foreword

Mā te huruhuru ka rere te manu.
Adorn this bird with feathers to enable it to fly.

Welcome to ***Te Puka Manaaki Pairuri o Aotearoa: Putanga Tuatahi – The Palliative Care Handbook New Zealand: First Edition***. This edition has been extensively revised and, for the first time, includes guidelines to specifically support the provision of generalist palliative care in New Zealand.

The handbook provides guidance on what is both safe and expected palliative care practice within a non-specialist (generalist) palliative care setting. It is a handbook suitable for medical, nursing, and wider allied health practitioners who, in addition to their usual area of practice, also assess and make clinical decisions for patients who are deteriorating and require a palliative care approach.

Palliative care has come a long way from the inception of the modern hospice movement in the 1960s and marked by the establishment of the first hospice in New Zealand in 1979. Since then, palliative care has evolved into being an integral component of end-of-life care, addressing the needs of the whole person during their life-limiting illness and in their dying phase.

Our understanding of palliative and end-of-life care continues to deepen with an increased awareness of the importance of providing palliative care when and where it is needed. This often means the integration of palliative care earlier in the course of illness, extending beyond hospitals or hospice, and into the home and residential care setting.

An important enhancement to the handbook is the consideration of wairuatanga or spiritual essence, an approach of particular importance for Māori but also to every person receiving palliative care along with their whānau-family. As clinicians and health professionals, acknowledging the spiritual needs of all patients transcends beyond the physical realm. Each chapter includes reflections from a patient or whānau-family "voice". They are used in this book for the purpose of encouraging health professionals to consider aspects other than simply the medical condition or situation. The patient and whānau voice notations are taken from real comments shared with Hospice Kaimahi over the last two decades.

This edition also includes a new chapter on Caring for the older person. New Zealand has an ageing society, and we expect a significant increase in the number of older people who often have multi-complexity needs requiring palliative care.

The Syringe Driver Compatibility Chart has also been updated to reflect the most up to date use of two-drug combinations in New Zealand health settings.

Te Puka Manaaki Pairuri o Aotearoa – Putanga Tuatahi – The Palliative Care Handbook New Zealand – First Edition continues to support excellence in palliative care in New Zealand, as being a well-equipped resource for any health professional dedicated to delivering quality palliative and end-of-life care.

Dr Warrick Jones

Director of Clinical Services – Kaiwhakahaere Tākuta
Te Korowai Hūmārie – North Haven Hospice

Wayne Naylor

Chief Executive Officer
Te Kahu Pairuri o Aotearoa –
Hospice New Zealand

Contents

Palliative Care Aims and Principles

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

The World Health Organisation defines palliative care as:

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

Palliative care:

- provides relief from pain and other distressing symptoms
- affirms life and regards dying as a normal process
- intends neither to hasten nor postpone death
- integrates the psychological and spiritual aspects of patient care
- provides support to help patients live as actively as possible
- provides support to the family during the illness and bereavement
- uses a multidisciplinary team approach
- enhances quality of life and influences the course of the illness
- is applicable early in the course of illness alongside therapies that are intended to prolong life (e.g. chemotherapy, radiotherapy) and diagnostic investigations

General symptom management principles

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

Ngā tapa e whā o te tangata **Whole person considerations**

Quality of life

He aha te mea nui o te ao – he tangata, he tangata, he tangata
What is most important in this world
– it is people, it is people, it is people.

The primary goal of palliative care is to optimise the quality of life for patients and their families. There are many views on the nature of quality of life but one enduring view by Calman in 1984 (see 'Journal Articles') is that quality of life 'can be defined as subjective well-being reflecting differences or gaps between hopes and expectations and current experiences.'

The aim of care near the end-of-life is to:

- provide 'appropriate' palliative care
- provide and maintain improvement in patients' quality of life
- achieve a 'good death' as defined by the patient and whānau-family. This is as varied as there are cultures and individuals

A challenge exists in that health professionals and patients often have different views on what aspects of disease and treatment are important. Hence it is always important that the patient and whānau-family voice is clearly heard, clarified and documented.

There are many 'expert-derived' tools available such as:

- McGill Quality of Life questionnaire
- Schedule for the Evaluation of Individual Quality of Life (SEIQoL)
- Missoula-VITAS quality of life index – encompasses a number of domains and is user-friendly (npcrc.org/files/news/missoula_vitas_quality_of_life_index.pdf). It contains questions about:
  - symptoms – the level of physical discomfort and distress
  - function – perceived ability to perform accustomed functions and activities of daily living and the emotional response, experienced in relation to expectations
  - interpersonal aspects – degree of investment in personal relationships and the perceived quality of one's relations/interactions with family and friends
  - well-being – the individual's internal condition i.e. a sense of wellness or unease, contentment or lack of contentment
  - transcendent – degree of connection with an enduring construct, and of a meaning and purpose

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

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

Again, this list of "milestones" must be prioritised by an individual's world view and culture. We can never presume anything, but rather engage in genuine enquiry and enablement.

Te Wairuatanga
Spirituality

He kākano ahau i ruia mai i Rangiātea.
I am a seed which was sewn in the heavens of Rangiatea.

Part of the 'task of dying' is to hold space to contemplate and possibly resolve spiritual concerns. Spiritual and existential concerns are not uncommon for people at end-of-life. Spirituality should be routinely assessed, documented and addressed just as other elements of the patient's care are. Spiritual concerns may influence other symptoms. Spiritual care needs to be patient-led and should be a normal part of history taking and care plans at end-of-life.

There are several points to remember when exploring someone's spirituality:

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

Assessing Spirituality

Many seriously ill patients are likely to want their spirituality attended to, however there are a proportion who will find this intrusive.

Chochinov's enquiry of ''What do I need to know about you as a person to give you the best care possible?'' (Chochinov et al. 2014) can open up this space allowing the patient to establish the direction and priorities. "Are you at peace?" (Steinhauser, K., et al. 2006) is an alternative engagement phrase.

This can be further expanded using a variety of subsequent explorative questions, such as

- what has sustained you through hard times in the past? i.e. sources of strength
- what is most important to you right now?
- what worries you most?

- what gives you meaning and purpose in life?
- if you could have/achieve one thing, what would it be?
- who are the people who are most important to you?
- the things or people who inspire you?
- what gives you hope?
- what is it that keeps you going?

The advantage of a genuine enquiry that is a patient led conversation is that assumptions are dispelled on behalf of the care professional and allows for the patient to hear the articulation of their own internal thoughts and beliefs. To hold this space for a patient to think, speak and explore their true hopes and beliefs requires the care professional to have settled many of these things in their own self.

Alternatively, a spiritual wellbeing survey may be used, for example:

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Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	Not at all	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
I feel peaceful	0	1	2	3	4
I have a reason for living	0	1	2	3	4
My life has been productive	0	1	2	3	4
I have trouble feeling peace of mind	0	1	2	3	4
I feel a sense of purpose in my life	0	1	2	3	4
I am able to reach down deep into myself for comfort	0	1	2	3	4
I feel a sense of harmony within myself	0	1	2	3	4
My life lacks meaning and purpose	0	1	2	3	4
I find comfort in my faith or spiritual beliefs	0	1	2	3	4
I find strength in my faith or spiritual beliefs	0	1	2	3	4
My illness has strengthened my faith or spiritual beliefs	0	1	2	3	4
I know that whatever happens with my illness, things will be okay	0	1	2	3	4

Spiritual distress

This may include a questioning of their own assumed beliefs and making peace with themselves, others or their God or Divine. Understanding and achieving forgiveness for themselves and forgiving others are often essential spiritual tasks that contribute to a "good death".

Assisting someone to do this requires:

- a non-judgmental approach involving presence, compassion, and empathic and contemplative listening should be used
- the creation of space ('a safe place to suffer'), being with and listening to ('to be with and to bear witness'), appropriate touch and encouraging experiencing the natural and artistic worlds are useful approaches
- spiritual care is generally agreed to be the role of all those involved in care, with the need to involve a specialist (chaplain, tohunga or spiritual care expert) as important as any other aspect of health care
- more specialised interventions include retreats, group therapy, meditation and religious rituals or facilitating engagement with who the patient or whānau-family identify as being able to give spiritual guidance
- ethical spiritual care is critical. Proselytising is widely understood to be unethical

Advance Care Planning (ACP) and Advance Directives (AD)

PATIENT VOICE

"I don't want to talk about dying. It's like I'm asking for it to happen."

ACP is the process of discussion and planning for future health care in the context of anticipated deterioration of health. Not everyone will choose to participate in ACP.

Advance care planning:

- involves the patient, health care professionals and family/carers
- incorporates the patient's beliefs, values, culture, preferences for care, current and anticipated medical status and treatment options
- needs a competent patient to participate
- should take place early in the course of a terminal illness but can happen at anytime
- may result in:
  - a conversation and shared understanding between patient and health professionals
  - documentation of an ACP plan
  - the writing of an Advance Directive (see below)
  - the appointment of an enduring power of attorney/surrogate decision-maker
- is the articulation of wishes, preferences, values and goals
- respects personal autonomy and medical reality
- should be used to inform decision-making, even in acute medical emergencies
- should be regularly reviewed and updated – it is a flexible 'living' document
- is open to change, revision, and cancelation
- is not confined to medical issues – may include spiritual or interpersonal issues

Barriers to ACP

- it is time consuming
- advanced cognitive impairment (e.g. from dementia). Currently, fewer than 1% of those with a diagnosis of dementia are felt to have an ACP in place. The formulation of an Advanced Care Plan should be done as early as possible in the course of a dementing illness so that the affected individual retains a greater degree of capacity to enable its completion
- there is sometimes a reluctance to discuss death and dying and the conversation may be difficult to initiate
- some patients prefer benign paternalistic medical care
- there may be an element of misinformation about the processes/rights/law
- acute/emergency interventions may not allow for consideration of the patient's history
- the 'disability paradox' – with age and emerging health disabilities (especially cognitive) there is a tendency to moderate the assertiveness of stated care wishes

Advance directive (AD) ('Living will')

- an AD is a written or oral directive/instruction about preferences for future care
- the process for completing advance directives should be raised early in the course of an illness when the patient is competent, free of undue influence and sufficiently informed
- the existence of an AD document or conversation needs to be established
- it becomes effective if the person loses capacity
- it may encompass refusal of, or consent to, a particular treatment
- there is no medical obligation or duty to provide treatments not offered, not effective or unavailable
- clinicians are obliged to give effect to an AD but in emergencies medical indications to save life may take priority (if AD not known about)

Competency or capacity

- an individual's ability to perform a particular task at a particular point in time e.g. a decision regarding their current or future health care includes competency and capacity
- all adults are presumed to have capacity unless it is proven otherwise
- in order to demonstrate capacity, three elements must be met:
  - the person is able to understand and appreciate key basic facts that are relevant to the decision to be made
  - the person is able to weigh the risks and benefits of any given course of action
  - the person is able to express a choice that is made in the absence of coercion
- competency may fluctuate depending on the issues under consideration
- the patient needs to be able to understand information relevant to the decision, to reason and deliberate, to retain the information (even for only a short time), to communicate by any means
- capacity does not necessarily imply rationality
- if capacity is not possessed decisions must be taken by others in that person's best interests and in the least restrictive manner possible

Legally authorised proxy/surrogate decision-maker

- health care practitioners can become familiar with the particular legal requirements by contacting relevant guardianship authorities for up-to-date information. The most up to date information can be found at *https://www.myacp.org.nz*
- all decisions must be made with the patient's best interest in mind and tend to be conservative and life-affirming

Testamentary Capacity

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

Caring for the older person

WHĀNAU-FAMILY VOICE

"Our elders are taonga to us. Look after our taonga."

- New Zealand has a rapidly ageing society, witnessing a faster increase in the proportion of older Māori, Pacific and Asian populations compared to older Europeans
- Ageing and frailty
  - normal ageing encompasses physiological changes in all organ systems, resulting in alterations in metabolism and a decline in physiological reserve
  - frailty is a multidimensional geriatric syndrome characterised by a decline in cognitive and physical reserves, with associated vulnerability to stress or illness
  - many different concepts of frailty exist, with key models being Fried's phenotype model and Rockwood's accumulated deficits model
  - frailty is not an inevitable part of ageing, but its prevalence increases with age. Māori experience frailty earlier than other ethnic groups
  - although frailty itself is seldom a direct cause of death, severe frailty should be considered a terminal illness
- Key aspects to consider when caring for an older person
  - the GERIATRIC 5M Tool is a clinical framework that can be used to integrate key geriatric-specific principles into the care of older adults to maximise their quality of life
  - Multicomplexity
    - › many older adults live with multimorbidity and complex psychosocial needs, necessitating a 'whole-person' approach to care
    - › coordination and integration of care across various disciplines and healthcare settings may be required
  - Mind
    - › regularly evaluate cognition and psychiatric health
    - › examine for the presence of early cognitive impairment, which can be easily overlooked and may impair an individual's understanding of their situation and prognosis, as well as their ability to make complex decisions
    - › address modifiable risk factors for delirium, including avoiding psychotropics and medications with anticholinergic activity if possible
    - › be vigilant for hypoactive delirium, which can be easily missed
    - › address mental health conditions such as depression and anxiety

(See respective chapters on Dementia, Delirium, and Depression for information on assessment and management).

- Mobility
  - regularly assess and optimise physical function, strength, and balance in order to maintain independence and reduce the risk of falls with potentially catastrophic consequences
  - assess falls risk factors and initiate targeted interventions which may include a combination of
    - improving continence
    - providing a mobility aid
    - advising on appropriate footwear
    - implementing strength and balance training
    - conducting home hazard assessment and modification
    - medication review – medications most likely to increase falls risk include antidepressants including SSRIs and tricyclics, antipsychotics, benzodiazepines, and beta-blockers
- Medications
  - Polypharmacy and inappropriate prescribing are prevalent, contributing to symptom burden, frailty, falls, and functional and cognitive decline
  - "start low and go slow," and "keep going" until adequate symptom control is achieved
  - consider using tools and technology, such as pill boxes, blister packs, medication alarms and reminders, to improve adherence
  - do not assume correct medication adherence and routinely reconcile medications with the patient and caregiver
  - regularly review medications, deprescribing those that are poorly tolerated, ineffective, duplicated, or inappropriate. Medication optimisation tools developed specifically for older adults like STOPP/START can assist in the process
  - consider medication adverse effects as explanations for development of symptoms requiring palliative intervention
  - minimise anticholinergic burden, recognising that older individuals are more susceptible to its adverse effects which may add to the symptom burden. Elevated anticholinergic burden is also associated with an increased risk of delirium and falls
- Matters most
  - uncover the individual's personal values, goals, and preferences to guide the care provided
  - advance care planning is particularly relevant for frail older adults given their vulnerability, and those with dementia, who may gradually lose the ability to make informed decisions over time
  - use healthcare crises, and hospital admissions, or admissions to long-term care facilities as opportunities for advance care planning discussions

SECTION 1:
Symptom Control

Pain

PATIENT VOICE

"I can cope with pain… pain pills don't help much."

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

Comprehensive assessment

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

Other assessment factors

PATIENT VOICE

"I might not tell you key information about myself.
Things such as my religious beliefs, inter-generational trauma, spirituality and visitations."

In a bio-medical model of practice it is tempting to assume that pain has a predominant physical component. Often, physical pain is only part of the symptom complex (through direct or indirect tumour effects or non-malignant processes).

Psychological, spiritual and sociological elements will also be identifiable in many people with pain. Fear, anxiety, sadness, anger, frustration and isolation are but a few of the feelings that can contribute to the total perception of pain. All of these elements help to build a realistic picture of the overall impact of pain on the individual's quality of life.

Assessment in the setting of dementia

PATIENT VOICE

"I have lived a meaningful life…
This person before you is only part of who I truly am."

People living with dementia who require palliative care may not, by virtue of cognitive impairment, be able to validly report either the presence of pain, or the level of pain they are experiencing. There is good evidence that those with dementia are likely to be prescribed up to 50% less analgesia in acute hospital settings than those with comparable needs who lack a dementia diagnosis.

There are a number of validated pain assessment scales that can inform pain assessment in the presence of dementia. They include the Abbey Pain Scale, the PAIN-AD and the electronic ePAT (electronic Pain Assessment Tool), which uses facial coding to determine the presence of pain. These are screening tools only and are no substitute for a comprehensive clinical assessment.

The emergence of new behavioural symptoms (such as withdrawal, agitation, anger, aggression and resistiveness to care) in a person with previously stable dementia symptoms should always be an indicator that pain may be an issue. It should be noted that the pain assessment tools mentioned above have not been validated in the presence of significant behavioural disturbance, as they do not reliably distinguish between pain and distress. In the absence of valid pain self-reporting in the setting of severe dementia, considering the views of a whānau-family caregiver who knows the patient and their usual behaviours well may be useful as part of the assessment process.

Unrecognised or undertreated pain can lead to the inappropriate prescription of psychotropic medication instead of adequate pain management.

Management

WHĀNAU-FAMILY VOICE

"Talk to us, include us, we are the main support people. Allow us space to ask for what we need."

Discuss realistic goals of pain management with patient and whānau-family. Treat any exacerbating factors and consider disease modifying interventions.

It is important to encourage patients to develop self-management strategies – recognising that this may not be possible in people with dementia – and to utilise non-pharmacological strategies such as rest, positioning, pacing etc. There are also a number of enabling strategies like goal setting, pain management plans, scripts and diaries that many will find useful.

Address emotional, psychological and spiritual issues as these are intimately connected with the experience of physical pain.

Analgesics

- some pains may not respond completely to opioids
- co-analgesics are useful when response to opioids is poor
- switching route can sometimes help e.g. from oral to subcutaneous
- in prescribing analgesics use a step-wise approach:

morphine
or oxycodone
or fentanyl
or methadone

codeine
or dihydrocodeine
or tramadol
or buprenorphine

paracetamol or NSAIDs/COXII e.g. diclofenac, naproxen, celecoxib

adjunct-analgesics, specific therapies e.g. radiotherapy

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

Initiating morphine/oxycodone in opioid naive patients

- start with small regular oral (if possible) immediate release doses
- titration with slow release morphine/oxycodone is less common than with immediate release
- if using immediate release prescribe morphine elixir (immediate release) (2.5 to 5 mg) every four hours (six hourly for oxycodone) regularly and titrate
- if impaired renal function, (eGFR 30 to 45) give morphine dose every 6 to 8 hours or consider using oxycodone
- if significant renal impairment (eGFR <30) do not use Morphine
- use oxycodone with caution for eGFR 15 to 30. Do not use oxycodone if eGFR <15
- prescribe 'when required' (every 2 hours) dose of ⅕ to ⅙ of the regular 24 hour dose for 'breakthrough', 'episodic' or 'incident' pain
- gradually titrate the dose of immediate-release morphine/oxycodone to effect before converting to sustained-release morphine. Consider titrating the dose up if the patient develops tolerance
- assess how effective each dose is, and how long analgesia lasts
- take additional (rescue) doses into account during dose titration
- if analgesia is achieved for only 2 to 3 hours, increase the dose, not the frequency
- aim to increase the elixir dose gradually every 3 to 4 doses (more often in very severe pain) until analgesia is achieved
- if an older adult, morphine metabolites can accumulate, so consider dosing every 6 to 8 hours and increasing doses more slowly to avoid developing toxicity
- document the amount of morphine/oxycodone taken
- once a stable dosing regimen is achieved (2 to 3 days) convert to a long-acting preparation
  - calculate the total 24 hour dose of immediate release morphine/oxycodone required from 'breakthrough' and regular dosing, divide by two and give twice daily
  - 'when required' every 2 hours dose of ⅕ to ⅙ of the regular 24 hour dose should be prescribed as immediate release once again for pain between doses
- if the patient can no longer swallow
  - give ½ the total 24 hour oral dose by continuous subcutaneous infusion
  - 'when required' doses of ⅕ to ⅙ of the regular 24 hour dose should be prescribed once again for pain between doses
- consider reducing dose if another mode of pain relief is used (e.g. radiotherapy, ketamine)

Initiating fentanyl patches in opioid naive patients

- **Don't!** – fentanyl patches should only be used in patients who have already been exposed to opioids and opioid need established with immediate release preparations

Initiating methadone in opioid naive patients

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

Adverse effects of opioids

- all opioids are associated with the following adverse effects but the incidence (incidences below are for morphine) and severity vary from opioid to opioid (e.g. fentanyl is less constipating than morphine)
- tolerance to some of these adverse effects can develop e.g. nausea/ vomiting but not to others e.g. constipation
  - constipation – 95% of patients (less with fentanyl (50%) – prescribe a laxative prophylactically
  - nausea/vomiting – 30 to 50% of patients – usually in the first 10 days until tolerance develops. Always prescribe an anti-emetic when initiating or increasing opioids
  - drowsiness – 20% of patients – usually in the first 3 to 5 days until tolerance develops
  - confusion – 2% of patients – either reduce the dose, change to a different opioid or consider adding haloperidol. Rates of worsening confusion are greatly elevated in those with a pre-existing cognitive impairment, due to diminished cognitive reserve. Frank delirium can be precipitated
  - hallucinations/nightmares – 1% of patients – give haloperidol or change to a different opioid
  - hyperalgesia – usually to touch as a result of too high a dose of opioid which may improve on dose reduction
  - hyperkatafeia – emotional lability induced by long-term opioid use

Opioid rotation

- opioid rotation (or changing from one opioid to another) is often used when tolerance to the analgesic effects of opioids (stimulation of NMDA receptors) or severe adverse effects occur
- works because of the difference in the mix of opioid receptors stimulated by each individual opioid in each patient (incomplete cross tolerance)
- most often from morphine to oxycodone, fentanyl or methadone
- rotation should only occur under supervision and by a specialist as conversion doses are difficult to predict and are often much smaller doses than those listed below – see Oxycodone, Fentanyl and Methadone in Section 2

Opioid equivalents

- the following are 'single dose' equivalences i.e. ONLY equivalents in healthy volunteers given a single dose
- equivalence in sick patients who are chronically dosed is difficult to quantify – use care when converting from one opioid to another
- pethidine is NOT recommended in palliative care

codeine	60 mg oral	=	6 mg oral morphine
tramadol	100 mg oral	=	10 mg oral morphine
oxycodone	5 mg oral	=	10 mg oral morphine
	5 mg subcut	=	5 mg subcut morphine
methadone	seek advice from Palliative Medicine Specialist		
fentanyl	see Fentanyl page in Section 2		
buprenorphine	see Buprenorphine page in Section 2		

Adjunct analgesics

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

Incident pain

- this differs from breakthrough pain as it occurs predictably with certain activities e.g. turning for cares, transferring on commode etc
- use immediate release preparation prior to this acitivity
- these additional doses should not be added to background opioid dose

Neuropathic pain

PATIENT AND WHĀNAU-FAMILY VOICE

"While you are considering the physical…
I/we will be focused on the spiritual."

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

Causes

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

Characterisation

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

Management

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

WHĀNAU-FAMILY VOICE

"Our person is a taonga to us.
Please treat them with kindness and respect."

Delirium

WHĀNAU-FAMILY VOICE

"It is hard to see our loved one like this."

Toxic confusional states, like delirium, are common in people who are dying

- if irreversible, may be an indication of impending death
- can be most distressing for patients, whānau-family and staff

Diagnosis

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

Causes

There are often multiple organic causes but in up to 50% of cases, specific causes are not found, despite investigations. Diagnosis is dependent on the presence of an appropriate history, rather than the results of a 'delirium screen'. Causes may include

- infection
- organ failure (liver, kidney) and underlying medical conditions
- drugs
  - sedatives
  - anticholinergics
  - opioids
  - benzodiazepine or alcohol withdrawal
  - steroids

- metabolic disturbances
  - dehydration
  - hypercalcaemia
  - hyponatraemia
  - hyper/hypoglycaemia
- hypoxia
- anaemia (severe)
- vitamin deficiency
- cerebral metastases
- cerebral haemorrhage
- epilepsy – post-ictal

Predisposing/precipitating/aggravating factors

- dementia and CNS immaturity
- any other cause of pre-existing cognitive impairment (e.g. intellectual disability, ABI)
- pain
- fatigue
- urinary retention
- constipation
- unfamiliar excessive stimuli
- change of environment
- sensory deprivation
- sleep deprivation

Management

- treat the underlying organic causes if identifiable and treatable
- treat fever, hypoxia, anaemia, dehydration, constipation, fear and anxiety and pain if possible
- ensure there is a safe and secure environment – have adequate staffing, remove potentially dangerous objects, have the bed lowered as far as possible
- prevent sensory over-stimulation – have a single room, minimise noise and staff changes and maintain a warm and comfortable environment
- psychological interventions
  - reassurance
  - orienting aids (clock, personal belongings, presence of a supportive whānau-family member)
  - cognitive strategies (clarification, reality testing, validation and repetition during lucid periods)
  - emotional support (touch, empathy)

- drugs – use if symptoms are severe (in combination with above management)
  - antipsychotics (goal is to calm or pacify rather than sedate)
    - haloperidol is traditionally the drug of choice BUT not in AIDS delirium (HIV makes the CNS more sensitive to dopamine antagonists), hepatic encephalopathy or alcohol withdrawal where benzodiazepines only should be used (see Haloperidol in Section 2)
      - Haloperidol regimen in acute, moderate to severe delirium (evidence suggested that treating mild delirium with haloperidol is ineffective) Oral (tablets, liquid) if compliant, subcut if not initial dosage – 0.5 to 1.5 mg orally
      - repeat and titrate every 30 to 40 minutes until controlled. In general, daily doses in excess of 3 mg should be avoided due to high risks of extrapyramidal side effects (EPSE) in older patients. Large doses (10 to 20 mg over 24 hours) are occasionally required for severe agitation. It may be preferable, however, to sedate with levomepromazine, with or without a benzodiazepine
      - maintenance – 50% of daily dose required to achieve control usually 1 to 3 mg/day (oral)
      - only add anticholinergic agent e.g. benztropine 1 to 2 mg if acute dystonia occurs. Routine use of anticholinergic agents will worsen delirium
      - extrapyramidal side effects are less pronounced with the parenteral route. Thus, if IV access is present, parenteral administration is preferable
    - risperidone (tablets, liquid, wafers) – dosage regimen as per haloperidol
    - olanzapine (tablets, wafers) – doses of up to 2.5 mg TDS can be considered. Doses in excess of this tend to have significant anticholinergic activity, and may make things worse
    - Levomepromazine – doses of 6.25 mg can be given subcutaneously and 12.5 mg over 24 hours via syringe driver. Doses of up to 75 mg over 24 hours may be needed
    - Quetiapine – doses of 12.5 to 25 mg are useful for acute sedation for short periods. Tolerance rapidly develops over several days to the sedative effects of this agent, leading to a tendency towards 'dose-creep' over time. If rapid control of distressing psychotic symptoms is required, however, this agent is not recommended, as it must be titrated up over several days in order to avoid both oversedation and postural hypotension
  - sedatives (should not be used alone in most cases of delirium as they may aggravate symptoms, particularly if inadequate doses are used, so use with an antipsychotic e.g. haloperidol or levomepromazine + midazolam via syringe driver)
    - benzodiazepines e.g. midazolam, clonazepam
    - barbiturates e.g. phenobarbitone
    - melatonin may be useful
  - anaesthetics e.g. propofol (rarely indicated)
  - drug-induced delirium
    - opioid-induced – decrease dose or change opioid
    - anticholinergic-induced – e.g. physostigmine may reverse this

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

Dementia

PATIENT VOICE

"Ko wai au? Who am I? I am more than this person you see today."

WHĀNAU-FAMILY VOICE

"It is like losing our person twice. It is heartbreaking."

Dementia is an insidious, global deterioration of cognition without impairment of consciousness. More than 100 causes are recognised, though most of these are exceedingly rare

- A terminal disease (albeit slow) with a median survival of 7 to 10 years post-diagnosis
- Almost 70,000 Kiwis are living with dementia mate wareware today
- Almost 170,000 Kiwis are likely to be living with dementia mate wareware by 2050
- Four out of five New Zealanders know or have known someone living with dementia mate wareware
- Dementia mate wareware impacts more women than men – around 30% higher
- The total cost of dementia mate wareware to Aotearoa New Zealand is now around $2.5b and will reach around $5.9b by 2050
- Residential care currently accounts for around half of the economic cost of dementia mate wareware borne by government ($1.21b)
- Dementia mate wareware numbers are increasing at a faster rate among Māori, Pacific peoples and Asian populations than those of European New Zealanders[1]

Types

- Alzheimer's is the most common (70% of all dementias)
  - Predominant early deficits are episodic memory and orientation to time
- Vascular (30% of all dementias)
  - accompanies a history of cardiovascular events (CVA/TIA)
  - islands of retained functioning
  - language may be preserved in dysexecutive syndrome
  - gait disturbance
  - subcortical signs
- Frontotemporal (FTD – 10% of all dementias; commonest cause of early-onset disease)
  - can occur in those with Motor Neurone Disease (10 to 15%)
  - disinhibition, apathy and loss of empathy
  - hyperorality, lability, poor insight and compulsive, perseverative behaviours

1 Used with permission from Alzheimers NZ webpage "Facts and Figures" https://alzheimers.org.nz/explore/facts-and-figures/

- Lewy Body Dementia (LBD)
  - Parkinsonism
  - visual hallucinations and cognitive fluctuations
  - cognitive fluctuations typically marked
  - REM-Sleep behaviour disorder
  - vulnerability to delirium
  - extreme sensitivity to antipsychotics – quetiapine is the agent of choice
- Treatable causes
  - depressive pseudodementia
  - subdural and hypothyroidism
  - B12/folate deficiency
  - syphilis
- Others
  - Parkinson's disease (essentially very similar to Lewy Body Dementia), Huntington's, alcoholic, post traumatic brain injury, paraneoplastic, post encephalitic
- Note that mixed types of dementia become increasingly common with age, and that end-stage dementia (regardless of cause) tends to assume a common phenotype. With the exception of Lewy body dementia, determining the exact type of dementia in a palliative/end-stage setting is much less important than recognition and appropriate treatment of a behavioural syndrome.

Assessment

- take an extensive history (in end-stage dementia this will invariably need to be from a whānau-family member or close caregiver)
- formally assess mental state, including the use of cognitive screening tools e.g. Mini-ACE, Montreal Cognitive Assessment (MoCA) – where the patient retains verbal skills
- In many cases a formal cognitive evaluation will not be possible in advanced dementia, but the broader mental status examination remains invaluable, particularly in relation to
  - General appearance and behaviour. Is the patient agitated, distressed, vocalising? Are there any signs of drug side effects (Parkinsonian facies, resting tremor, dyskinetic movements – oro-lingual dyskinesias are particularly common), dystonic reactions, motor tics or perseveration?
  - Affect – does the patient's expression reflect sadness, anxiety, anger? Are they guarded and suspicious? Lability may reflect frontal involvement, and should be differentiated from depression
  - Perception. Does the person appear to be responding to external stimuli?

Behavioural and Psychological Symptoms of Dementia (BPSD)

- delirium
  - a careful history is vital. The biggest single risk factor for delirium is the presence of pre-existing cognitive impairment, so those with dementia are at vastly increased risk. Reduced cognitive reserve lowers delirium threshold
  - A history of acute deterioration (cognitive, functional, behavioural) in the setting of previously stable impairments should always suggest delirium, and should be treated as such

- depression (treat early initially with a SSRI or mirtazapine)
  - this is a difficult diagnosis to make in the presence of advanced dementia, where the patient's ability to report symptoms accurately is compromised
  - clinicians are advised to fall back on the presence of 'hard-core' biological symptoms of depression in this setting (recent change in sleep or appetite patterns, complete anhedonia, self-harm behaviour)
  - if there is any doubt, erring on the side of a trial of treatment is often advisable. Depression should be on the list of differential diagnoses for most behavioural disturbances in dementia, and modern antidepressants are much less toxic than the antipsychotic drugs that might otherwise be prescribed
  - Mirtazapine is a useful drug in this patient group. It has beneficial effects on sleep, appetite and anxiety that occur early in the course of treatment and which are independent of its antidepressant effects
  - the minimum antidepressant dose of mirtazapine is 30 mg. If treating depression there is generally no advantage to commencing at a lower dose (often justified on the basis of minimising sedation, mirtazapine is an inverse agonist at the histamine receptor, however, and thus is more sedating at lower doses)
- agitation/aggression (consider low dose short term antipsychotics, benzodiazepines)
  - identify precipitants (can be difficult)
  - avoid confrontation
  - if the issue is agitation alone, antipsychotics hold no advantage over benzodiazepines, and are considerably more toxic
  - an intermediate half-life benzodiazepine with no active metabolites (e.g. oxazepam 7.5 to 15 mg, temazepam 10 mg) is the safest choice
  - there is evidence for the use of low-dose risperidone in the management of aggression, but the effect size is small
- anxiety
  - peaks in early/mid stages
- delusions (treat with antipsychotic)
  - particularly paranoid
  - beware 'delusions of theft' and 'misidentification delusions.' These may well be beliefs that have arisen as the artefact of cognitive impairment and/or to reflect neurological impairment (e.g. prosopagnosia) and are not likely to be antipsychotic responsive
- hallucinations
  - visual (up to 50% in LBD, although 20% of Alzheimer's patients will hallucinate at some stage during the course of the disease)
- sleep/wake cycle reversal/sundowning
- loss of insight/judgement
- wandering (60% of patients)
  - pacing and lapping (exclude akathisia)
  - (dangerous) eloping i.e. getting lost, accidents
- rejection of care
  - of food, hydration (consider artificial hydration) and hygiene

Complications

- eating and swallowing difficulties, cachexia
- infections – pneumonia, urinary tract
  - in pneumonias, the mortality is sevenfold that of a non-dementia patient
  - treat if symptomatic, but antibiotics may have limited efficacy
- falls – due to impulsivity, frailty, benzodiazepines and other sedatives
- pain – common in very elderly (50%)
  - may present behaviourally (non-verbally, crying, irritability)
  - roughly 70% of patients with significant BPSD are likely to have under-treated or unrecognised pain as a contributing factor
- adverse reactions to drugs
  - antipsychotics – sensitivity (Lewy body disease), parkinsonism, akathisia, acute dystonic reactions, sedation, peripheral oedema, chest infections, accelerated cognitive decline, stroke risk (3 fold that of non-dementia patients, 1.5 fold mortality), hypotension
  - benzodiazepines – sedation, falls

Treatment

As curative treatment does not exist, ensure that end-of-life discussions/advance directives/appointment of enduring power of attorney all happen early before loss of capacity. The environment of care is important – it should be simple, safe, involve attentive and patient staff, include support and education for whānau-family and carers, person-centred, proactive, include distractions, activities, routine, memory cues and benign paternalism.

- Mild – cholinesterase inhibitors may have temporary cognitive benefit
- Moderate – focus on quality of life and maintenance of function
- Severe – maximise comfort, avoid aggressive, burdensome or futile treatments, avoid enteral tube nutrition, consider a secure facility, allow a natural death (AND)

Depression

WHĀNAU-FAMILY VOICE

"We have a big back story of distrust and trauma. This makes it hard for us to accept and understand what is happening."

In end-of-life care it is important to distinguish between clinical depression and profound sadness.

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

Psychological symptoms of major depression may include

- hopelessness
- anhedonia (loss of pleasure)
- morbid guilt and shame
- worthlessness and low self esteem
- persisting suicidal ideation
- lowered pain threshold
- decreased attention and concentration
- cognitive slowing
- impaired memory
- indecisiveness
- early morning wakening
- ruminative negative thoughts
- nihilistic and depressive delusions
- feeling of unreality

Depression in older people and people with dementia

It is worth noting that the 'textbook' symptoms of major depression as they appear in references such as DSM-V have not been validated in older persons. Many older people with depression will not use the word 'depression' to describe their feeling state, but will instead use terms such as 'anxiety,' or 'I'm just worried, doctor.' Taking these terms at face value may lead to the inappropriate prescription of anxiolytics. Older persons also tend to express their depression more frequently in terms of somatic symptoms than younger persons do, which can clearly present diagnostic difficulties in a setting where palliative care is being provided.

Similarly, the diagnosis of depression in the setting of dementia is fraught. In cognitively intact populations, the diagnosis is made on the basis of symptom self-report. In advanced dementia, however, most patients will be unable to reliably verbalise their symptoms. The psychological distress that depression causes may instead be expressed in terms of externalising behaviours, which may include agitation, aggression, pacing and calling out, themselves common behavioural and psychological symptoms of dementia (BPSD). Two of the more reliable 'biological' symptoms of depression in the setting of dementia are recent worsening in sleep or appetite.

SSRI antidepressants are considered first-line pharmacological management for symptoms of BPSD. One of the likely reasons for their apparent success in controlling BPSD is that many cases labelled as BPSD are, in fact, cases of depression manifesting as disturbed behaviour. In a similar vein, while drug treatment trials of depression in the setting of dementia have been disappointing/contradictory, part of the problem inherent in such trials is a lack of certainty around diagnosis. In other words, these trials may well have included persons with undifferentiated BPSD, rather than depression.

A number of screening tools for depression in dementia exist. Perhaps the most commonly used tool is the Cornell Scale for Depression in Dementia. Clinicians should be wary of placing too much faith in the Cornell, however, as it has not been validated in patients with an MMSE of 10 or less, nor in patients with significant BPSD.

The role of antidepressants in treating depression in advanced dementia is controversial, and is likely to remain so, given the methodological problems in 'true case' ascertainment. When in doubt, however, clinicians are advised to err on the side of a trial of treatment.

Risk factors

- inadequate symptom control – unrelieved pain, nausea
- poor quality of life
- lack of social support
- past and/or whānau-family history of depression
- older age
- substance abuse
- misinformed prognosis
- polypharmacy
- specific drugs
  - steroids, cytotoxics, antibiotics, anti-hypertensives, neuroleptics, sedatives, beta-blockers, opioids
- immobility
- advanced malignant disease

Differential diagnosis

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

Management

- mild to moderate depression
  - support, empathy, clarification of stressors or precipitators, explanation, cognitive therapy, symptomatic relief
- severe depression
  - supportive psychotherapy plus drug therapy
  - drug therapy – antidepressants are effective in 50 to 70% of cases
    - › a therapeutic trial is usually appropriate
    - › if in doubt, refer to a specialist psychiatrist
    - › SSRI e.g. escitalopram, sertraline, fluoxetine
    - › although full response to antidepressant therapy may not be evident for 4 to 6 weeks, the lack of any response in the first 10 to 14 days should prompt consideration of a dosage increase or change of agent
    - › alternative agents include mirtazapine, duloxetine and venlafaxine
    - › mirtazapine – can be useful due to its beneficial early effects on appetite, sleep and anxiety, which can be expected to occur well in advance of its antidepressant effects
    - › tricyclic antidepressants should be avoided, as the doses required for adequate response are likely to produce significant anticholinergic side effects, and may thus precipitate delirium, particularly in those with dementia
  - psychostimulants e.g. methylphenidate
    - › not as effective as SSRIs – may help retarded/withdrawn, frail patients for a few weeks only
    - › a response may be achieved from small doses (5 to 30 mg each morning) within days either alone or in combination with an SSRI – watch for additive serotonergic effects. Modafinil may be a useful alternative to methylphenidate

Disorders of sleep and wakefulness

PATIENT VOICE

"I can't sleep… I'm afraid I won't wake up. I want mirimiri to help me sleep."

Sleep disturbance in people who are dying is a frequent occurrence and it requires careful assessment and management.

- sleep patterns change with age and with illness e.g. cancer
  - a reduction of depth and continuity of sleep and an increasing propensity for day-time naps occurs
  - many cancer patients have difficulty falling and staying asleep
  - cytokines are implicated in these changes

Drowsiness/hypersomnia

These are common symptoms, particularly as the end-of-life approaches.

Causes

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

Management

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

Insomnia

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

Causes

- poor symptom control of
  - anxiety, depression, pain, urinary frequency, faecal incontinence, nausea, vomiting, delirium, cough, delirium
- environmental changes
  - admission to hospital or hospice
  - disturbance by staff or whānau-family
- fear of going to sleep and never waking up

- drugs
  - stimulants e.g. methylphenidate
  - steroids (particularly if given after noon)
  - bronchodilators
  - alcohol, caffeine
- withdrawal of benzodiazepines, alcohol or tobacco

Management

- symptom control of above
- establish good sleep hygiene
  - regular bedtimes
  - minimise daytime napping
  - reduce evening stimulants e.g. caffeine, alcohol
  - comfortable bedding
  - comfortable temperature
- relaxation techniques
- drugs
  - hypnotics
    - › short acting benzodiazepines e.g. temazepam
    - › longer acting benzodiazepines e.g. oxazepam
    - › melatonin 2 to 4 mg at night
  - sedative antidepressants e.g. mirtazapine 7.5 to 15 mg nocte
  - sedating antipsychotics e.g. quetiapine 25 to 50 mg at night may be considered if insomnia is resistant to above. Note that tolerance to sedation from quetiapine can occur rapidly (within several days)

Sleep phase (circadian) disorder

(Delayed Sleep Phase Syndrome or Sleep-Wake Reversal)

- a dysregulation of the sleep-wake cycle
  - profound initial insomnia and
  - the inability to arise at desirable hours
- particularly associated with cerebral tumours
- presents a major burden for carers

Management

- shifting the circadian rhythm with behavioural strategies and bright light therapy is impractical in the terminally ill
- relief care for the whānau-family and a night nurse may be necessary as this tends to be an intractable symptom
- drugs are of limited benefit
  - sedatives e.g. benzodiazepines
  - psychostimulants e.g. methylphenidate can promote daytime alertness
  - sedating antipsychotics e.g. quetiapine 25 to 200 mg at night
  - pericyazine 20 to 30 mg at night
  - melatonin 2 to 6 mg at night

Fear and anxiety

PATIENT VOICE

"Ata haere. Slow down… you talk too fast and I need to sit with what you are telling me before I can understand and feel more comfortable about what is happening."

Fear

A brief, reflexive, rational and unpleasant emotional response (being afraid) caused by anticipation or awareness of danger. A present-focused, reality-based reaction initiating avoidant behaviours. Associated with physiological and psychological arousal. May be adaptive and enhance safety, or non-adaptive.

- innate fear (pain, bleeding, being alone, odours, confined spaces, novel places)
- learned fear (dying, death, being buried alive, needles, chemotherapy)

Anxiety

Sustained and excessive uneasiness. Future-focused, irrational, grossly exaggerated response to perceived threat to the 'self', to one's existence. An intrapsychic conflict. Encourages (unsuccessful) attempts to resolve threat.

- may be a normal alerting response
- may be a symptom of a medical condition (e.g. delirium, depression, hormone-secreting tumour), or a symptom of an impending medical catastrophe
- may be the result of an adverse reaction to a drug e.g. bronchodilators, steroids, methylphenidate
- may be a symptom of Generalised Anxiety, Panic or Depressive disorders

Common anxieties and fears centre on

- being ill
- separation from loved ones, homes or jobs
- becoming dependent on others (being a 'nuisance' or 'burden')
- losing control of physical faculties
- failing to complete life goals or obligations
- uncontrolled pain or other symptoms
- abandonment
- not knowing how death will occur
- 'death anxiety' (the fear of non-being)
- spirituality

Management of fear

- avoid threat if possible
- forewarning and preparations
- emotional first aid
- behaviour desensitisation for phobias (a syndrome of pathological fear)
- psychotropic medications of limited effectiveness

Management of anxiety

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

Gastrointestinal system

WHĀNAU-FAMILY VOICE

"It is important for us that we feed our person the kai that they like."

Bowel management

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

Constipation

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

Causes

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

Symptoms

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

Management

- prevention is the key
- if a cause (or causes) are identified remove it (or them) if possible
- exercise reduces the risk of constipation so encourage it where possible
- occasionally increased fibre is useful e.g. bran, kiwi crush or soluble fibre formulations (require activity and fluids to avoid impaction) but in most situations avoiding bulking laxatives, lactulose and high fibre diets is recommended
- laxatives
  - when opioids are prescribed anticipate constipation and prescribe an oral softener with a stimulant laxative e.g. docusate with senna or bisacodyl which may prevent the need for rectal intervention later (NB if combinations cause cramps reduce the dose or use an osmotic laxative such as macrogol 3350 with electrolytes (Molaxole™, Lax-Sachets™)
  - low dose opioid antagonists such as naloxone (marketed in combination with oxycodone and methylnaltrexone) are effective in opioid-induced constipation without affecting analgesia
  - if constipation is already present give a bisacodyl 10 mg suppository and a glycerin suppository or a sodium lauryl sulphoacetate enema (Micolette™)
  - avoid stimulant laxatives in people with signs of GI obstruction
  - if the patient has a partial obstruction use an osmotic/softener laxative e.g. docusate, and avoid stimulant laxatives
  - if the patient has a spinal cord compression where evacuation is difficult keep the bowel motion firm (avoid softeners) and use a stimulant
  - if a patient taking laxatives has no bowel motion for two days and this is not their normal bowel habit give extra laxatives and, if appropriate, kiwi fruit or prune juice
  - if a patient taking laxatives has no bowel motion for three days and this is not their normal bowel habit a rectal examination should be carried out
    - › if soft faeces are found give two bisacodyl 10 mg suppositories or one to two Micolette™ enemas
    - › if hard faeces are found give one or two glycerine suppositories or two bisacodyl 10 mg suppositories or consider macrogol 3350 with electrolytes (Molaxole™, Lax-Sachets™)
    - › if rectum is empty (or no result from first action) repeat abdominal palpation and consider an abdominal X-ray
  - suppositories must make contact with the bowel wall to work
  - methylnaltrexone
- faeces consist of approximately 50% water, 25% bacteria and 25% food residue so even if the patient is not eating there will be faeces in the bowel

Diarrhoea

PATIENT VOICE

"My tinana is telling me that something is wrong."

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

Causes

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

Management – dependent on cause

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

Intestinal obstruction

WHĀNAU-FAMILY VOICE

> *"We want to care for our person in a way that is culturally acceptable to them (and us)."*

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

Symptoms and signs

- constipation or diarrhoea
- intermittent nausea and vomiting, often taking on a faeculent nature with bacterial colonisation
- continuous or colic abdominal pain
- abdominal distension
- altered bowel sounds

Causes

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

Management

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

- explain the predicament
- give dietary advice in order to rest the gut e.g. foods with minimal residue
- minimise colic by stopping osmotic/stimulant laxatives (continue softeners)
- commence Dexamethasone 4 to 8 mg mane subcut as a trial for 5 to 7 days
- start and titrate subcut opioids
- give subcutaneous hyoscine butylbromide (20 mg bolus followed by 60 to 80 mg subcut infusion over 24 hours)
- reduce vomiting by giving appropriate antiemetics e.g. cyclizine with or without haloperidol – metoclopramide should only be used if there is clear evidence that there is only a partial obstruction
- consider alternative measures e.g. surgery, radiotherapy
- iv fluids and nasogastric tubes should be avoided but may be preferred where drug treatment has not worked. Subcut fluids may have a role in some

- somatostatin analogues (octreotide) may be used subcutaneously in specialist practice to reduce secretions and minimise symptoms
- if subacute intestinal obstruction, the aim may be to clear the obstruction using steroids e.g. dexamethasone to reduce the inflammation around the obstruction and hyoscine butylbromide to minimise secretions and colic then, at an appropriate time, to push gut contents through with a prokinetic agent e.g. metoclopramide
- the timings of each change in therapy will depend on the individual patient and their condition
- review the situation regularly

Malignant ascites

WHĀNAU-FAMILY VOICE

"We want to celebrate our person while facing this new reality"

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

Assessment

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

Causes

- peritoneal fluid build-up in the abdomen due to a failure of the lymph system to adequately drain
- tumour in the peritoneal cavity
- low serum albumin
- excess fluid production
- venous compression or vena cava/hepatic vein thrombosis

Management

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

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

Mouth care

WHĀNAU-FAMILY VOICE

"Dental care is very expensive… it has often been out of reach for us."

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

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

Assessment/causes

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

Management – prevention is a priority

- regular tooth and denture brushing, twice daily at least
- regular use of anti-bacterial and anti-fungal mouthwash
- consider using oral probiotic lozenges
- check fit of dentures
- regular dental checks if possible

- regular mouthcare; frequency dictated by assessment
- check for infection
- check for bone or nerve damage
- check mucosa
- reduce caffeine and alcohol, diet drinks (have a low pH)

Hypersalivation

- may be helped with atropine eye drops 1%, (1 to 2 drops in the mouth three to four times a day), ipratropium bromide nasal spray, (1 to 2 puffs in the mouth three to four times a day), radiotherapy or botulinum toxin to salivary glands

Dirty mouths

- chlorhexidine mouthwash is a useful cleansing agent
- sodium bicarbonate mouthwash is used by many, especially in oncology
- there is little point in cleaning the mouth if dentures are worn unless those dentures are also meticulously cleaned (including soaking overnight in ¼ strength Milton™)

Dry mouths

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

Infected mouths

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

Painful mouths

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

Nausea/vomiting

WHĀNAU-FAMILY VOICE

"Please explain in ways that we can understand what is happening."

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

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

Causes

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

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

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

The causes can be summarised as

- higher centre stimulation – fear/anxiety
- direct vomiting centre stimulation – radiotherapy to the head, raised intracranial pressure
- vagal and sympathetic afferent stimulation – cough, bronchial secretions, hepatomegaly, gastric stasis, constipation, intestinal obstruction
- chemoreceptor trigger zone stimulation – uraemia, hypercalcaemia, drugs e.g. opioids, cytotoxics
- vestibular nerve stimulation – motion

Management

- non-drug measures including mouth hygiene, small frequent snacks/meals, sipping cool fluids throughout day rather than large volumes, avoid triggering smells etc
- higher centre stimulation (emotion – fear/anxiety)
  - counselling/explanation/listening
  - a benzodiazepine
- direct vomiting centre stimulation (radiotherapy to the head, raised intracranial pressure)
  - cyclizine
  - dexamethasone
- vagal and sympathetic afferent stimulation (cough, bronchial secretions, hepatomegaly, gastric stasis, constipation, intestinal obstruction)
  - cough – see Cough
  - bronchial secretions – see retained secretions
  - constipation – see Constipation
  - hepatomegaly
    - › dexamethasone
    - › cyclizine
  - gastric stasis
    - › domperidone (minimal extrapyramidal effects)
    - › metoclopramide
    - › erythromycin – has some prokinetic action
  - intestinal obstruction
    - › cyclizine
    - › levomepromazine (methotrimeprazine)
    - › avoid prokinetics e.g. metoclopramide in complete obstruction although use in partial obstruction may help – see Intestinal Obstruction
- chemoreceptor trigger zone stimulation (uraemia, hypercalcaemia, drugs e.g. morphine)
  - haloperidol
  - levomepromazine (methotrimeprazine)
- vestibular nerve stimulation (motion)
  - cyclizine
  - hyoscine patch (scopolamine)
- other drugs which may be useful where others have failed
  - atypical antipsychotics e.g. olanzapine
  - ondansetron (may cause constipation) – experience in palliative care is limited
  - aprepitant (a neurokinin 1 (NK1) antagonist from the class of drugs known as substance P antagonists) – used with steroids and ondansetron for delayed emesis following highly emetogenic chemotherapy. Its place in palliative care has not been established
- other therapies with little evidence include acupuncture, ginger, cannabis

Swallowing difficulties

WHĀNAU-FAMILY VOICE

"What does it mean when our person has trouble swallowing?"

There are many reasons for someone having difficulty in swallowing (e.g. muscle weakness, tumour mass, consequence of stoke etc)

Seek advice from a Speech Language Therapist and/or dietician.

Often changing the consistency and texture of fluid and food can improve swallowing

- thicken thin fluids
- purée foods

Changes in the ability to swallow is a natural part of a person's declining physical condition. If someone is approaching end-of-life, prepare the whanau/family for the changes in oral intake that are naturally going to occur.

Swallowing oral formulations of drugs often becomes difficult for palliative care patients.

- drugs which are available in the capsule form may be more easily swallowed using the 'leaning forward' technique
  - this involves bending the head down rather than tipping it back when swallowing capsules
  - when leaning the head down and forward the capsule floats to the back of the throat ready to be swallowed
  - the standard way of swallowing solid oral formulations – head is tipped back – results in the capsule floating to the front of the mouth making swallowing the capsule difficult
  - this 'leaning forward' technique will not work for tablets as they do not float so use the standard tilting the head back approach
- if swallowing remains an issue consider crushing tablets or opening capsules if appropriate (do not crush slow or modified release or enteric coated solid dose forms), oral liquids or other routes e.g. subcut, intranasal, sublingual, rectal

Taste alteration

PATIENT VOICE

"Food tastes so different to me now. It has affected my appetite."

- reduction in taste sensitivity i.e. hypogeusia
- absence of taste sensation i.e. ageusia
- distortion of taste i.e. dysgeusia

Causes

- local disease of mouth and tongue
- systemic diseases
- partial glossectomy
- nerve damage
- zinc deficiency
- alteration to cell renewal via malnutrition, metabolic endocrine factors, viral infections, hyposalivation
- dental pathology/hygiene
- diabetes
- gastric reflux
- drugs
  - cyclizine
  - anticholinergics (leads to dry mouths)
  - chemotherapy
  - lithium
  - ACE inhibitors
  - citalopram (uncommon)

Management

- remove or treat causes e.g. give, pilocarpine for dry mouth, stop likely drugs
- zinc (but only if zinc is deficient)
- use sialogogues such as chewing sugar-free gum or sour-tasting drops
- may be unresponsive to interventions

Respiratory System

PATIENT VOICE

"Breathing is hard for me… I am tired."

Respiratory symptoms are among the most common at the end-of-life. Dyspnoea (breathlessness), for example, can occur in more than half of patients who are dying, and the incidence increases as death approaches. In addition, cough, haemoptysis, hiccup and pleural pain are present in a considerable number of people who are dying.

Dyspnoea (breathlessness)

PATIENT VOICE

"My whānau can help calm me in times of stress."

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

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

Causes

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

- neuromuscular failure (paraplegia, motor neurone disease, phrenic nerve palsy, cachexia, paraneoplastic syndromes)
- left ventricular failure (congestive heart failure)
- ascites/pleural effusion

- increased ventilatory demand (due to anxiety, anaemia, metabolic acidosis)

Assessment

- careful assessment of each situation to identify probable causes is an essential starting point
- pay particular attention to the descriptions the patient gives of the sensation and experience of breathlessness and ask specifically, 'How would you describe your breathlessness today?'
- severity and meaning for each individual is important as dyspnoea may have a variable effect on quality of life at the end-of-life, varying with the cause(s) and the individual's perception of the meaning of the symptom
- in a broad sense, dyspnoea has at least five main components, each of which must be attended to
  - sensation (what it feels like)
  - perception (how it is viewed in the context of the illness)
  - distress (does it cause suffering or grief?)
  - response (how individuals react)
  - reporting (the language used to relay these elements)

Management

- treat/remove causes where possible with treatments that are similar to those used in general medicine
  - the cancer itself together with radiation or chemotherapy
  - the complications of cancer e.g. pleural effusions, anaemia
  - concurrent non-cancer causes e.g. heart or lung disease
- non-pharmacological management
  - psychosocial support
    - address anxiety and fear by active listening and exploration of the meaning of breathlessness
    - explanation and reassurance
    - relaxation techniques
    - relearning breathing patterns and control
    - discuss coping strategies
  - positioning
  - adaptation and energy conservation which is often most effectively undertaken with the help of occupational or physiotherapists or specialist nurses
  - physiotherapy
  - drainage of effusions or ascites
  - blood transfusion may be useful if anaemia is present and it is appropriate
  - bronchial stents, brachytherapy

- complementary therapies e.g. aromatherapy
- music engagement, therapy and the arts
- draughts of fresh air using fans and open windows

- at the end-of-life non-pharmacological interventions become less effective so greater reliance on drugs is common, although both may be used together
- drugs
  - opioids (usually morphine as efficacy of others have not been studied)
    - › oral/parenteral – oral seems to be more effective than subcutaneous but low dose morphine infusion has proved effective in some patients.
    - › doses are usually small 2.5 to 5 mg every 4 hours or prn and titrate as for pain with aim of comfort rather than resolution of dyspnoea.
  - oxygen
    - › a draught of fresh air (open widow of fan) may be as effective as oxygen so only use in hypoxic patients
    - › efficacy of oxygen varies between patients but if saturations are < 90% oxygen may have some benefits
  - nebulised normal saline
  - bronchodilators (nebulised/inhaled) e.g. salbutamol
    - › for patients with reversible airway obstruction
  - corticosteroids e.g. dexamethasone
    - › for patients with lymphangitis carcinomatosis, bronchial obstruction or radiation pneumonitis
  - benzodiazepines (short acting) e.g. midazolam
    - › in anxious or fearful patients where other methods have failed
  - antibiotics e.g. amoxicillin
    - › if infection is suspected may decrease secretions
  - diuretics
    - › if congestive heart failure or pulmonary oedema are present
  - anticholinergics e.g. hyoscine, glycopyrrolate
    - › if secretions are bothersome – see Excessive (retained) Secretions

Cough

WHĀNAU-FAMILY VOICE

"It is hard to see our loved one struggle. We want to use Rongoā Māori to help them"

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

Causes and treatment

- acute respiratory infection
  - antibiotic (if appropriate), physiotherapy, nebulised saline
- airways disease
  - bronchodilator e.g. salbutamol, inhaled or systemic corticosteroids, physiotherapy
- malignant obstruction (tumour)
  - corticosteroids, anti-cancer therapy, radiation, stenting
- oesophageal reflux
  - prokinetic agents e.g. metoclopramide, positioning, proton pump inhibitors e.g. pantoprazole
- salivary aspiration
  - anticholinergic agent e.g. hyoscine
- cardiovascular causes
  - usual cardiac drugs
- pulmonary oedema
- drugs which can cause cough
  - angiotensin converting enzyme inhibitors e.g. captopril – change or discontinue therapy

Management

- cough with tenacious sputum i.e. a productive cough
  - may respond to steam inhalation, nebulised saline, bronchodilators or physiotherapy
- drugs (as above and below)
  - cough suppressants e.g. codeine, pholcodine, morphine
    - › may be useful in dry non-productive coughs
    - › titrate dose to effect
    - › may not be appropriate in productive coughs as retaining the mucus may encourage infection

- Simple linctus or honey
  - this is a soothing syrup which may be an effective first choice
- paroxetine (for itch of the respiratory tract)
- oxygen
  - may be useful in cough associated with emphysema
- corticosteroids e.g. dexamethasone, prednisone
  - often used to treat cough associated with endobronchial tumours, lymphangitis or radiation pneumonitis

Excessive (retained) secretions

WHĀNAU-FAMILY VOICE

> *"Help us understand what happens at the end-of-life, so we can be prepared to best support our person."*

This phenomenon occurs when a patient is too weak to clear respiratory secretions particularly near the end-of-life.

- air passing through these secretions produces a gurgling or rattling sound ('death rattle') which, although not obviously distressing to the patient may be distressing for whānau-family and carers
- reassurance that the patient is not distressed is important for whānau-family

Causes

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

Management

- Explain and provide support and reassurance to whānau-family and carers
- appropriate repositioning may allow some postural drainage
- drugs
  - treat infective cause if appropriate
  - Furosemide if fluid secondary to cardiac or renal failure
  - anticholinergics e.g. hyoscine butylbromide, hyoscine hydrobromide, glycopyrrolate
    - › can help **prevent the development** of excessive retained secretions but are often started too late in life to effect a major change as secretions already present have to evaporate first
    - › hyoscine hydrobromide may cause delirium while glycopyrrolate and hyoscine butylbromide do not get into the CNS readily
- occasionally suction is needed to remove plugs of mucus but is not always successful and **should be avoided** if possible
- avoid parenteral fluids

Haemoptysis

PATIENT VOICE

"I don't want my whānau-family to see me like this."

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

Causes

It is not always possible to identify the cause and it has been suggested that up to 40% of cases remain undiagnosed.

- tumour erosion – lung or oesophagus
- infection
- pulmonary embolism
- clotting disorders

Management

- anticipate this in high risk patients and prepare them and family/whanau with an explanation, DNR order available, proximity of dark-coloured towels and appropriate medication
- treat/remove the causes if appropriate
- if minor coughing up of blood i.e. flecks or spots of blood
  - not usually helpful to give any specific treatment but patient reassurance may help
- if the bleeding is persistent or is major
  - haemostatics such as tranexamic acid may be useful (1 to 1.5 g two to four times daily)
  - consider radiotherapy which may have some benefit
- if the bleeding is massive
  - the normal 'life saving' interventions of bronchoscopy and intubation are inappropriate
  - reduce the patient's awareness, fear and anxiety with subcutaneous midazolam (10 to 15 mg) with or without subcutaneous morphine. A midazolam plastic vial (15 mg) can be opened and squirt into the side of the mouth.
  - staff should stay with the patient and whānau-family until all concerned feel safe

Hiccup

PATIENT VOICE

> *"Please help us learn calming techniques that would be useful for our person."*

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

Causes

- gastric stasis and distension
- diaphragmatic irritation
- phrenic or vagal nerve irritation
- uraemia
- neurological disease affecting the medulla e.g. brain stem tumour, infarction, encephalitis
- liver disease (hepatomegaly)

Management

- remove any correctable cause
  - e.g. reduction in gastric distension with a prokinetic – metoclopramide – if not obstructed
- pharyngeal stimulation with cold water
- elevation of pCO_2 using paper bag rebreathing or breath holding
- phrenic nerve block may be considered
- drugs
  - Prokinetic e.g. metoclopramide, domperidone
  - corticosteroids e.g. dexamethasone, prednisone
  - antipsychotics e.g. haloperidol, chlorpromazine, levomepromazine (methotrimeprazine)
  - muscle relaxants e.g. baclofen
  - benztropine
  - anticonvulsants may be useful if a CNS cause is present e.g. phenytoin, valproate, carbamazepine
  - gabapentin

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

WHĀNAU-FAMILY VOICE

"We want to use Rongoā to help our person."

Fungating wounds and tumours

PATIENT VOICE

"I don't want people to see me like this… I am embarrassed."

Fungation of wounds or tumours (smelly, exuding necrotising wounds) presents an obvious manifestation of disease that can cause major distress to patient, carers and whānau-family.

- 'fungating' wounds are malignant in nature and combine ulceration with proliferation
- usually seen in the area of the breast or head and neck
- as healing of the wound is rare, the aim in managing these wounds is to achieve maximum patient comfort together with a reduction in the distortion of body image
- odour is often caused by anaerobic bacterial infection of compromised tissue
- the wound may bleed as blood vessels are eroded

Causes

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

Management

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

Itch (pruritus)

PATIENT VOICE

"I want to use my Rongoā to stop the itch."

Itching can be as unpleasant and disruptive as pain and can have just as adverse an effect on quality of life.

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

Causes

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

Management

- treat/remove causes
- attempt to break the itch/scratch cycle by short clipping nails, wearing cotton gloves, applying paste bandages
- apply surface cooling agents with emollients e.g. 0.25 to 1% menthol in aqueous cream, tepid showers, humid environment
- avoid washing with soap and use emulsifying ointment instead and Alpha-keri™ as bath oil
- light therapy may help
- drugs
  - oral anti-histamines e.g. promethazine, cetirizine
  - bile sequestrant e.g. cholestyramine 4 to 8 g per day
  - night sedation e.g. temazepam
  - H2 antagonists (act on histamine receptors in the skin) e.g. cimetidine 400 mg twice daily

- NSAIDs e.g. diclofenac
- anxiolytics e.g. benzodiazepines
- chlorpromazine 10 to 50 mg TDS
- steroids e.g. dexamethasone (lymphoma itch), topical hydrocortisone
- rifampicin 150 to 300 mg per day (chronic cholestasis)
- 5HT3 antagonists e.g. ondansetron (uraemic)
- gabapentin (uraemic)
- paroxetine, mirtazapine (paraneoplastic itch)

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

Lymphoedema

WHĀNAU-FAMILY VOICE

"We know mirimiri… let us help our person."

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

Causes

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

Management

- provide analgesia if painful
- early referral to an appropriately trained professional (usually a physiotherapist) produces best results
- success requires the patient's full cooperation, so management may be suboptimal in those with significant cognitive impairment. In others, a simple explanation of lymph flow and the cause of swelling is essential, together with instruction on daily skin care
- infections must be cleared before commencing treatment
- gentle massage of the affected area helps to shift fluid from one area to another, local practitioners in the techniques may be available
- regular measurement of both normal and affected limbs is essential to monitor progress
- in most cases containment hosiery of an appropriate size and strength should be worn all day, complemented by specific exercises and massage if possible
- if the limb is not in a suitable shape or condition to use hosiery or if the fingers are swollen, compression bandaging or taping may be necessary for approximately two weeks
- diuretics are not usually useful (except when the patient has heart failure or hypoalbuminaemia), may be detrimental and can cause dehydration

Pressure injury care

WHĀNAU-FAMILY VOICE

"Teach us how to prevent pressure sores."

Pressure injuries occur when the blood supply is shut down by pressure e.g. from a hard bed or other surface resulting in tissue death.

Causes

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

Assessment

- A comprehensive assessment should include
  - clinical history
  - pressure injury risk scale
  - skin assessment
  - mobility and activity assessment
  - nutritional assessment
  - continence assessment
  - cognitive assessment
  - assessment of extrinsic risk factors

Management

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

Sweating

WHĀNAU-FAMILY VOICE

"We want to help our person to relax and feel comfortable."

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

Causes

- environmental temperature changes
- endocrine (oestrogen or androgen deficiency, hypoglycaemia, hyperthyroidism)
- emotion
  - usually confined to the axillae, palms and soles
- lymphomas, hepatic metastases and carcinoid
  - may produce drenching night sweats
- intense pain precipitating or manifesting through anxiety and fear
- infection
- drugs
  - alcohol
  - antidepressants (especially venlafaxine)
  - opioids

Management

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

Systemic effects of terminal diseases

WHĀNAU-FAMILY VOICE

"There is so much to understand."

Anaemia

WHĀNAU-FAMILY VOICE

"Why is our person so weak? What can we do?"

A significant proportion of people with advanced or chronic disease are anaemic.

- symptomatic anaemia usually presents when the haemoglobin is below 80 g/L although, if chronic, patients may adapt to this concentration

Symptoms

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

Causes (often multiple)

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

Management

- blood transfusion
  - rarely improves symptoms significantly for any length of time BUT may be considered, prior to further active treatment or a significant whānau-family event
  - it is often easier to give a transfusion rather than deal with the negotiation involved in not treating although the latter may be more appropriate
  - time, attention to detail and information for the patient and the whānau-family are all essential in the decision making and consent process
- erythropoietin
  - expensive, not readily available and response can be slow and limited

Cachexia

WHĀNAU-FAMILY VOICE

"Why is this happening?"

Cachexia can be distressing for both the patient and their whānau-family and carers. It is difficult to watch a person 'waste away' and is often perceived as a sign of impending death.

- cachexia (derived from the Greek *kakos* (bad) and *hexis* (condition))
- defined as a multifactorial syndrome with ongoing loss of skeletal muscle mass that cannot be fully reversed leading to progressive functional impairment
- diagnosis – weight loss greater than 5%, or 2% in individuals already showing depletion
- develops progressively through various stages – precachexia, cachexia, and refractory cachexia
- refractory cachexia or cancer anorexia cachexia syndrome – very advanced cancer (preterminal), active catabolism low performance status (WHO score 3 or 4), and life expectancy less than 3 months
- may complicate many chronic or end-stage diseases in addition to cancer
- not starvation, which can be reversed with nutrition
- distinct from age-related loss of muscle mass, primary depression, malabsorption syndromes and hyperthyroidism
- in the setting of **advanced dementia**, the presence of cachexia will often reflect a deteriorating oral intake over the preceding weeks/month rather than a more traditional 'ominous' cause. Declining oral intake leading to significant weight loss is a poor prognositic sign in this group, however, and its presence may be a marker that the person with dementia is entering a palliative stage of management

Causes

The metabolic mechanism of the progressive wasting is uncertain.

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

Assessment

Cachexia should be considered if the patient has lost ≥ 5% of their body weight and/or has a BMI < 20 kg/m^2 and 3 out of the following are present

- decreased muscle strength
- fatigue or reduced physical activity
- anorexia – lack of hunger, early satiety, disinterest in food, altered sense of smell and taste
- low fat-free mass index (low muscle mass)
- abnormal biochemistry
  - CRP > 5 mg/L
  - IL-6 > 4 pg/mL
  - Hb < 12 g/dL
  - serum albumin < 32 g/L

Treatments

- favourite foods
- support to patient and whānau-family to allow un-pressured eating
- referral to a dietician for advice and prescribing of nutritional suppliments
- drugs (efficacy is minimal for most)
  - dexamethasone 4 mg/day for 5 days
  - medroxyprogesterone
  - megestrol
  - EPA (up to 2 g per day)
  - cannabinoids
  - prokinetics e.g. metoclopramide
  - antidepressants e.g. mirtazapine
  - thalidomide
  - olanzapine

Nutrition

PATIENT VOICE

"I am not hungry, and food tastes different."

WHĀNAU-FAMILY VOICE

"It is important to us to feed our person."

Good nutritional advice from a dietician improves patients' quality of life.

- ensuring food choices that are
  - of good quality and attractively presented
  - appealing on multiple sensory levels (sight, taste, aroma, texture) to maximise cues to eating, particularly in those with impaired cognition
  - appropriate to the patients' cognitive level (e.g. provision of finger foods where the ability to use cutlery has been lost)
  - appropriate to the maintenance of quality of life
  - not detrimental to the patient i.e. aggravate nausea, or be of a difficult texture/ moisture content to swallow
  - preferred foods which may entail lifting dietary restrictions and discussing with the patient's whānau-family that food intake is no longer for the purpose of sustaining life and fuelling bodily processes but rather for pleasure
- providing an environment that allows for social interaction around meal times i.e. central dining room, playing of music during meal times
- note that for people with advanced dementia, a quieter environment that minimises distractions during mealtimes may be more useful
- maintaining comfort
- providing weight gain may be appropriate initially, but during the terminal phase it is not an appropriate nutrition intervention goal

In some instances, it may become inappropriate to hydrate or feed a patient, these cases should be discussed by a multidisciplinary team on a case-by-case basis.

A dietitian can provide

- complete nutrition assessments
- nutritional care plans considering an individual's life expectancy, treatment plan and overall functional status
- assessments of nutritional factors impairing the patient's physical and psychological well being
- patient-centred strategies such as food fortification, meal timing/ frequency and oral nutrition support
- flexible menus by liaising with catering staff to enable inpatients to enjoy their preferred foods
- an advocate role for the patient (both for and against) regarding more aggressive forms of nutrition support on a case by case basis
- clarification for the team and the patient the place of artificial nutrition when the patient is approaching the terminal phase

Organ failure

PATIENT VOICE

"I am scared."

WHĀNAU-FAMILY VOICE

"We are afraid."

Cardiac failure

The treatment of patients with end stage cardiac failure centres around the relief of the accompanying symptoms

- dyspnoea
- cough
- fatigue
- immobility
- oedema

Treatment of the symptoms is the same as for other causes in palliative care.

Perhaps the most difficult part of the management of these patients is when and how to discontinue the many cardiac medications prescribed (See Deprescribing section). As yet there is no clear evidence for the order or rate of discontinuation. Negotiation with patient, whānau-family and cardiologist may produce agreement on a process for this. Once swallowing becomes a problem consideration should be given to stopping medications.

Hepatic failure

End stage liver failure is usually seen with liver metastases, liver primary and/or past alcohol abuse/hepatitis.

Symptoms

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

Drug dosing

- there is no single marker for liver dysfunction but albumin concentrations and INR are a measure of how well the liver can clear drugs (its metabolic capacity)
- doses of metabolised drugs (drugs that are mainly cleared from the body by the liver rather than the kidneys i.e. approx 70% of drugs) should be adjusted in severe liver failure (albumin of < 30 g/L and an INR of > 1.2) by approximately 50% especially drugs with low therapeutic index e.g. antidepressants, antipsychotics, opioids, paracetamol, anticonvulsants, NSAIDs

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

Renal failure

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

Symptoms

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

Management

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

Drug dosing

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

Creatinine clearance (CrCl)

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

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

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

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

Paraneoplastic syndromes

WHĀNAU-FAMILY VOICE

"Please get to know us, so that we can trust you to help us."

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

Dermatological syndromes

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

- acanthosis nigricans (treatment generally ineffective)
- dermatomyositis (treatment requires removal of the cause but symptoms may be managed with corticosteroids)
  - associated with lung, breast, ovarian, pancreatic, stomach, colorectal cancers and non-Hodgkin's lymphoma
- acquired ichthyosis (treat the underlying cause)
- paraneoplastic pemphigus (use steroids and ciclosporin)

Metabolic syndromes

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

Neurological/psychiatric syndromes

- Lambert-Eaton myasthenic syndrome (LEMS)
  - associated with small-cell lung cancer
  - manifests as muscle weakness and fatigue
  - may respond to immunosuppression, plasmapheresis and 3,4 diaminopyridine (3,4 DAP)
- sub-acute cerebellar degeneration
  - associated with ovarian and lung cancer
- polymyositis
  - associated with non-Hodgkin lymphoma, lung cancers, bladder cancers
- motor neuropathy
  - associated with lymphoma
- peripheral neuropathy
  - associated with small-cell lung cancer

- limbic encephalitis
  - changes in mood, personality
  - memory impairment (recent more than remote)
  - seizures

Management

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

Venous thromboembolism

PATIENT VOICE

"What is happening, and what does this mean?"

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

Diagnosis/symptoms

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

Causes and risk factors

- malignant disease
- recent chemotherapy or surgery
- immobility
- malignant pelvic disease
- familial (hereditary factors)
- age (over 40)
- obesity

Management

If the patient is at risk of VTE

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

Treatment for VTE (DVT – includes prevention of PE and/or recurrent thrombosis)

- anticoagulation with a LMW heparin or a DOAC e.g. enoxaparin or rivaroxaban should be started immediately unless there is a contraindication – enoraparin has previously been the preferred option but increasingly rivaroxaban is being prescribed due to ease of use
- warfarin requires blood tests (INR may be very difficult to keep stable in those with advanced disease and variable nutritional intake)
- re-assess the patient regularly to confirm the management plan is appropriate to the stage of their illness and their wishes
- if warfarin is used start at the same time as LMW heparin and continue the LMW heparin for 2 days after achieving therapeutic INR
- haemorrhagic complications occur in almost 50% of people with advanced cancer (due to drug interactions or hepatic dysfunction)

Weakness/fatigue

PATIENT VOICE

"Please don't rush me, I need time to settle into this new reality."

Weakness and fatigue are amongst the most common and debilitating symptoms at or near the end-of-life.

- it is often assumed that weakness is an inevitable consequence of approaching death BUT there are many factors that may exacerbate or precipitate weakness
- careful assessment may result in interventions that can improve quality of life
- there are often two main contributing factors
  - cachexia
    - › a debilitating state of involuntary weight loss complicating chronic malignant, infectious and inflammatory diseases that contributes to mortality. See Cachexia section
  - asthenia
    - › fatigue or lassitude
- easily tired and a decreased capacity to maintain adequate performance
  - › generalised weakness
- anticipatory subjective sensation of difficulty in initiating a certain activity

Causes

Cancer related

- cachexia (see Cachexia section)
- decreased food intake
  - nausea, vomiting, constipation, intestinal obstruction, diarrhoea, malabsorption, 'squashed stomach syndrome' in hepatomegaly, tumours, ascites, mouth and throat problems including infection, poor teeth, thrush, taste alteration
- metabolic problems
  - hyponatraemia, uraemia, liver failure, hypercalcaemia, anaemia from any cause

- emotional causes
  - anxiety, depression, fear, isolation, apathy, stress
- neuromuscular damage by tumour
  - to brain, spinal cord, peripheral nerves
- paraneoplastic syndromes e.g. Lambert-Eaton myasthenic syndrome, motor neuropathy
- radiotherapy and chemotherapy
- sleep disturbance
- depression

Non-cancer related

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

Management

- establish and, where possible, treat or remove cause
  - review the drug regimen
  - correct metabolic abnormalities
- give dietary advice/support
  - increase calorific intake if possible and appropriate
- exercise
  - exercise may be effective particularly in fatigue caused by radiotherapy
  - limited exercise programmes have been shown to be beneficial even in those close to the end-of-life
- drug therapy
  - hormones e.g. megestrol acetate, medroxyprogesterone
    - › mechanism of action is unclear but dose related weight gain, improved calorie intake and improved sense of well-being have been reported
    - › effect on fatigue is thought to be minimal
  - prokinetic antiemetics e.g. metoclopramide
    - › decrease nausea and vomiting, increase food intake and appetite
    - › no evidence of weight gain has been reported

- steroids e.g. dexamethasone
  - weight gain and fat deposition has been documented but with no increase in lean body mass
  - benefit may be transient
- eicosapentaenoic acid (EPA) and nutritional support in combination with anti-inflammatory agents (COX2 inhibitors) have been used
- stimulants e.g. methylphenidate, modafinil

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

Other considerations

PATIENT VOICE

"Understand that my past informs my future."

Complementary and alternative medicine

WHĀNAU-FAMILY VOICE

"Rongoā Māori will have a positive effect on all areas of our person's wellbeing."

- There is no universally agreed definition of Complementary and Alternative Medicines (CAM) but The World Health Organisation defines it as:
  'A broad set of health care practices that are not part of a country's own tradition and not integrated into the dominant health care system.' Other terms sometimes used to describe these health care practices include 'natural medicine', 'non-conventional medicine' and 'holistic medicine'.
- Complementary and Alternative Medicines (CAM) are widely used in Australasia
- a drug history should include all medicines including CAMs
- CAMs can sometimes adversely impact on conventional therapies
- CAMs use may be influenced by cultural beliefs and behaviours

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

Deprescribing in palliative care

WHĀNAU-FAMILY VOICE

"Does stopping medications mean my loved one will die sooner?"

Deprescribing is the process of ceasing inappropriate medications safely and effectively.

- an individualised process, focusing on the patient, and taking into account their physical function, comorbidities, preferences, and lifestyle
- an ongoing process as medicines that were initially appropriately prescribed may become inappropriate over time
- often not carried out in palliative care when it perhaps should be e.g. in cancer patients who are transitioning from curative to palliative treatment or in terminally ill patients on medications with long term benefits only e.g. statins
- important because polypharmacy may lead to an underuse of essential medications and a reluctance to start new medications and an increased risk of harm due to the 'prescribing cascade', where more medications are prescribed to treat the side effects of others
- always consider the time required to obtain the expected benefits from medications vs expected life expectancy

Benefits

- improved quality of life
- reduced pill burden
- reduced potential adverse drug reactions
- improved medication adherence

Triggers

- older patients presenting with falls, delirium, or cognitive impairment
- development of adverse drug reactions
- worsening physiological function (cardiac/ hepatic/ renal failure)
- transition of care moments (hospital <=> home <=> palliative care unit <=> nursing home/respite)
- end-of-life

Enablers for deprescribing

- fear of increased adverse effects, addiction or tolerance
- inconvenience of medication taking

Barriers to deprescribing

- patient reluctance
- feelings of hopelessness (e.g. 'not worth treating anymore')
- whānau-family pressure to continue treatment, and concern from general practitioners about stopping medications first prescribed by medical specialists

When deprescribing a medication remember that the pharmacodynamics and pharmacokinetics of other medications may be affected; use recognised tools as a starting point

- Beers criteria
- STOPP (Screening Tool of Older Person's Prescriptions)
- START (Screening Tool to Alert doctors to Right Treatment)
- anticholinergic risk scale

The deprescribing process

- take a comprehensive medication history
- ascertain indications, compliance, and potential adverse reactions
- use medication review/reconciliation services provided by pharmacists if available
- estimate life expectancy and identify any medications unlikely to provide meaningful benefit
- set goals and create a plan
  - reduced pill burden to the patient, adverse drug reactions
  - improved symptom relief and the quality of life
- emphasise that if medications are being ceased, it is not because the patient is not worth treating, but rather that the medications are causing harm or have no benefit
- relax targets of therapy e.g. levels for blood pressure, blood sugar levels, and whether blood tests should be performed
- deprescribe one or two medications at a time, not all at once
- consider a trial withdrawal to determine continuing efficacy
- provide education around what to do if symptoms return or withdrawal reactions occur
- a multidisciplinary approach should be used, with all involved and informed in the process

Common deprescribing

- anti-hypertensives
  - monitor blood pressure post cessation, as many patients remain normotensive
  - beta-blockers need to be weaned slowly to prevent rebound hypertension/ tachycardia. NB use caution when ceasing in heart failure
- aspirin – time to benefit usually exceeds life expectancy
- diuretics – do not deprescribe if being used for symptomatic treatment or for heart failure
- statins – no evidence of benefit in shortened life expectancy or in older patients (when used for secondary prevention)
- oral hypoglycaemics (OHGs) – short term risks of continuing treatment outweigh benefits – see sections on Diabetes, Hyperglycaemia and Hypoglycaemia
- bisphosphonates – no evidence in shortened life expectancy, unless used for hypercalcaemia due to malignancy or for bone pain
- complementary alternative medicines (CAMs) – no evidence of benefit, unless treating a low blood plasma concentration, or to treat a symptom (zinc for taste disturbance)
- proton pump inhibitors (PPIs) – determine indication for use, as this is often not clear. Continue use if patient is on long term steroid treatment, has a history of peptic ulcer disease, active bleeding, or GORD
- cancer directed therapies – often continued in many palliative patients to improve symptoms and quality of life (e.g. preventing tumour flare at the end-of-life)

Dexamethasone use

PATIENT VOICE

"I am scared to use this medicine."

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

Adverse effects

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

Prescribing

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

Diabetes, hyperglycaemia and hypoglycaemia

The pathophysiology of diabetes in the palliative care setting (and particularly in the terminal phase) may be complex as the control of blood glucose may be lost due to insulin resistance associated with illness and also because of erratic nutritional intake. Certain malignancies e.g. pancreatic cancer also affect the beta cells directly.

Key considerations include

- the patient's diabetes management plan is likely to need revising. This may include raising glucose targets, reducing dietary restrictions, and simplifying diabetes medications. Marked hyperglycaemia should be avoided as this may exacerbate pre-existing cachexia – in the catabolic state insulin has an anabolic effect, so may be useful treatment
- management must balance treatment tolerability (including tolerability of blood glucose monitoring if required) with treatment efficacy and symptom control

Diabetes

Type 2 diabetes

- tight control of blood glucose concentrations is not necessary, although if it is easily achievable it may increase quality of life
- relax usual dietary restrictions and adjust insulin/glucose lowering agent doses as appropriate
- if the patient is taking metformin consider discontinuing it to avoid the adverse effects of metformin e.g. nausea, weight loss and lactic acidosis. If this results in hyperglycaemia, the addition of other agents may be considered, including insulin
- if the patient is taking a dipeptidyl peptidase inhibitor e.g. vildagliptin this may be continued if renal function allows
- SGLT2 inhibitors (empagliflozin) – withdrawal should be considered if hydration is an issue, or if oral intake is limited/variable. The risk of euglycemic ketoacidosis is increased in acute illness and the fasting state – test ketones in this setting if SGLT2 inhibitor has been continued
- GLP-1 agonists (dulaglutide, liraglutide) should be discontinued if the patient has reduced appetite, weight loss, abdominal pain or other gastrointestinal symptoms or if there are other risk factors present for pancreatitis
- weight loss and decreased appetite may reduce blood glucose concentrations and dose requirements for antidiabetic agents
  - once weight loss begins or appetite decreases, halve the dose of antidiabetic agent in previously well controlled patients
  - reduce doses further or stop as required
- on admission to a hospice, oral hypoglycaemic agents i.e. sulphonylureas will not be required unless there is an infection or other serious stress in which case
  - monitor blood glucose concentrations every two days (1 to 2 hours after the main meal if possible) and treat hyperglycaemia if symptomatic
- symptoms of HYPERGLYCAEMIA will usually appear at blood glucose concentrations of > 15 mmol/L so treatment should begin only above this concentration (in the near terminal phase, may consider treatment if blood glucose > 20 to 25 mmol/L)
  - avoid HYPOGLYCAEMIA during this treatment as it may be difficult to reverse without systemic therapy especially if the patient is vomiting or not eating

- give a fast-acting insulin analogue e.g. lispro (Humalog™), aspart (NovoRapid™) or glulisine (Apidra™) insulin 2 to 4 hourly initially (usually for 24 hours) in doses determined by monitoring – usually 5 to 10 units BUT tailor dose to both the size of the patient and food intake
- once glucose is in the range 10 to 15 mmol/L, convert to an intermediate or long acting insulin e.g. isophane insulin (Protaphane™) or glargine (Lantus™) once or twice daily injections at 75% of the 24 hour short acting dose. Chart a fast-acting insulin analogue insulin to be used for correction of hyperglycaemia (post-prandially if eating)
- monitor fasting blood glucose concentrations daily for several days then twice per week
- discuss management with the patient to ensure that the treatment goals of the patient and health care team are aligned

Type 1 diabetes – patients with Type 1 diabetes make little or no insulin themselves; these are the minority of patients who are on insulin.

- insulin must be continued even in the terminally ill to avoid diabetic ketoacidosis. Consider capillary beta hydroxybutyrate monitoring – if > 1.4 mmol/L ketosis is likely and should be treated if appropriate
- tight control is not necessary
  - a blood glucose concentration of 10 to 15 mmol/L is a good target unless patient is symptomatic
- if the patient is well nourished and has a steady oral intake negotiate with the patient (or substitute decision-maker) re the following
  - maintain the usual dose of insulin
  - monitor blood glucose concentrations twice a day every 3 days
  - when appetite decreases, increase blood glucose concentration monitoring and decrease insulin
- If the patient is using continuous glucose monitoring, discuss whether the patient finds this technology useful or whether they want to modify or discontinue this technology
- if a patient is using an insulin pump (continuous subcutaneous insulin infusion) – discuss with the patient +/- their specialist team the options of continuing this or changing to multiple daily injections with long and short-acting insulins. If the patient wishes to continue with their insulin pump, discuss adjusting pump settings with the patient and, if necessary, their diabetes care team
- if patient is vomiting, is no longer eating or has a variable appetite
  - use a base line long-acting insulin e.g. glargine (Lantus™) daily and chart a fast acting insulin analogue e.g. lispro (Humalog™) or glulisine (Apidra™) insulin to be used for breakthrough hyperglycaemia (post-prandially if eating)
  - monitor frequently
- if the patient is near to death
  - discuss continuation of insulin with patient and whānau-family

Hyperglycaemia

Symptoms

- at blood glucose concentrations of < 15 mmol/L
  - major symptoms are rare
- at blood glucose concentrations of 15 to 40 mmol/L
  - dehydration, dry mouth
  - thirst
  - polyuria
  - lethargy
  - blurred vision
  - candidiasis
  - skin infection
  - confusion
- at blood glucose concentrations of > 40 mmol/L
  - drowsiness
  - obtundation
  - coma

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

Causes

- in patients with diabetes
  - lack of insulin or hypoglycaemic agent
  - loss of dietary control
  - stress, illness
  - infection
  - myocardial infarction
  - GI motility disorders and obstruction
- in patients without diabetes
  - malignant disease
    - › over ⅓ of cancer patients will develop Type 2 diabetes – an effect on metabolism
- drugs (even in patients without diabetes)
  - corticosteroids e.g. dexamethasone, prednisone
  - diuretics (at high dose) e.g. bendrofluazide, frusemide

Management

- in active palliative care patients
  - closely monitor blood glucose concentrations as this may help them to retain function
- in patients who are close to death
  - aim for minimal monitoring and maximal comfort
  - 'treat the patient rather than blood glucose concentration'
  - aim for maximum quality of life by loosening control of blood glucose and encouraging eating if appropriate
- in patients with Type 2 diabetes
  - often rehydration will partially reverse hyperglycaemia
  - BUT insulin may be necessary – often once daily intermediate or long-acting insulin will provide adequate control
- in patients with Type 1 diabetes
  - continue with the patient's usual regimen if possible. If treatment simplification is required, ensure to give insulin at least twice a day (at least one dose of long acting insulin and one short acting insulin correction dose), basing the doses on body weight and predicted carbohydrate intake
  - withdrawal of insulin in these patients will lead to diabetic ketoacidosis (acidosis, shock then death), often over a period of hours or days
  - if diabetic ketoacidosis occurs treat with rehydration and iv insulin if appropriate
- drug related monitoring of blood glucose
  - corticosteroids e.g. dexamethasone, prednisone
    - › often cause hyperglycaemia, even in patients with no history of diabetes
    - › any patient who has taken them for longer than three weeks should have intermittent blood glucose concentration monitoring
    - › patients with diabetes taking them should have more intense blood glucose monitoring depending on the prognosis
- monitor fasting blood glucose concentrations daily for a week then three times a week for three weeks or until stable then weekly
- in terminal patients take a fasting blood glucose concentration every two days for one week and then according to clinical status
- patients who are already on insulin are likely to need an increase in their dose of insulin when they start corticosteroids

Hypoglycaemia

Symptoms – CNS

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

Symptoms – peripheral

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

Causes

- diseases
  - infection, sepsis
  - organ failure – renal, hepatic, cardiac
  - rare causes – insulinomas, autoimmune disease, neuroendocrine tumours
- failure to adhere to good glucose monitoring technique
- decreased food/carbohydrate intake
- drugs
  - insulin
  - hypoglycaemic agents e.g. sulphonylurea
  - alcohol
  - quinine
  - pentamidine

Management

- treat/remove causes where possible
- If alert and able to eat – oral glucose followed by longer acting carbohydrate (e.g. sandwich)
- If decreased consciousness or not able to eat – iv glucose, glucagon (depending on setting)
- monitor blood glucose concentrations

Palliative chemotherapy

WHĀNAU-FAMILY VOICE

"Help us understand what is happening, because we won't accept that life is ending, until it ends."

- palliative (i.e. non-curatative) active treatments include surgery, chemotherapy and radiotherapy
- monoclonal antibody and immunotherapy drugs are being used more commonly with effect
- signal transduction inhibitors are also being used for longer (such as EGFR, BRAF, BCR-ABL, HER2 and ALK inhibitors)
- two thirds of all chemotherapy treatments given are with 'palliative' intent
- the aim is the palliation of symptoms but the benefit of treatment should exceed the adverse effect on quality of life
- patients of all ages who present late with chemoresponsive tumours may benefit from chemotherapy
- a few patients will gain improved survival while others may get symptom relief or time to prepare for death
- patients need to be carefully supported medically, especially if frail at the time of treatment
- although doctors may be reluctant to give chemotherapy to very ill patients, patients are often keen to try it, even if the benefits may be small

Benefits

- an often only modest survival gain of months
- chemotherapy-induced symptoms are less disruptive to quality of life than the effects of the cancer itself
- may also improve the patient and their whānau-family psychological well being because 'something is being done'
- decreased tumour bulk

Adverse effects

- terminal cancer patients who receive chemotherapy during the last months of their lives are less likely to die where they wish and are more likely to undergo invasive medical procedures
- patients may express more concern about chemotherapy-induced symptoms than about the ultimate effect of the cancer
- bone marrow failure (anaemia, neutropenia, thrombocytopenia)
- unrealistic hope
- avoidance of 'death talks' and preparations
- nausea / vomiting
- lethargy / fatigue
- mucosistis and loss of taste
- peripheral neuropathies e.g. with vincristine
- alopecia
- diarrhoea
- constipation
- stomatitis

Palliative sedation

WHĀNAU-FAMILY VOICE

"We don't want to give those drugs to our loved one… why should we allow this medicine."

This is considered when all other symptom-relieving measures have failed and the patient is clearly distressed. This is a MDT decision with significant discussion with patient and whānau-family.

Reasons for palliative sedation

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

How palliative sedation is achieved

- the level of sedation should be titrated stepwise to the level required for the removal of distress
- drugs
  - benzodiazepines e.g. midazolam (subcut 5 to 60 mg/24 hours) in combination with a sedating antipsychotics e.g. levomepromazine (methotrimeprazine) (subcut 12.5 to 200 mg/24 hours) with appropriate PRN dosing
  - barbiturates e.g. phenobarbitone (subcut 600 to 1,200 mg/24 hours)
  - dexmedetomidine – experience in palliative care is limited
  - opioids
    - › BUT increasing doses may not result in increased sedation (opioids tend only to be sedating in the opioid naive) and may instead induce respiratory depression or seizures

Regularly review the target level of sedation and effectiveness of sedation e.g. using RASS-PALL tool.

Involve specialist palliative care team early in discussions.

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

Terminal agitation

WHĀNAU-FAMILY VOICE

"Why is this happening?... what can we do to help?"

Perhaps best conceptualised as a prolonged delirium, this may indicate physical, psychological and/or spiritual discomfort. It is usually a 'pre-death' event.

A significant proportion of new-onset BPSD-type behaviours in fact represent terminal agitation. Early recognition of the syndrome enables appropriate palliative measures to be instituted early.

In the residential care setting, predictors of terminal agitation can include chest infections, unexplained fevers, poor oral intake, significant recent weight loss, the presence of bed sores, and increases in verbal and motor behaviours.

Terminal agitation is poorly recognised and is often interpreted by care staff as a worsening of behavioural and psychological symptoms of dementia (BPSD). Early data from the Australian national Severe Behaviour Response Teams (SBRT) found that up to 10% of referrals to this service were ultimately revealed to have been on a terminal trajectory.

Causes

- physical discomfort
  - unrelieved pain
  - distended bladder or rectum
  - physical restraint
  - insomnia
  - uncomfortable bed or environment
- delirium (see Delirium section)
- psychological discomfort
  - anger
  - fear
  - guilt
  - unfinished business
- spiritual discomfort/ distress
  - helplessness
  - hopelessness
- drugs
  - akathisia induced by dopamine antagonists e.g. metoclopramide, haloperidol (and occasionally via sedating antihistamines such as promethazine)

Management

- assess and treat/remove possible causes
- explain what's happening to the whānau-family, patient (if appropriate) or main carers
- have the whānau-family present to reassure and support
- discuss psychological discomfort e.g. anger, fear, guilt
- drugs
  - see Delirium section and Anxiety and Fear section
  - benzodiazepines e.g. midazolam in inadequate doses can aggravate (by disinhibition) rather than relieve restlessness in some patients
  - if levomepromazine (methotrimeprazine) with a benzodiazepine are ineffective consider phenobarbitone or dexmedetomidine

WHĀNAU-FAMILY VOICE

"We want to be prepared for what lies ahead."

Convulsions

WHĀNAU-FAMILY VOICE

"This is frightening to see… what can we do?"

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

Causes

- previously diagnosed epilepsy, brain trauma/surgery, brain tumour/mets
- drugs
  - some lower seizure threshold e.g. phenothiazines, tricyclics
  - interactions – antiepileptics have many variable and unpredictable interactions – see individual drug pages
  - withdrawal e.g. of steroids, alcohol (Section 2)
- metabolic disturbance, e.g. hypoxia, hyponatraemia, hypoglycaemia

Management

Prophylaxis

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

- if oral route is not available consider
  - clonazepam 1 to 4 mg/24 hours by subcut infusion
  - midazolam 10 to 60 mg/24 hours by subcut infusion
  - levetiracetam 1 to 3 mg via CSCI/24 hours
  - consider the use of phenobarbitone if convulsions are not effectively managed by other agents

Grand mal convulsions or status epilepticus management

- make the patient safe, explain what is happening and reassure
- drugs
  - rectal diazepam 10 to 20 mg
  - buccal midazolam 5 to 10 mg – between the cheek and gum
  - subcut boluses of clonazepam or midazolam
  - if these measures are not effective consider the use of phenobarbitone

Haemorrhage

WHĀNAU-FAMILY VOICE

"Blood is tapu to us."

Haemorrhage is distressing for all concerned and should be treated with urgency.

- in many situations, the sight of blood is indicative of impending death and many patients and whānau-family experience a significant increase in anxiety – use red towels if possible
- staff are often alarmed by haemorrhage, as they often feel helpless to 'do' anything to prevent it
- anticipate this in high risk patients and prepare them and whānau-family with an explanation, DNR order available, proximity of dark-coloured towels and appropriate medication

Management

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

If the bleeding is massive

- the normal 'life saving' interventions are inappropriate, reduce the patient's awareness, fear and anxiety with subcutaneous midazolam (10 to 15 mg) with or without subcutaneous morphine. A midazolam plastic vial (15 mg) can be opened and squirt into the side of the mouth
- staff should stay with the patient and whānau-family until all concerned feel safe

Haemoptysis/ENT cancers

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

Upper gastro-intestinal tract

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

Lower gastro-intestinal tract

- radiotherapy and/or surgery may be appropriate
- drug therapy
  - tranexamic acid rectally
  - rectal steroids e.g. hydrocortisone rectal foam

Haematuria

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

Vaginal

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

Hypercalcaemia of malignancy

WHĀNAU-FAMILY VOICE

"What does this mean? What can we do?"

The symptoms and signs of hypercalcaemia are often insidious in their onset. It can be classified as a paraneoplastic syndrome.

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

Symptoms

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

Causes

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

Management

- make the diagnosis
- decide about the most appropriate course of action together with the patient, whānau-family and team
- consider stopping diuretics, vitamin D and calcium
- the aim is to provide symptom relief and reduce serum calcium to an acceptable level using minimal intervention
  - mild to moderate (serum calcium 2.6 to 3 mmol/L)
    - initially oral then, if necessary, iv rehydration
    - consider steroids
  - moderate to severe (serum calcium 3 to 3.5 mmol/L)
    - initially iv or subcut rehydration
- 2 to 3 L normal saline/24 hours
  - then iv/subcut bisphosphonate (may take 72 hours to work)
- pamidronate 30 mg iv infusion (depending on renal function and degree of hypercalcaemia)
- zoledronic acid 3 to 4 mg iv infusion depending on renal function
- calcitonin may be useful when bisphosphonates begin to fail

Raised intracranial pressure

WHĀNAU-FAMILY VOICE

"How can we keep our person as comfortable as possible."

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

Symptoms

- severe headache which is worse when lying down or straining
- vomiting
- convulsions
- drowsiness, delirium
- diplopia
- restlessness
- personality changes

Causes / risk factors

- cerebral metastases (more common with some primaries, e.g. lung, breast, melanoma than with others, e.g. prostate)
- primary brain tumour
- abscess
- cerebro-vascular event
- sagittal sinus thrombosis
- secondary hydrocephalus following surgery

Management

If raised intracranial pressure is suspected look for papilloedema and signs of cerebral irritation. Computerised tomography or MRI may be appropriate

- raise the head of the bed
- consider cranial radiotherapy or neurosurgery for malignancy if prognosis/status warrants it
- drugs
  - dexamethasone up to 16 mg per day. Avoid doses after noon as may add to insomnia. Gradually reduce dose to minimum effective. Withdraw after 7 days if ineffective (note – some anticonvulsants can reduce effectiveness – see Dexamethasone Section 2)
  - opioids (sometimes eases head pain)
  - consider anticonvulsants particularly if seizures are present

Spinal cord compression

PATIENT VOICE

"I don't want to be a burden to my whānau."

This is a relatively uncommon problem that requires urgent and effective management.

- it is one of the true medical emergencies in palliative care
- once paralysed 95% will not walk again

Symptoms

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

Management

- urgent assessment
  - history and clinical findings
  - MRI examination
- referral to radiation oncology is usually most appropriate
- as soon as the diagnosis is made or suspected
  - dexamethasone 16 mg daily, for a few days then tapered down according to symptom response
  - radiation therapy should be given concurrently

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

Te Matehaere me te Pāpōuri
Dying and Grief

WHĀNAU-FAMILY VOICE

"The weight of grief has made me exhausted and restless. It is emotional, spiritual and physical."

The last days or hours

WHĀNAU-FAMILY VOICE

"Our person matters to the last moment of their life, and beyond."

Recognising end-of-life may seem relatively easy or obvious but in practice the 'diagnosis of dying' may be challenging for individuals or teams. Signs may include

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

Management

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

Common symptoms

Pain (see Pain section)

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

Nausea/vomiting (see Nausea/Vomiting section)

- not usually a great problem unless there is intestinal obstruction or it has previously not been controlled

Agitation/ distress/anxiety (see Fear and Anxiety, and Delirium sections)

Non-pharmacological management

- if there are fears/worries/tensions/spiritual issues consider what has helped in the past
- consider and address constipation/urinary retention/pain

Oral/buccal drugs

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

Subcutaneous drugs

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

Confusion (see Delirium section)

Non-pharmacological management

- look for reversible causes
- aim for minimal disruption and have familiar people in the room

Oral drugs

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

Subcutaneous drugs

- haloperidol by continuous infusion 1 to 3 mg over 24 hours
- boluses of 1 to 2 mg may also be used
- if more sedation is required, use levomepromazine (10 to 25 mg in CSCI/24 hours with 5 mg prn Q3HR) instead of halperidol

Excess secretions (see Excessive (retained) Secretions section)

Non-pharmacological management

- consider position change
- it may be distressing to the whānau-family and carers rather than the patient

Drugs

- to be most effective, drugs need to be introduced early before excessive secretions build up
- glycopyrrolate 0.6 to 1.2 mg subcut over 24 hours as a starting dose may help (may increase to 2.4 mg)
- hyoscine (Scopaderm™) patch may be applied behind the ear although confusion and other anticholinergic side effects may occur
- hyoscine butylbromide may be useful 20 mg subcut followed by 30 to 60 mg by continuous subcutaneous infusion over 24 hours
- secretions may become thickened and plugs may form

After death review

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

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

Grief and loss

WHĀNAU-FAMILY VOICE

"We have each other to help us through our loss. What can you do to support us?"

Grief is the distressing emotional response initiated by the death of a loved and attached person, or a loss. It is a normal, adjustment process. Spontaneous recovery occurs over time for the majority.

- grief begins at loss/diagnosis
- there are no specific stages of grief. Grief is never fully resolved
- modern society is death-denying and death-defying
- symptoms include sadness, anger, waves of distress, tearfulness, initial insomnia, pining, haunting reminiscences, fleeting auditory or visual pseudo-hallucinations or a sense of presence of the departed
- mourning is the behavioural responses of grieving. Culture and social norms are determinants. Mourning customs serve to organise, protect and support the grief-stricken
- grief is age-influenced. Children do not develop the capacity to appreciate the permanency of death until aged 9 to 10. In the elderly grief may be curtailed if the death is expected
- grief counselling is age appropriate, person centred and supports a person of any age to adjust to the many changes at their own pace in their own timing
- grief counselling and therapy should be provided by qualified and experienced practitioners

Grief and loss in dementia

Dementia has been characterised as 'the long goodbye'. Due to personality changes and a decline in the ability of a person with dementia to recognise even close relatives, whānau-family members can feel as though they lost the person long before the time of their death, perhaps due to the person being perceived as physically present but psychologically absent for some years prior to death. Feelings of ambivalence and guilt are common, and the grief of a close relative of someone with dementia can occur in a vacuum of social isolation if the wider social circle of an affected whānau-family member has drifted away during their loved one's decline.

Relatives may become affected by a phenomenon known as disenfranchised grief, where their grief is not validated by others in circumstances where their relationship with the departed is not recognised and their loss unacknowledged. In a similar vein, stigma against those with dementia may lead to a disenfranchised or devalued death, where the value of the departed's very personhood is no longer acknowledged by others who might otherwise lend support.

Depression rates in whānau-family caregivers of people with dementia can be as high as 50%. The grief of dementia caregivers frequently goes unrecognised by attending health professionals.

Complicated grief

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

Management of grief

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

SECTION 2:
Drug Information & Syringe Drivers

Drugs listed are preferred choices in palliative care.

Amitriptyline

Class: Tricyclic antidepressant

Indications: Depression, neuropathic pain, migraine prophylaxis

Contraindications/cautions: Recent MI or heart block; urinary retention without urinary catheter insitu; angle-closure glaucoma. Caution in epilepsy; bipolar disorder, suicidal ideation.

Adverse reactions: ***common:*** Constipation, dry mouth, blurred vision, sedation (increased in hepatic impairment); ***less common:*** photophobia, urinary retention, tachycardia, confusion, delirium, postural hypotension, sweating, QT-prolongation.

Metabolism/clearance: metabolised to nortriptyline by CYP2C19 and CYP2C8/9 in the liver. Negligible renal clearance.

Interactions: serotonin syndrome with other serotonergic drugs (caution); QT-prolonging drugs, MAOI's (contraindicated)

Dosing:

oral:	neuropathic pain: 10 mg at night – increase gradually to 25 to 50 mg at night. Maximum 75 mg but rarely tolerated in palliative patients
subcut:	N/A
rectal:	N/A

Syringe driver: N/A

Mechanism of action: analgesic effects may be through noradrenaline & serotonin pathways – also opioid agonism, alpha adrenoreceptor blockade and ion channel blockade to reduce transmission.

Half life: 15 hours (metabolite nortriptyline half life of 30 hours)

Onset: ***oral:*** can take a few weeks or up to 6 weeks for full effect vs pain

Notes: lower doses used for pain; higher doses used in depression.

Tablets may be film coated – can be halved and likely to be able to be crushed

Availability:

- tablets 10 mg, 25 mg, 50 mg

Baclofen

Class: GABA derivative musculoskeletal muscle relaxant

Indications: relief of musculoskeletal spasm & associated pain; Intractable hiccup in palliative care

Contraindications/cautions: epilepsy, psychosis, schizophrenia, depression, mania, peptic ulceration (oral use), cerebrovascular disease, alcoholism, diabetes (may increase blood glucose concentrations), hypertension; hypertonic bladder sphincter; porphyria

Adverse reactions: ***common:*** nausea, sedation (caution driving), somnolence; ***less common:*** decreased cardiac output, hypotension, GI disturbance (constipation, nausea, vomiting), respiratory depression, light-headedness, personality changes, headache, insomnia, euphoria, depression, weakness, tremor, hallucinations, dry mouth, tinnitus, anxiety, agitation, urinary disturbances; visual disorders; rash, hyperhidrosis

Metabolism/clearance: mainly excreted in urine unchanged (80%) so dose adjust in renal impairment or increase dose interval. Use with caution if eGFR < 15 mL/min/1.73m^2

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

Dosing:

Oral:	5 to 20 mg 3 times a day (start at 5 mg 3 times a day); increase slowly every 3 days up to 10 to 20 mg 3 times daily. Assess risk/benefit
Subcut:	not available

Intrathecal use: seek specialist advice
Syringe driver: only intrathecal inj available – not for subcut use

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

Onset: variable – hours to weeks

Notes:
- stopping abruptly may result in a withdrawal reaction (confusion, psychosis, tachycardia, hyperthermia and rebound spasticity). Gradual dose reduction recommended over 1 to 2 weeks

Availability:
- tablets 10 mg
- intrathecal 50 micrograms/mL; 10 mg/5 mL; 10 mg/20 mL
- extemporaneously compounded liquid may be available from pharmacy (1 mg/mL)

Bisacodyl

Class: laxative – stimulant

Indications: constipation

Contraindications/cautions: acute abdominal pain, intestinal obstruction; acute IBD; severe dehydration

Adverse reactions: *common:* abdominal cramps, diarrhoea, nausea, vomiting, perianal irritation (usually with suppositories); ***less common:*** atonic colon (on prolonged use), hypokalaemia

Metabolism/clearance: mainly excreted in faeces

Interactions:
- *decreased clinical effects of* ***antispasmodics (e.g. hyoscine butylbromide)*** may occur due to stimulant effects of bisacodyl

Dosing:

oral:	5 to 10 mg at night or 5 mg twice a day
subcut:	not available
rectal:	10 mg daily (morning may be preferred)

Syringe driver: not available

Mechanism of action: stimulates colonic activity via nerves in the intestinal mucosa

Onset: ***oral:*** 6 to 12 hours ***rectal:*** 10 to 30 minutes (usually 20 minutes)

Notes:
- second line to Laxsol. May be useful in opioid induced constipation especially in combination with a softener

Availability:
- 5 mg tab; 10 mg supp

Buprenorphine

Class: analgesic – opioid, partial mu agonist/weak kappa antagonist (partial agonist so ceiling effect to analgesia occurs)

Indications: moderate to severe pain

Contraindications/cautions: buprenorphine hypersensitivity/allergy, use with other opioids, adverse effects such as respiratory depression may not completely respond to naloxone, COPD, use with benzodiazepines; caution with MAOIs, hypotension, obstructive bowel disorders, hepatic impairment, renal impairment

Adverse reactions: *see* ***morphine***

Metabolism/clearance: metabolised by unclear pathway

Interactions:

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

Dosing:

sublingual combo: not used

subcut: not used

patch: 5 to 20 micrograms/hour (each patch lasts for 3 to 7 days depending on brand). Start on 5 micrograms patch; increase if required every 3 days

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

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

Peak effect: ***patch:*** 60 hours after initial application

Onset: 11 to 21 hours

Duration: ***patch:*** 3 to 7 days – depending on brand

Notes:

- as buprenorphine is only a partial agonist of mu receptors and an antagonist of kappa receptors it should not be used with other opioids or within 24 hours of them as it may lead to severe opioid withdrawal
- as concentrations occur at 60 hours do not use in rapidly escalating pain
- for acute toxicity give naloxone 2 mg and repeat as required (max 10 mg) over a prolonged time but be aware that full reversal of toxicity may not occur as buprenorphine binding to opioid receptors is high
- do not cut patches. Apply patch to clean, dry skin – not to broken skin and not to a hairy area
- avoid exposing the patch to heat such as heating pads, hot water bath or shower
- equivalence to other opioid data are sparse but 20 micrograms/hour patch may be equivalent to 90 mg oral morphine per day
- it is recommended that no more than 2 patches be applied at the same time regardless of the patch strength
- a new patch should not ne applied to the same skin site for the subsequent 3 to 4 weeks

Celecoxib

Class: COX-2 selective NSAID

Indications: pain – visceral, inflammatory, pleuritic; pain and inflammation in OA, RA and ankylosing spondylitis; acute pain; primary dysmenorrhoea

Contraindications/cautions: severe heart failure; active peptic ulcer disease; severe renal impairment and not on dialysis; NSAID-induced asthma (contraindicated); mild or moderate renal impairment; previous peptic ulceration, cardiovascular disease (caution)

Adverse reactions: ***common:*** nausea, dyspepsia; ***less common:*** vomiting, acute kidney injury, oedema, peptic ulceration

Metabolism/clearance: metabolised to inactive metabolites by CYP2C9; negligible renal clearance

Interactions: Increased risk of peptic ulceration with glucocorticoids; increased risk of bleeding with antiplatelets/anticoagulants; increased risk of kidney injury with loop diuretics. Weak inhibitor of CYP2D6

Dosing:

oral:	100 to 200 mg twice daily; maximum 400 mg daily
subcut:	N/A
rectal:	N/A

Syringe driver: N/A

Mechanism of action: celecoxib selectively inhibits cyclooxygenase-2 (COX-2) – reducing prostaglandin production resulting in analgesic, anti-inflammatory and anti-pyretic effects. Selective inhibition of COX-2 is associated with less GI-intolerance

Half life: 11 hours

Onset: ***oral:*** peak plasma levels 3 hours after oral dose

Notes:
- does not impair clotting
- capsules can be opened, and contents sprinkled onto soft food or administered down a PEG/NG tube
- risk of cardiovascular events with COX-2 inhibitors are usually not a significant contraindication in palliative patients
- consider gastroprotection with a proton-pump inhibitor or H2 antagonist especially if other risk factors
- reduce dose in moderate hepatic impairment; avoid in severe impairment
- avoid if eGFR less than 30 mL/min/1.73m^2

Availability:
- capsules 100 mg & 200 mg

Cholestyramine

Class: anion exchange resin ; bile acid sequestrant

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

Contraindications: complete biliary obstruction

Cautions: diabetes, nephrotic syndrome, phenylketonuria, prolonged use, constipation

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

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

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

Dosing: oral 4 to 16 g per day – initially 4 g per day; increase by 4 g at weekly intervals – give in 1 to 4 divided doses daily. Pruritis – 4 to 8 g usually sufficient

Syringe driver: not available

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

Onset: ***pruritus:*** 4 to 7 days

Notes:
- as absorption of other drugs will be affected take all other drugs 1 hour before or 4 to 6 hours after cholestyramine. Sachet contents must be mixed with 100 to 150 mL of fluid (fruit juice, skim milk, thin soup) before administering

Citalopram

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

Indications: depression, anxiety (chronic)

Contraindications/cautions: hepatic impairment, epilepsy, bleeding disorders, abrupt withdrawal; caution in QT prolongation – sertraline may be an alternative

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

Metabolism/clearance: metabolised hepatically by CYP2C19, CYP2D6 & CYP3A4 – caution when used with drugs that inhibit CYP

Hepatic impairment – max daily dose 20 mg

Renal impairment – no information for use if eGFR < 20 mL/min/1.73m^2

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

Dosing:
oral: 10 to 40 mg once a day
Adult 20 mg once daily, increased if necessary in steps of 10 mg daily at intervals of 2 to 3 weeks; maximum 40 mg daily; elderly 10 mg once daily, increased if necessary after 2 to 3 weeks to a maximum of 20 mg daily
Note: The daily dose of citalopram should not exceed 40 mg daily as doses above this are associated with an increased risk of QT-interval prolongation
subcut/rectal: not available

Syringe driver: not available

Mechanism of action:
SSRIs selectively inhibit the re-uptake of serotonin (5-hydroxytryptamine, 5-HT) in the pre-synapse, increasing the available serotonin in the brain

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

Peak response: 5 to 6 weeks

Notes:
- escitalopram is available. Doses used are approximately half
- doses of greater than 40 mg per day have been associated with QT interval prolongation
- may be useful in pruritis due to primary biliary cholangitis

Clonazepam

Class: anticonvulsant – benzodiazepine

Indications (NB some may be unlicensed): epilepsy, convulsions, sedation, agitation, restless leg syndrome, neuropathic pain, dyspnoea, hiccups, panic disorder (with or without agoraphobia) resistant to antidepressant therapy (unapproved); generalised anxiety disorder (unapproved) but ***see notes***; prevention of seizures in palliative care; treatment of prolonged grand mal seizures or status epilepticus in palliative care; myoclonus (unapproved); agitation or confusion in the last days of life (usually in conjunction with an antipsychotic) (unapproved)

Contraindications/cautions: avoid sudden withdrawal, respiratory depression; acute pulmonary insufficiency; sleep apnoea syndrome; marked neuromuscular respiratory weakness including unstable myasthenia gravis

Adverse reactions: ***common:*** fatigue, drowsiness (at higher doses); ***less common:*** respiratory depression, incontinence, co-ordination problems, disinhibition, increase in salivation, confusion

Metabolism/clearance: metabolised by enzyme CYP3A mainly in the liver

Interactions:

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

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

oral:	0.5 to 8 mg a day (1 to 2 mg a day usually adequate); See NZF for specific dosing
subcut:	1 to 8 mg/24 hours
rectal:	not available

Mechanism of action: Benzodiazepines act on GABA receptors in the central nervous system (CNS) to enhance activity of the inhibitory neurotransmitter GABA resulting in CNS depression

Onset: ***oral (seizure control):*** 20 to 40 minutes

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

Clonazepam (CONTINUED)

Notes:

- a long acting benzodiazepine so difficult to titrate to response
- benzodiazepines may reduce dyspnoea by anxiolytic and sedative effects
- approximate equivalent oral anxiolytic/sedative doses:

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

Pharmacological properties of benzodiazepines

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

Codeine phosphate

Class: analgesic – opioid (metabolised to morphine, noting that there is individual variability in hepatic metabolism)

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

Contraindications/cautions: avoid use with other opioid analgesics; caution renal impairment; hepatic impairment
Adverse reactions: as for morphine – very constipating; drowsiness
Metabolism/clearance: metabolised by metabolising enzyme CYP2D6 mainly in the liver to an active metabolite – morphine. Minor metabolism by 3A. Caution in ultra-rapid metabolisers – may result in morphine toxicity; poor metabolisers may experience reduced therapeutic effect

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

Dosing: pain, cough and diarrhoea:

oral:	15 to 60 mg 4 to 6 hourly (Max. 240 mg in 24 hours for pain & diarrhoea; max 120 mg for cough)
subcut:	not available
rectal:	not available

Syringe driver: N/A

Mechanism of action: metabolised to morphine (analgesic action) and other active metabolites; codeine reduces intestinal motility by binding opioid receptors in intestinal tract; cough suppression by acting on cough centre in the medulla

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

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

Cyclizine

Class: antiemetic – antihistaminic, antimuscarinic

Indications: nausea/vomiting (including motion sickness, vertigo). Nausea related to vestibular system irritation or raised intracranial pressure

Contraindications/cautions: prostatic hypertrophy, urinary retention, narrow angle glaucoma

Adverse reactions: *common:* drowsiness, headache, psychomotor impairment, restlessness, dry mouth, blurred vision, constipation; ***less common:*** insomnia, hallucinations (more common: in elderly), cardiac arrhythmias

Metabolism/clearance: extensively hepatically metabolised mainly to inactive metabolites that are predominantly renally excreted

Interactions:

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

Dosing:

oral:	50 mg 2 to 3 times a day (cyclizine hydrochloride) & 50 mg prn – usual maximum dose 200 mg/24 hours
subcut:	bioavailability is 50% so subcut dose 75 to 150 mg/24 hours (cyclizine lactate) (well diluted)
rectal:	not available

Syringe driver: see syringe driver compatibility table. Diluent WFI. Incompatible with NaCl

Mechanism of action: An H1 and muscarinic antagonist thought to act on the vestibular system & in the vomiting centre in the CNS and has anticholinergic properties

Onset of action: 30 to 60 minutes **Duration of action:** 4 to 6 hours

Peak concentration: approx 2 hours

Notes:

- although there is a theoretical interaction with prokinetic antiemetics (prokinetics stimulate the gut while cyclizine slows it down) use together is common and may be justified on the basis of central nervous system receptors antagonism
- can accumulate in repeated use – caution in elderly & in hepatic & renal impairment & reduce dosing frequency to twice daily

Dexamethasone

Class: corticosteroid – glucocorticoid

Indications (NB some may be unlicensed): cerebral oedema (raised intracranial pressure), allergy/anaphylaxis, replacement, shock, collagen diseases, asthma, respiratory insufficiency, leukaemia, lymphoma, rheumatic disease, psoriasis, colitis, enteritis, hypercalcaemia of malignancy, nausea/vomiting, sweating, itch, hiccup, pain, liver capsule pain, tenesmus, to improve appetite & wellbeing in palliative care

Contraindications/cautions: infections, GI bleeding; caution in diabetes & psychotic illness; renal or hepatic impairment

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

Metabolism/clearance: metabolised by CYP3A (major) mainly in the liver – caution with drugs that inhibit or induce CYP3A

Interactions:

- *increased clinical effect/toxicity of dexamethasone* (due to increased blood concentrations) may occur with some CYP metabolising enzyme ***inhibitors*** (see above) as the metabolism of dexamethasone decreases & thus plasm concentration increases e.g. ***aprepitant, clarithromycin, grapefruit juice, indinavir, itraconazole, ketoconazole, nelfinavir, ritonavir, telapravir, voriconazole***
- *decreased clinical effect/toxicity of dexamethasone* (due to decreased blood concentrations) may occur with some CYP metabolising enzyme inducers (see above) e.g. ***carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's wort***
- *decreased clinical effect/toxicity of other drugs metabolised by CYP enzymes* (due to induction of their metabolism by dexamethasone) may occur e.g. ***aprepitant, carbamazepine, clonazepam, diazepam, domperidone, fentanyl, itraconazole, ketoconazole, methadone, midazolam, prednisone, quetiapine, triazolam***
- *increased risk of GI bleed/ulceration* when given with ***NSAIDs (e.g. diclofenac)***
- In patients taking warfarin, INR may increase when on dexamethasone – dose reduction required in 50% of cases. Check INR weekly for 2 to 3 weeks

Dosing:

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

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

Mechanism of action: decreases inflammatory response via induction of lipocortin

Onset: 8 to 24 hours

Dexamethasone (CONTINUED)

Notes:

- anti-inflammatory effect: 3 mg dexamethasone = 20 mg prednisone = 80 mg hydrocortisone
- on discontinuation decrease dose slowly (taper) unless the patient has been taking it for less than 5 days in which case dose tapering is not necessary
- alteration in mood is not usually seen below 6 mg dexamethasone (40 mg prednisone) per day
- monitor blood glucose before commencing and every 1 to 2 weeks during treatment
- corticosteroid-induced insomnia responds to benzodiazepines (e.g. temazepam)
- corticosteroid induced mood disorder is usually depression and rarely mania
- the use of steroids in palliative care is common and sometimes, particularly at high dose, consideration should be given to the appropriateness of their use
- the use of 0.5 to 1 mg dexamethasone in a syringe driver may reduce the risk of local irritation at the subcutaneous site but adverse effects can occur even at low dose

Diclofenac

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

Indications (NB some may be unlicensed): pain associated with inflammation, itch, sweating (neoplastic fever)

Contraindications/cautions: Hypersensitivity to aspirin or other NSAIDs, GI ulceration, asthma (in sensitive patients), renal, cardiac or hepatic impairment, bleeding or other bleeding disorders

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

NB inhibits platelet aggregation – may prolong bleeding time. Caution if concurrent prescription with warfarin (PCF) – monitor INR

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

Interactions:

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

Dosing:

oral:	50 to 150 mg per day in 3 divided doses for normal release and 2 divided doses (sometimes just one) for long acting preparations
subcut:	inj available but not for subcut injection as too irritant
rectal:	as for normal release oral

Syringe driver: not recommended

Mechanism of action: inhibits prostaglandin synthesis – resulting in analgesic, anti-inflammatory and anti-pyretic action

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

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

Notes:

- co-analgesic often used with opioids in bone and soft tissue pain
- NSAID of choice in palliative care
- patients at risk of gastro-intestinal bleeds should be prescribed gastric protection (e.g. pantoprazole, omeprazole) prophylactically

Docusate

Class: laxative – faecal softener

Indications: constipation

Contraindications/cautions: acute abdominal pain; appendicitis, undiagnosed rectal bleeding; intestinal obstruction

Adverse reactions: *less common:* abdominal cramps, atonic colon (on prolonged use), bitter taste, nausea, rash, diarrhoea

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

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

Dosing:

oral:	Available as 50 mg or 120 mg tab. Adult: 100 to 150 mg twice daily or 240 mg at night – up to 480 mg daily in divided doses Also available as docusate with sennosides (Laxsol tabs)
subcut:	not available
rectal:	1 suppository as required

Syringe driver: not available

Mechanism of action: acts by lowering surface tension of the stool allowing water and salts into the hardened stool to soften it

Onset: oral 1 to 3 days

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

Domperidone

Class: antiemetic – prokinetic, dopamine antagonist

Indications: nausea, vomiting, dyspeptic symptom complex including gastro-oesophageal reflux oesophagitis, epigastric sense of fullness, feeling of abdominal distension, upper abdominal pain, eructation (belching), flatulence and heartburn, hiccups, delayed gastric emptying

Contraindications/cautions: complete intestinal obstruction; QT prolongation; underlying cardiac disease

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

Metabolism/clearance: metabolised by enzyme CYP3A mainly in the liver and gut. Caution in moderate to severe hepatic impairment – reduce dose

Interactions:

- *increased clinical effect/toxicity of domperidone* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. ***aprepitant, clarithromycin, grapefruit juice, indinavir, itraconazole, ketoconazole, nelfinavir, ritonavir, telapravir, voriconazole***
- *decreased clinical effect/toxicity of domperidone* (due to decreased blood concentrations) may occur with some CYP metabolising enzyme inducers (see above) e.g. ***carbamazepine, phenobarbitone, phenytoin, rifampicin, St John's wort***
- *decreased prokinetic effect of domperidone* may occur with ***anticholinergic drugs (e.g. amitriptyline, hyoscine)***
- *additive increased risk of QT interval prolongation* (cardiac adverse effect which may lead to arrhythmias) with tricyclic antidepressants (e.g. amitriptyline), flecainide, erythromycin, theophylline, methotrimeprazine (levomepromazine)

Dosing:

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

Syringe driver: not available

Mechanism of action: similar to metoclopramide – blocks dopamine receptors in the upper gastrointestinal tract, chemo-receptor trigger zone (CTZ) and the CNS (penetration of BBB is negligible so minimal effect on CNS therefore less likely to cause extrapyramidal side effects than metoclopramide)

Peak: ***concentration:*** 30 to 120 minutes

Onset: ***of action:*** 30 minutes

Duration: ***of action:*** 12 to 24 hours

Domperidone (CONTINUED)

Notes:

- main advantage over metoclopramide is less extrapyramidal side effects but not available in injectable form
- useful in nausea and vomiting associated with gastric stasis
- the United States Federal Drug Agency has warned of domperidone induced QT interval prolongation and recommend a maximum of 30 mg in 24 hours. A risk benefit assessment should be carried out when higher doses are considered along with a baseline QT interval assessment
- bioavailability relatively poor after oral dose (12 to 18%) due to first pass metabolism in wall of GIT and liver – bioavailability nearly doubled if taken after a meal (24%)
- maximal absorption requires acid environment – H2-antagonists, PPIs and antacids all reduce absorption

Enoxaparin

Class: anticoagulant – low molecular weight heparin

Indications: prophylaxis of venous thromboembolic disease post-op and bedridden patients

Treatment of deep vein thrombosis and pulmonary embolism, unstable angina and myocardial infarction, prevention of thrombus during haemodialysis, duration of more than 30 days treatment

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

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

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

Interactions:

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

Dosing:

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

Syringe driver: not available

Mechanism of action: has high anti-Xa activity

Peak anti-Xa activity: 3 to 5 hours post inj

Notes:

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

Famotidine

Class: Histamine H2-receptor antagonist

Indications: reduction of gastric acid secretion in gastric/duodenal ulcers, reflux disease and malignant bowel obstruction

Contraindications/cautions: hypersensitivity to other H2-receptor antagonists/ H2-receptor antagonists may mask symptoms of gastric cancer; particular care is required in patients presenting with 'alarm features', in such cases gastric malignancy should be ruled out before treatment; increased risk of CNS adverse effects

Adverse reactions: *Common:* diarrhoea, constipation, headache, dizziness.
Less common: dry mouth, nausea, vomiting, flatulence, taste disorders, anorexia, fatigue

Metabolism/clearance: 25 to 30% metablolised by CYP450 in the liver – first pass metabolism. Minimal inhibitory effect on other drugs. 70% eliminated renally

Interactions: No significant interactions known with common palliative care drugs

Dosing:

Oral:

Oesophageal reflux	20 mg bd
Severe oesophagitis	40 mg bd
Peptic ulcer or peptic ulcer prevention	20 mg bd or 40 mg nocte
Paraneoplastic sweating	20 to 40 mg once daily (benefit within 2 to 3 days)

Syringe driver:

Malignant bowel obstruction	40 mg/24 hours via syringe driver – WFI or NaCl 0.9% as diluent

Mechanism of action: inhibits acid concentration and volume of gastric secretion as well as basal and nocturnal gastric acid secretion

Peak effect: 1 to 3 hours after oral dose

Onset: onset of action 1 hour orally

Duration: 6 to 10 hours after single dose

Notes:

- reduce dose in hepatic and renal impairment
- famotidine injection must be stored in the fridge until added to a syringe driver

Fentanyl

Class: analgesic – opioid – full opioid agonist

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

Contraindications/cautions: fentanyl hypersensitivity/allergy (not nausea/hallucinations)

Adverse reactions: ***see morphine*** – less constipating (reduce dose of laxatives when converting from morphine), perhaps less sedating and less emetogenic than other opioids

Metabolism/clearance: metabolised by metabolising enzyme CYP3A mainly in the liver

Interactions:

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

Dosing:

subcut:	50 to 300 micrograms in 24 hours initially
patch:	12.5 to 300 micrograms /hour (each patch lasts for 3 days) – see notes
intranasal:	Not commercially available in NZ; consult local hospice for availability

Syringe driver: see syringe driver compatibility chart

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

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

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

Fentanyl (CONTINUED)

Notes:

- patches are unsuitable for opioid naïve patients. Initial dose based on previous 24 hour opioid requirement
- allow patch to be applied for 24 hours before evaluating analgesic effect; phase out previous analgesic gradually
- adjust dose at 48 to 72 hour intervals in steps of 12.5 micrograms subcut /hour to 25 micrograms subcut /hour
- if patient is hot, or there is a heat pad near the patch, rate of absorption may increase
- if patch comes unstuck use Micropore™ round edges to reattach
- for acute toxicity give naloxone 2 mg and repeat as required (max 10 mg) over a prolonged time (depot in skin – see below)
- patches leave a depot in the skin which will carry on releasing fentanyl after removal (at least 17 hours for concentrations to drop by 50%)
- use another opioid or the fentanyl injection subcut/sublingual/intranasal for breakthrough – for fentanyl the dose may not relate to background so start at 25 micrograms fentanyl and titrate to effect
- approximate conversion is morphine (po): fentanyl (subcut/patch) = 150:1 i.e. 10 mg morphine po = 66 micrograms fentanyl subcut but in chronic use this can only be used as an estimate

CONVERSION CHART

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

Fluconazole

Class: antifungal – triazole

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

Contraindications/cautions: renal impairment, hepatic impairment; Susceptibility to QT-interval prolongation

Adverse reactions: ***common:*** gastrointestinal upset, nausea, diarrhoea, flatulence, headache ***less common:*** rash (discontinue), blood disorders, arrhythmias, dizziness, convulsions, hypokalaemia, taste disturbance

Metabolism/clearance: mainly excreted by the kidneys (fraction excreted by the kidneys unchanged = 0.8) so care in renal failure; halve dose if eGFR less than 50 mL/min/1.73m^2

Interactions:

- *increased clinical effect/toxicity* of some drugs (see below) (due to increased blood concentrations of them) may occur due to inhibition of metabolising enzymes by fluconazole e.g. ***diazepam, diclofenac, gliclazide, ibuprofen, indomethacin, lansoprazole, naproxen, omeprazole, pantoprazole, phenytoin, warfarin***
- *decreased clinical effect* of ***amphotericin*** may occur with concomitant fluconazole

Dosing:

oral:	vaginal candidiasis	150 mg as a single dose
	cryptococcal infections/ systemic candidiasis	200 to 400 mg once a day for 7 days
	oropharyngeal candidiasis	50 to 100 mg once a day for 7 to 14 days
	prophylaxis in malignancy	50 mg once a day
subcut:	not usually used subcut, iv: refer to package insert	
rectal:	not available	

Syringe driver: not applicable

Mechanism of action: inhibits fungal cell membrane formation

Notes:

- useful in severe or recurrent fungal infections
- may be less likely to interact with other CYP metabolised drugs (see above) than ketoconazole – check QT interactions

Fluoxetine

Class: antidepressant – SSRI (Selective Serotonin Re-uptake Inhibitor) – increases serotonin in the brain

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

Contraindications/cautions: epilepsy, bleeding disorders (decreases platelet aggregation); use of MAOI within 14 days; QT prolongation; serotonin syndrome (oxycodone; fentanyl)

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

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

Interactions:

- *increased clinical effect/toxicity of fluoxetine* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. ***bupropion, paroxetine (not citalopram), quinine***
- *increased clinical effect/toxicity of some drugs* (due to increased blood concentrations of them) may occur with fluoxetine due to metabolising enzyme inhibition by fluoxetine e.g. ***amitriptyline, codeine*** (decreased morphine concentrations so decreased clinical efficacy of codeine), ***haloperidol, metoclopramide, nortriptyline, promethazine, tamoxifen*** (decreased endoxifen (active metabolite) concentrations so decreased clinical effects)
- *additive risk of serotonin syndrome* (potentially fatal syndrome – symptoms include sweating, diarrhoea, confusion) with other serotonergic drugs e.g. ***carbamazepine, citalopram, tricyclic antidepressants (e.g. amitriptyline), lithium, tramadol, some opioids***

Dosing:

oral:	20 to 60 mg in the morning
subcut:	not available
rectal:	not available

Syringe driver: not available

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

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

Peak response: 5 to 6 weeks

Notes:

- fluoxetine has a half life of 48 hours but its active metabolite (norfluoxetine) has a half life of 11 days
- reduce dose or increase dose interval in hepatic impairment
- watch for serotonin syndrome if switching antidepressants as it takes 4 to 5 half lives to clear a drug from the body i.e. 44 to 55 days for fluoxetine/norfluoxetine
- withdrawal symptoms on stopping fluoxetine are unlikely to occur
- tablets are dispersible in water allowing dosing increments of < 20 mg. Capsule contents are also dispersible in water

Gabapentin

Class: anticonvulsant (gabapentinoid)

Indications: partial seizures, including secondarily generalised tonic-clonic seizures, initially as add-on therapy in patients who have not achieved adequate control with standard antiepileptic drugs, neuropathic pain, ***(NB some may be unlicensed)***:insomnia; pruritis; hot flushes; sweating; refractory hiccup; restless legs syndrome; spasticity; refractory cough; alcohol withdrawal

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

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

Metabolism/clearance: not metabolised, mainly excreted unchanged by the kidneys (fraction excreted unchanged by the kidney = 0.8) adjust dose in renal dysfunction

Interactions:

- *decreased clinical effect/toxicity of gabapentin* with antacids containing aluminium or magnesium e.g. ***Mylanta P™*** due to decreased absorption of gabapentin
- *additive CNS depression* with other CNS depressants e.g. ***benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), opioids, alcohol***

Dosing:

oral:	epilepsy	900 to 1,800 mg/day in 3 divided doses max 3,600 mg
	peripheral neuropathic pain	900 to 3,600 mg/day in 3 divided doses – commence low dose and increase slowly – 300 mg once daily and increase by 300 mg daily until 3 times daily – increase every 2 to 3 days up to maximum 3600 mg daily
	Pruritis in ESRD	after dialysis; increase gradually to 300 mg daily if necessary
	Intractable hiccup	100 to 300 mg daily increasing every 2 to 3 days as tolerated & according to response – max 1200 mg daiy in divided doses (NZF)
subcut:	not available	
rectal:	not available	

Syringe driver: not available

Mechanism of action: Gabapentin is thought to bind to voltage-gated calcium channels, reducing calcium influx into presynaptic terminals and possibly decreasing the release of excitatory neurotransmitters associated with neuropathic pain and seizure propagation

Glycopyrrolate (glycopyrronium bromide)

Class: antimuscarinic – antisecretory/antispasmodic

Indications (NB some may be unlicensed): antisecretory premedication, excessive respiratory secretions; antispasmodic & inoperable intestinal obstruction; paraneoplastic pyrexia & sweating; localised hyperhidrosis

Contraindications/cautions: urinary retention, prostatic enlargement, glaucoma, myasthenia gravis; paralytic ileus, pyloric stenosis

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

Metabolism/clearance: excreted in the bile and unchanged by the kidneys

Interactions:

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

Dosing:

oral:	not available (not absorbed orally)
subcut:	200 micrograms up to every 4 hours when required; occasionally hourly use is necessary
Syringe driver:	600 micrograms to 1200 micrograms (0.6 to 1.2 mg) over 24 hours
rectal:	not available
Topical:	Can be applied topically to treat localised hyperhidrosis as a 0.5 to 4% cream or aqueous solution once to twice daily – avoid eyes, nose & mouth – do not wash treated skins for 3 to 4 hours (unregistered)

Syringe driver: see compatibility chart – incompatible with dexamethasone

Mechanism of action: blocks cholinergic receptors

Initial response *(im):* 30 to 45 minutes

Duration: *(im):* 7 hours

Notes:

- may be a useful alternative to hyoscine particularly in the elderly because it is less likely to cause CNS adverse effects as it does not readily cross the blood brain barrier

Haloperidol

Class: antipsychotic – butyrophenone

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

Contraindications/cautions: hepatic encephalopathy, epilepsy, dementia, Parkinson's disease, DLB; caution in cardiac disease (QT prolongation)

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

Metabolism/clearance: metabolised by metabolising enzyme CYP2D6 and CYP3A4 mainly in the liver

Interactions:

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

Dosing:

oral : parenteral = 3:2 (bioavailability variable 40 to 85% orally)

nausea/vomiting		delirium (see notes)	
oral:	1.5 to 3 mg once a day	***oral:***	1.5 to 20 mg per 24 hours
subcut:	1 to 2 mg/24 hours	***subcut:***	1 to 15 mg/24 hours
		iv:	2 to 5 mg (at 1 mg/minute)

Intractable hiccup: 1.5 to 3 mg twice to 3 times daily – can reduce to 0.5 to 1 mg 3 times daily once controlled

Syringe driver: see syringe driver compatibility chart

Haloperidol (CONTINUED)

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

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

Duration: up to 24 hours

Notes:

- useful as an antiemetic where causes of nausea and vomiting are biochemical imbalance or toxins
- particularly useful in opioid induced nausea and vomiting. It may be given as a single oral dose at night. Doses greater than 3 mg daily add no benefit. Start with 0.5 mg in elderly
- delirium: The primary pharmacological intervention for delirium is to tranquillise (to control psychotic features). Occasionally sedation (to induce sleep) is an additional requirement. (See Delirium page)

Hyoscine butylbromide

Class: antispasmodic – gastrointestinal tract

Indications (NB some may be unlicensed): GI spasm/colic, some action as anti-emetic and antisecretory, sialorrhoea, excessive respiratory secretions

Contraindications/cautions: toxic megacolon,pyloric stenosis, glaucoma, prostatic enlangement; tachycardia, urinary retention

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

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

Interactions:

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

Dosing:

oral:	20 mg 4 times a day
subcut:	40 to 100 mg/24 hours
rectal:	not available

Syringe driver: see syringe driver compatibility table

Mechanism of action: blocks the effect of acetylcholine on gastrointestinal smooth muscle causing relaxation

Onset: ***oral:*** 1 to 2 hours ***subcut:*** 5 to 10 minutes

Duration: ***oral:*** 2 hours or less

Notes:

- may be useful with steroids in intestinal obstruction
- doesn't cross the blood-brain barrier so doesn't cause drowsiness or have a central antiemetic action
- only 8 to 10% absorbed orally

Hyoscine hydrobromide

Class: anticholinergic – antisecretory

Indications (NB some may be unlicensed): premedication for sedation/amnesia, nausea/vomiting from motion sickness, excessive respiratory secretions

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

Adverse reactions: ***common:*** dry mouth, tachycardia, hypotension (especially with morphine); ***less common:*** urinary retention, visual problems, dizziness, constipation, drowsiness, hallucinations (commoner in the elderly)

Interactions:

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

Dosing:

oral:	not available
subcut (as the hydrobromide):	0.4 to 2.4 mg/24 hours (usually 0.8 to 1.2 mg stat)
rectal:	not available
transdermal patch:	1 patch (1.5 mg)/72 hours (behind the ear)

Syringe driver: see syringe driver compatibility table

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

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

Duration: ***im:*** 8 hours

Notes:

- thought to cross the blood brain barrier more easily then hyoscine butylbromide
- risk of confusion in the elderly is high
- may be particularly useful in nausea and vomiting related to motion
- has a transdermal preparation – funded under Special Authority

Ketamine

Class: anaesthetic – NMDA-receptor antagonist

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

Contraindications/cautions: hypertension, tendency to hallucinations, alcohol abuse, epilepsy; severe cardiac disease

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

Metabolism/clearance: may be metabolised in the liver by CYP metabolising enzymes. Consider dose reduction in hepatic impairment. Active metabolite – norketamine

Interactions:

- *additive CNS effects* with other ***CNS depressants*** e.g. ***benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), opioids, alcohol***
- Caution with drugs metabolised by CYP enzymes

Dosing:

oral:	injection has been given orally
subcut:	100 to 500 mg in 24 hours as a 'pulse' over 5 days. Give a test dose of 10 mg before starting infusion
Subcut	Typically 10 to 25 mg prn; some use 2.5 to 5 mg (PCF8) – if necessary increase dose in steps of 25 to 33%
rectal:	not available

Syringe driver: see syringe driver compatibility table – ketamine is irritant; use largest volume possible; consider use of NaCl 0.9% as diluent. Start with 1 to 2.5 mg/kg/24 hours – if necessary increase by 50 to 100 mg/24 hours. Usual maximum 500 mg/24 hours

Mechanism of action: in pain thought to act at NMDA receptors in the dorsal horn

Peak effect: *iv:* 10 to 15 minutes

Duration: *iv:* 15 to 30 minutes

Ketamine (CONTINUED)

Notes:

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

Levetiracetam

Class: anticonvulsant

Indications: seizure control – can be adjunctive treatment or first line in palliative care for focal seizures

Contraindications/cautions: monitor for behavioural changes, hepatic and renal impairment; check renal function prior to treatment; reduce dose in renal impairment

Adverse reactions: *very common:* fatigue, drowsiness, headache ***common:*** somnolence, asthenia, infection, GI disturbance, blurred vision, hostility, pruritis, rash, cough, vertigo

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

Interactions:

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

Dosing:

Oral/ IV:	500 mg twice daily initially (reduce in renal impairment) can start with 250 mg bd – Maximum 1.5 g twice daily
subcut:	continuous subcut infusion is an alternative to BD IV administration
rectal:	not available

Syringe driver: not available

Mechanism of action: inhibits Ca^{2+} currents and reduces the release of Ca^{2+} from intraneuronal stores. Reverses the reductions in GABA- and glycine-gated currents induced by zinc and β-carbolines

Onset: peak concentrations at 1.5 hours

Levomepromazine

Class: antipsychotic/neuroleptic – phenothiazine

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

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

Adverse reactions: *common:* dry mouth, somnolence, postural hypotension, sedation; *less common:* hypotension, extrapyramidal side effects (long term high dose usually)

Metabolism/clearance: metabolised by sulphonation then glucuronidation. Metabolites may be active and are excreted by the kidneys so care in renal dysfunction. May inhibit CYP2D6

Interactions:

- *increased clinical effect/toxicity of some drugs* (due to increased blood concentrations of them) may occur with levomepromazine due to metabolising enzyme inhibition by levomepromazine e.g. ***amitriptyline, codeine*** (decreased morphine concentrations so decreased clinical efficacy of codeine), ***fluoxetine, nortriptyline, oxycodone, paroxetine, promethazine***
- *additive CNS effects* with other CNS depressants e.g. ***benzodiazepines (e.g. lorazepam), other phenothiazines (e.g. chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), opioids, alcohol***
- *additive increased risk of QT interval prolongation* (cardiac adverse effect which may lead to arrhythmias) with ***tricyclic antidepressants (e.g. amitriptyline), flecainide, erythromycin, theophylline, domperidone***

Dosing:

	pain, restlessness, distress, delirium	*nausea/vomiting*
oral:	6.25 to 50 mg every 4 to 8 hours	6.25 to 12.5 mg daily
subcut:	6.25 to 200 mg/24 hours	6.25 to 12.5 mg/24 hours

rectal: not available

Syringe driver: see syringe driver compatibility chart

Mechanism of action: suppresses sensory impulses in the CNS via various neurotransmitters

Onset: *im/subcut (analgesia):* 20 to 40 minutes

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

Notes:

- only phenothiazine with analgesic properties
- D2, 5HT alpha adrenergic, H1 and muscarinic antagonist
- doses of less than 25 mg/24 hours are associated with minimal sedation
- benztropine 2 mg may be useful in alleviating extrapyramidal side effects
- may be a useful option in patients with multiple symptoms
- only available as a 25 mg tablet – quarter of a tablet = 6.25 mg for nausea
- for smaller doses disperse tablets in water and give a fraction of it

Loperamide

Class: antidiarrhoeal – peripheral opioid receptor agonist

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

Contraindications/cautions: diarrhoea due to infection or antibiotics

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

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

Interactions:

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

Dosing:

oral:	4 mg stat then 2 mg after each loose stool (max. of 16 mg/24 hours)
subcut:	not available
rectal:	not available

Syringe driver: not available

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

Onset: 1 to 3 hours

Notes:

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

Lorazepam

Class: anxiolytic – short acting benzodiazepine

Indications (NB some may be unlicensed): short term use: anxiety, insomnia, premedication, muscle spasm, nausea/vomiting (anxiety related)

Contraindications/cautions: respiratory failure; severe hepatic impairment; renal impairment

Adverse reactions: *common:* sedation, dizziness, unsteadiness; ***less common:*** respiratory depression (high dose), disorientation, depression, disinhibition, amnesia, excitement

Metabolism/clearance: Mainly metabolised by glucuronidation

Interactions:

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

Dosing:

oral:	anxiety 1 to 3 mg/day in 2 to 3 doses (max. 10 mg/24 hours)	insomnia 1 to 2 mg at bedtime
subcut:	injection available (unregistered) but difficult to obtain	
rectal:	not available	

Syringe driver: not available

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

Onset:	oral: 20 to 30 minutes	sublingual: shorter onset
Duration:	oral: 6 to 8 hours	**Half life:** 10 to 20 hours

Notes:

- lorazepam is a short acting benzodiazepine
- tablets may be tried sublingually
- not metabolised by metabolising enzymes CYP450 so less likely to interact with other drugs compared with other benzodiazepines
- theoretically most appropriate benzodiazepine to use in hepatic failure
- for approximate equivalent oral anxiolytic/sedative doses see clonazepam page
- for pharmacological properties of benzodiazepines see clonazepam page

Methadone

Class: analgesic – opioid agonist; NMDA antagonist

Indications (NB some may be unlicensed): step 3 in the WHO analgesic ladder, opioid dependence; moderate to severe pain; intractable cough in palliative care

Contraindications/cautions: may accumulate as long half life; individually variable half life; history of cardiac conduction abnormalities

Adverse reactions: *see **morphine*** but less drowsiness, nausea, vomiting and constipation; dry mouth. Has a long and variable half life so watch for signs of accumulation e.g. decreased respiratory rate or mental status (particularly in the elderly). QT-interval prolongation

Metabolism/clearance: metabolised by metabolising enzyme CYP3A mainly in the liver. Demethylation is the major route of metabolism and metabolites are excreted by the kidney

Interactions:

- *increased clinical effect/toxicity of methadone* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. ***aprepitant, clarithromycin, grapefruit juice, indinavir, itraconazole, ketoconazole, nelfinavir, ritonavir, telapravir, voriconazole***
- *decreased clinical effect/toxicity of methadone* (due to decreased blood concentrations) may occur with some CYP metabolising enzyme inducers (see above) e.g. ***carbamazepine, phenobarbitone, phenytoin, rifampicin, St John's wort***
- *additive CNS effects* (including respiratory depression) with ***other CNS depressants*** e.g. ***benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), other opioids, alcohol***
- *additive increased risk of QT interval prolongation* (cardiac adverse effect which may lead to arrhythmias) with other drugs that prolong it

Dosing: (and see notes)
oral: 2.5 to 5 mg twice daily initially
subcut: 50 to 75% of oral dose
rectal: not available in NZ

Syringe driver: see syringe driver compatibility table

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

Onset: 0.5 to 1 hour initially

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

Methadone (CONTINUED)

Notes:

- may be useful in opioid rotation
- dose conversion ratios from other opioids is variable as individuals have differing methadone half lives and the ratio varies with dose (see next page)
- as affects NMDA receptors may prevent 'wind up' (rapidly escalating doses) on long term use and is useful in neuropathic pain
- renal and hepatic impairment are rarely a problem
- subcutaneous injection/infusion may be irritant – may need larger volume syringe
- some centres use low dose methadone alongside other opioids as adjuvant pain relief
- in opioid naïve patients starting doses are usually 2.5 to 5 mg twice a day with 3 hourly prn breakthrough doses, usually of another opioid. Titrate dose weekly

Conversion to methadone[1]

Table 2: Suggested safe and effective starting doses when changing patients from oral morphine to oral methadone

Morphine dose (mg/day)	Morphine to methadone equianalgesic dose ratio	Methadone starting dose
30–90	4:1	e.g. 90 mg morphine per day = 22.5 mg methadone per day
90–300	8:1	e.g. 200 mg morphine per day = 25 mg methadone per day
>300	12:1	maximum = 30 mg methadone per day as outpatient

[1] *https://bpac.org.nz/BPJ/2008/December/docs/bpj18_methadone_pages_24-29.pdf*

Methylnaltrexone bromide

Class: Peripherally acting opioid-receptor antagonist

Indications: Opioid-induced constipation where oral and rectal treatments are ineffective or not tolerated

Contraindications/cautions: Contraindications: acute surgical abdomen, gastrointestinal obstruction, post-operative ileus. Cautions: active diverticulitis, faecal impaction, conditions or concomitant medications affecting the structural integrity of the GIT (cancer, peptic ulcer, NSAIDs), – risk of perforation, patients with colostomy or peritoneal catheter

Adverse reactions: abdominal pain, diarrhoea, flatulence, vomiting, nausea, dizziness, hyperhidrosis, opioid withdrawal symptoms (usually mild), injection site reactions. ***Rare:*** GI perforation

Metabolism/clearance: minimally metabolised and predominantly excreted unchanged

Interactions: Nil reported

Dosing:

Adult: under 38 kg – 150 micrograms/kg
38 to 62 kg – 8 mg (=0.4 mL)
62 to 114 kg – 12 mg (=0.6mL)
Over 114 kg – 150 micrograms/kg

Given once daily on alternate days – dose can be repeated after 24 hours if no bowel movement occurs. Inject into upper arm, abdomen or thigh; rotate sites and avoid areas that are tender, bruised, red or hard

Syringe driver: not available

Mechanism of action: Binds to mu-opioid receptor in the GIT (8-fold affinity for mu receptor over kappa receptor), blocking constipating effects of opioids. Limited ability to cross the blood brain barrier so does not antagonise opioid analgesia

Onset: May work within 30 minutes after subcut injection

Notes:

- hepatic impairment: mild to moderate hepatic impairment – no dose adjustment necessary; no information available for use in severe hepatic impairment – advice is to avoid use
- renal impairment: if eGFR < 30 mL/min/1.73m^2, halve the dose; avoid in end stafe renal failure requiring dialysis (no information available)

Availability: Vial 12 mg/0.6 mL

Methylphenidate

Class: central stimulant – amphetamine related

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

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

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

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

Interactions:

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

Dosing:

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

oral:	normal release	10 to 30 mg a day (morning and mid-day) Commence with 2.5 to 5 mg twice daily (morning & noon) – increase in 2.5 mg increments to 20 mg twice daily if necessary. Max 30 mg twice daily
subcut:	not available	
rectal:	not available	

Syringe driver: not available

Mechanism of action: acts as a stimulant in the CNS

Onset: *depression:* 2 to 5 days

Notes:

- patients may respond to short courses of 2 to 3 weeks then withdraw
- methylphenidate is occasionally used to treat opioid-induced drowsiness

Metoclopramide

Class: antiemetic – prokinetic – dopamine receptor antagonist

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

Contraindications/cautions: complete intestinal obstruction. Young persons (< 20 years old) are more prone to extrapyramidal side effects so use lower doses; caution also in the elderly, renal & hepatic impairment

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

Metabolism/clearance: metabolised in the liver partially by the metabolising enzyme CYP2D6 to inactive metabolites which are mainly excreted with some parent drug by the kidneys

Interactions:

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

Dosing:

oral:	10 mg 3 to 4 times a day (max. 0.5 mg/kg) (nausea, vomiting, hiccups)
subcut:	30 to 60 mg over 24 hours (watch for extrapyramidal effects at > 30 mg/24 hours)
rectal:	10 mg up to 3 times a day

Syringe driver: see syringe driver compatibility chart

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

Peak effect: ***oral/ rectal:*** 1 to 3 hours

Notes:

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

Metronidazole

Class: antibiotic – anti-anaerobe

Indications (NB some may be unlicensed): anaerobic bacterial infections, useful in controlling malodorous wounds

Contraindications/cautions: hypersensitivity to nitroimidazoles such as ornidazole; caution in renal & hepatic impairment

Adverse reactions: *common:* GI upset (abdominal pain, nausea, vomiting, diarrhoea), urticaria, metallic taste, furry tongue; ***less common:*** QT prolongation, drowsiness, headache, dizziness, urine darkening, blood disorders, muscle/joint pain

Metabolism/clearance: metabolised in the liver to some active and some inactive metabolites which are excreted with some parent drug by the kidneys

Interactions:

- *disulfiram-like reaction* (nausea, vomiting, sweating) may occur with concomitant ***alcohol***
- *increased toxicity of* ***lithium*** may occur with metronidazole
- Metronidazole can increase INR in patients on warfarin
- Increased plasma concentrations of cyclosporin, fluorouracil, phenytoin

Dosing:

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

Syringe driver: not applicable

Mechanism of action: in malodorous wounds kills anaerobes responsible for the smell

Topical use:

- useful for malodourous wounds
- availability of 0.75% gel limited in NZ and not funded
- tablets can be crushed finely and applied to wound in lubricating gel or as a powder

Miconazole

Class: antifungal – imidazole

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

Contraindications/cautions: hepatic impairment

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

Metabolism/clearance: metabolised by the liver

Interactions:
Oral gel/vaginal preparations (absorption is likely)
- *decreased clinical effect* of ***amphotericin*** may occur with miconazole
- may affect INR of patients taking ***warfarin***. Monitor even if only using oral gel

Dosing:

mouth (topical):	Oral gel 20 mg/g – Use 2.5 mL (50 mg) 4 times a day for 7 days
subcut:	not available
rectal:	not available
topical:	apply twice a day
vaginal:	use at night for 7 nights

Syringe driver: not available

Mechanism of action: increases fungal cell membrane permeability

Oral gel: place half a measuring spoonful (2.5 mL) on tongue and hold in mouth for as long as possible before swallowing

Microlax™/Micolette™

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

Class: rectal laxative – stimulant, faecal softener and osmotic

Indications: constipation, bowel evacuation

Dosing:

oral:	not available
subcut:	not available
rectal:	insert contents of ONE enema into the rectum as required; repeat in 20 minutes if no result

Syringe driver: not available

Mechanism of action: may stimulate colonic activity via nerves in the intestinal mucosa (sodium citrate) and increased fluid uptake by stools thus softening them (sodium lauryl sulphoacetate, sorbitol)

Onset: almost immediate

Midazolam

Class: sedative – benzodiazepine

Indications (NB some may be unlicensed): sedation, anaesthetic induction agent, intractable hiccup refractory to other treatment, epilepsy, muscle spasm, dyspnoea, insomnia, agitation or confusion in the last days of life

Contraindications/cautions: avoid sudden withdrawal, respiratory depression; sleep apnoea

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

Metabolism/clearance: metabolised by metabolising enzyme CYP3A (major) mainly in the liver

Interactions:

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

Dosing:

oral:	7.5 to 15 mg at bed-time (to sleep)
subcut:	5 to 60 mg/24 hours (up to 150 mg in sedation at the end-of-life) – doses adjusted according to response
Intractable hiccup:	2.5 to 10 mg subcut prn – max dose 60 mg daily CSCI 10 mg-60 mg over 24 hours
rectal:	not available

Syringe driver: see syringe driver compatibility table

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

Peak concentrations: oral 20 to 50 min subcut 5 to 10 min iv 2 to 3 mins

Duration: 15 minutes to several hours **Half life:** 2 to 5 hours

Notes:

- midazolam is a very short acting benzodiazepine so dose titration to response is easier than with longer acting benzodiazepines e.g. clonazepam
- IV administration can result in hypotension and transient apnoea
- benzodiazepines may reduce dyspnoea by anxiolytic and sedative effects
- for approximate equivalent oral anxiolytic/sedative doses see clonazepam page
- for pharmacological properties of benzodiazepines and other hypnotics see clonazepam page
- may be used bucally or sublingually
- bioavailability 95% subcut and 85% sublingually

Mirtazapine

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

Indications (NB some may be unlicensed): major depression, nausea; pruritis in palliative care

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

Adverse reactions: ***common:*** increased appetite, weight gain, drowsiness in first few weeks of treatment, dizziness, headache, dry mouth; ***less common:*** convulsions, tremor, nightmares, mania, syncope, hyponatraemia, nausea

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

Interactions:

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

Dosing:

oral:	15 to 45 mg at bed-time (start with 15 mg and increase slowly)
subcut:	not available

Syringe driver: not available

Mechanism of action: blocks presynaptic alpha 2 and $5HT_2$ and $_3$ receptors increasing central noradrenaline and serotonin (blocking $5HT_2$ and $5HT_3$ receptors allowing stimulation of $5HT_1$ receptors)

Peak concentrations: ***oral:*** 2 hours **Half life:** 20 to 40 hours

Morphine

Class: analgesic – full opioid antagonist

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

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

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

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

Interactions:

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

Dosing:

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

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

- prescribe rescue doses (normal release) of ⅕ to ⅙ of the total 24 hour dose 4 to 6 hourly
- there is no real maximum dose but it is usually less than 200 mg/24 hours. If it is >400 mg/24 hours consider the aetiology of the pain and the use of co-analgesia or opioid rotation
- review doses regularly

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

breathlessness, cough:

oral: normal release 5 to 10 mg 4 hourly prn

Syringe driver: see syringe driver compatibility chart

Morphine (CONTINUED)

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

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

Notes:

- tolerance to effect does occur but progressive disease is also a cause of dose fade
- if dose of slow release morphine is increased remember to also increase the prescribed dose of normal release morphine for breakthrough pain/rescue
- toxicity: decrease in respiratory rate, mental status and blood pressure – give naloxone (see naloxone page)
- for conversion to oxycodone, fentanyl or methadone, see relevant pages
- morphine can affect the ability to drive. Some patients may need to be told not to drive while taking morphine. Always advise patients not to drive for several days after a dose increase
- topical morphine may be useful for wound pain. It is usually used as 0.05 to 0.1% morphine (i.e. 0.5 to 1 mg/mL) in Intrasite™ gel, metronidazole gel or KY Jelly™
- care with prescribing oral liquids – 1 mg/mL strength preferred. Be aware of strengths such as 10 mg/mL & potential for dosing errors
- SR capsules available in 10 mg, 30 mg, 60 mg & 100 mg; immediate release tablets 10 mg and 20 mg

Molaxole™

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

Class: laxative – osmotic

Indications: constipation including faecal impaction

Contraindications/cautions: intestinal obstruction or perforation, ileus and severe inflammatory conditions of intestinal tract eg Crohns, cardiac disease (contains sodium and potassium); monitor for fluid imbalance

Adverse reactions: *less common:* abdominal distension and pain, nausea

Metabolism/clearance: not absorbed

Interactions: few as not absorbed – may affect the absorption of some drugs

Dosing:

Movicol™, Lax-sachet™:

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

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

Movicol-Half™:

constipation	1 to 6 sachets/day
faecal impaction	16 sachets/day taken within 6 hours for a max. of 3 days If cardiovascular problems, do not take more than 4 sachets over any 1 hour

- Each sachet should be dissolved in 60 mL of water

Mechanism of action: osmotic action in the gut to increase liquid content of stools but with no net loss of sodium, potassium or water

Onset: *faecal impaction:* most cleared after 3 days

Notes:

- effective laxative in palliative care
- more acceptable to many than lactulose

Naloxone

Class: opioid antagonist

Indications: opioid overdose – reverses opioid effects

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

Contraindications/cautions: cardiovascular disease

Adverse reactions: ***common:*** nausea, vomiting, tachycardia, sweating, raised blood pressure (opioid withdrawal), headache, dizziness; ***less common:*** diarrhoea, dry mouth

Metabolism/clearance: metabolised mainly in the liver by glucuronidation

Interactions:

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

Dosing:

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

iv:	0.1 to 0.2 mg every 2 to 3 minutes for reversal of CNS depression post-op 400 micrograms; if no response after 1 minute, give 800 micrograms, and if still no response after another 1 minute, repeat dose of 800 micrograms; if still no response, give 2 mg (4 mg may be required in a seriously poisoned patient), every 2 to 3 minutes up to 10 mg for opioid overdose
oral:	not available alone
subcut:	see below
rectal:	not available

Syringe driver: not applicable

Mechanism of action: blocks action of opioids at opioid receptors

Onset: ***iv:*** 2 to 3 minutes ***subcut/im:*** 15 minutes

Duration: 15 to 90 minutes

Notes:

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

Naproxen

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

Indications (NB some may be unlicensed): pain associated with inflammation (including bone pain), dysmenorrhoea, itch, sweating; acute migraine; post-operative pain; acute gout

Contraindications/cautions: Sensitivity to aspirin or other NSAIDs (includes asthma, angioedema, urticaria or rhinitis precipitated by aspirin or NSAID); GI ulceration (active or history of), severe heart failure; renal or hepatic impairment (avoid in severe impairment) and caution in other cardiac conditions. Caution in use in the elderly & those with coagulation defects

Adverse reactions: *common:* GI discomfort, nausea, diarrhoea, indigestion; can lead to GI ulceration (caution*:* if elderly, on steroids or aspirin), increased blood pressure, headache, dizziness, sodium & fluid retention ***less common:*** rash, nephrotoxicity, hepatitis, oedema, tinnitus, proctitis (rectal administration). NB Inhibits platelet aggregation – may prolong bleeding time

Metabolism/clearance: metabolised by metabolising enzyme CYP2C8/9 mainly in the liver

Interactions:

- increased clinical effect/toxicity of naproxen (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. fluconazole, ketoconazole, voriconazole
- decreased clinical effect/toxicity of naproxen (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. phenobarbitone, phenytoin, rifampicin
- increased clinical effect/toxicity of lithium, digoxin, methotrexate and warfarin may occur with naproxen due to increased concentrations of these drugs via kidney excretion competition so monitor
- decreased clinical effects of diuretics (e.g. furosemide) and beta blockers (e.g. propranolol) may occur with naproxen
- increased risk of renal toxicity and hyperkalaemia with ACE inhibitors may occur with naproxen
- additive risk of bleeding may occur with warfarin and heparin in combination with naproxen

Dosing:

oral:	normal release	500 to 1,000 mg per day in 2 divided doses or 275 mg every 6 to 8 hours (max 1,375 mg)
	sustained release	750 to 1,000 mg per day as a single dose
subcut:		not available
rectal:	not available (try diclofenac)	

Syringe driver: not available

Mechanism of action: NSAIDs reduce prostaglandin production by inhibiting cyclo-oxygenase, resulting in analgesic, anti-inflammatory and anti-pyretic effects

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

Duration: 7 hours

Nortriptyline

Class: antidepressant – tricyclic

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

Contraindications/cautions: arrhythmias (particularly heart block), recent MI, epilepsy (lowers seizure threshold), urinary retention; use of MAOI within 14 days; manic phase of bipolar disorder. Caution in cardiovascular disease, QT prolongation, hyperthyroidism, prostatic hypertrophy; concommittant serotonergic drugs and drugs that prolong QT

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

Metabolism/clearance: metabolised by the metabolising enzyme CYP2D6 (major) mainly in the liver to active metabolites; increased sedative effects in hepatic impairment

Interactions:

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

Dosing:

	depression	*pain*
oral:	25 to 100 mg at night (max. of 50 mg in elderly)	10 to 50 mg at night (start 10 mg; increase gradually)
subcut:	not available	
rectal:	not available	

Syringe driver: not available

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

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

Notes:

- metabolite of amitriptyline, less adverse reactions (including sedation) than amitriptyline
- 25 mg nortriptyline Ξ 75 mg amitriptyline (approx)
- nortriptyline may be better tolerated than amitriptyline. It is less likely to cause postural hypotension and has fewer troublesome antimuscarinic effects. At least 4 to 8 weeks of treatment with a first-line medicine is necessary to allow for dose titration and sufficient duration of treatment at a therapeutic dose to assess efficacy. For patients who experience a partial response but feel that response is inadequate, increasing the dose or switching to another first-line medicine may be considered. Amitriptyline (or other tricyclic antidepressants) and either gabapentin or pregabalin can be used in combination if the patient has an inadequate response to either drug at the maximum tolerated dose (NZF)

Nystatin

Class: antifungal – polyene

Indications: fungal infections – topical, oral, gastrointestinal, vaginal

Adverse reactions: ***less common:*** nausea, vomiting, diarrhoea (at high doses), local irritation

Dosing:

oral:	(not absorbed orally)
oral candidiasis:	100,000 units (1 mL) 4 times a day usually for 7 days
gastrointestinal candidiasis:	500,000 to 1,000,000 units 3 times a day
subcut:	not available
rectal:	not available
topical:	apply 2 to 3 times a day
vaginal:	insert 5 g of cream once or twice a day

Syringe driver: not available

Mechanism of action: increases fungal cell membrane permeability

Notes:

- administer dose on the tongue or in the buccal cavity and hold in the mouth for as long as possible before swallowing
- continue treatment for 48 hours after resolved
- if infection is severe or recurrent use a systemic antifungal e.g. fluconazole

Octreotide

Class: growth hormone inhibitor – somatostatin analogue

Indications (NB some may be unlicensed): acromegaly, gastro-entero pancreatic endocrine tumours, post pancreatic surgery, emergency treatment to stop bleeding oesophageal varices, antisecretory in intestinal obstruction, nausea & vomiting due to inoperable malignant intestinal obstruction (specialist use; unapproved); secretory diarrhoea, high fistula output, variceal bleeds

Contraindications/cautions: diabetes; monitor thyroid & liver function

Adverse reactions: nausea, vomiting, abdominal pain, bloating, flatulence, diarrhoea; *less common:* injection site reaction, hepatitis, gallstones, hyper/hypoglycaemia, bradycardia, dizziness, drowsiness, headache, hypothyroidism

Metabolism/clearance: metabolised by the liver; half-life prolonged in cirrhosis

Interactions:

- *decreased absorption* of ***ciclosporin*** may occur with octreotide
- hypoglycaemic drugs and insulin (dose reduction may be required)

Dosing:

oral:	not available
subcut:	200 to 600 micrograms/24 hours (max. 1 mg/24 hours) LAR – not usually used in palliative care
rectal:	not available
iv:	not available

Syringe driver: see syringe driver compatibility chart

Mechanism of action: blocks somatostatin receptors

Peak effect: 30 minutes

Duration: 12 hours

Notes:

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

Olanzapine

Class: atypical antipsychotic

Indications (NB some may be unlicensed): acute and chronic psychoses including schizophrenia, bipolar disorder, acute mania, nausea and vomiting in palliative care, delirium

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

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

Metabolism/clearance: metabolised mainly in the liver by the metabolising enzymes CYP1A2 to inactive metabolites which are partially excreted by the kidneys; use lower doses in renal & hepatic disease

Interactions:

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

Dosing:

oral tabs/disp tabs:	2.5 to 5 mg daily at bedtime; may be increased if required in steps of 2.5 to 10 mg daily at bedtime – if 10 mg daily ineffective seek palliative care specialist advice
subcut:	inj available but recommended for im use only
rectal:	not available

Syringe driver: not available

Mechanism of action: Olanzapine, a second generation (atypical) antipsychotic, acts as an antagonist at dopamine ($D_{1\text{-}5}$), serotonin (5-HT_2, 5-HT_3, 5-HT_6), histamine-1, α_1-adrenergic, and muscarinic ($M_{1\text{-}5}$) receptors with varying affinity

Notes:

- lower potential for neurological adverse effects than conventional antipsychotics
- can be used in acute delirium and behavioural disturbances associated with brain tumours
- available in oro-dispersable tablets

Omeprazole

Class: ulcer healing/prophylactic – proton pump inhibitor

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

Contraindications/cautions: renal impairment; no more than 20 mg daily in hepatic impairment

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

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

Interactions:

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

Dosing:

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

Syringe driver: short infusions only

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

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

Notes:

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

Ondansetron

Class: antiemetic – specific $5HT_3$ antagonist

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

Contraindications/cautions: contraindicated in congenital prolonged QT; caution with other QT prolonging drugs & serotonergic drugs, caution in hepatic impairment (max dose 8 mg daily), subacute gastro-intestinal obstruction

Adverse reactions: ***common:*** headache, flushing, constipation; ***less common:*** hiccups, hypotension, injection site reaction, dizziness, cardiac effects (iv usually tachycardia, chest pain, arrhythmias); ***rarely:*** QT prolongation (Torsade de Pointes)

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

Interactions:

- *increased clinical effect/toxicity of ondansetron* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. ***bupropion, fluoxetine, paroxetine, quinine***
- QT prolongation risk with domperidone (contraindicated together in UK) and other QT drugs (NZF)

Dosing:

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

Syringe driver: see compatibility chart

Mechanism of action: Ondansetron reduces the vomiting reflex by blocking serotonin at $5HT_3$ receptors both peripherally in the GI tract and centrally in the CTZ

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

Notes:

- may be of use in nausea and vomiting refractory to all other antiemetics
- available as an oro-dispersable tablet – place on top of tongue and allow to dissolve before swallowing
- 0.8 mg/mL oral suspension can be prepared

Oxycodone

Class: analgesic – full opioid agonist

Indications: step 3 in the WHO analgesic ladder; moderate to severe pain

Contraindications/cautions: severe renal failure, respiratory disease

Adverse reactions: *see morphine*

Metabolism/clearance: metabolised by metabolising enzymes CYP2D6 mainly in the liver

Interactions:

- *increased clinical effect/toxicity of oxycodone* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. ***bupropion, fluoxetine, paroxetine, quinine***
- *additive CNS effects* with ***other CNS depressants e.g. benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), other opioids, alcohol***
- *additive respiratory depression* with ***benzodiazepines (e.g. midazolam), other respiratory depressants***

Dosing: (and see notes)

oral:	immediate release	initially in opioid naïve 1 to 3 mg 4 to 6 hourly
	slow release	initially 5 mg every 12 hours
subcut:	oral: subcut	2:1
rectal:	not available	

Syringe driver: see syringe driver compatibility chart

Renal impairment: effects of opioids may be increased & prolonged

- eGFR 10 to 30 mL/min/1.73m^2 initially give 75% of estimated dose and titrate cautiously with appropriate monitoring
- eGFR <10 mL/min/1.73m^2 give 50% of estimated dose; titrate cautiously & monitor
- Care required with slow release formulations – accumulation may occur

Hepatic impairment: manufacturer recommends reduce initial dose 30 to 50% of usual dose in mild impairment; avoid in moderate to severe impairment

Mechanism of action: binds to opioid receptors in the brain and spinal cord inhibiting the ascending pain pathways thus altering perception and response to pain

Onset: oral: 20 to 30 minutes

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

Notes:

- may be useful in opioid rotation
- dose conversion from oral morphine to oral oxycodone is 2:1 i.e. 10 mg oral morphine = 5 mg oral oxycodone because oral availability of oxycodone is twice that of morphine
- the slow release tabs should not be crushed/chewed
- oral liquid 5 mg/5 mL is available
- in renally impaired patients, one of oxycodone's active metabolite may accumulate (see dose recommendations above)
- the combination oxycodone+naloxone slow release tablets are designed to reduce opioid induced constipation

Pamidronate disodium

Class: bisphosphonate calcium regulator

Indications: hypercalcaemia of malignancy; osteolytic lesions and bone pain with bone metastases or multiple myeloma

Contraindications/cautions: severe renal impairment, dental surgery, oral disease, ensure adequate hydration; caution in severe hepatic impairment

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

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

Interactions:
- incompatible with calcium containing infusion fluids

Dosing:

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

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

Syringe driver: not applicable

Renal impairment: maximum infusion rate 20 mg/hour; avoid if CrCl < 30 mL/min except in life-threatening hypercalcaemia if benefit outweighs risk

Mechanism of action: bisphosphonates are adsorbed onto hydroxyapatite sites in bone, reducing osteoclast bone resorption and therefore reducing rate of bone turnover

Onset: *hypercalcaemia:* 1 to 2 days

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

Notes:
- 50% of patients with metastatic bone pain may be responsive
- Hypercalcaemia of malignancy (slow IV infusion):
  Adult – according to initial serum Ca conc:
  - Serum calcium <3 mmol/L – 15 to 30 mg
  - Serum calcium 3 to 3.5mmol/L – 30 to 60 mg
  - Serum calcium 3.5 to 4mmol/L – 60 to 90 mg
  - Serum calcium > 4mmol/L – 90 mg

Pantoprazole

Class: ulcer healing/prophylaxis – proton pump inhibitor

Indications: duodenal/benign gastric ulcer, reflux oesophagitis, dyspepsia, NSAID-associated gastro-duodenal ulcer

Contraindications/cautions: moderate to severe renal impairment; max dose 40 mg daily in mild impairment; maximum dose 20 mg daily in severe hepatic impairment

Adverse reactions: ***common:*** headache, GI disturbances (nausea/vomiting/diarrhoea) ***less common:*** abdominal pain, flatulence, insomnia, pruritus, dizziness, dry mouth, increased sweating, rash, pruritis

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

Interactions:

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

Dosing:

oral:	20 to 40 mg once a day
subcut:	inj available but not usually used subcut
rectal:	not available

Syringe driver: not usually used

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

Onset: ***oral (antacid effect):*** 2 hours

Paracetamol

Class: analgesic – non-opioid

Indications: step 1 on the WHO analgesic ladder, co-analgesic, antipyretic – mild to moderate pain; pyrexia with discomfort

Contraindications/cautions: severe hepatic impairment

Adverse reactions: ***less common:*** rash, pancreatitis on prolonged use, liver damage in overdose (> 6 g in 24 hours) or in combination with heavy alcohol intake, nephrotoxicity

Metabolism/clearance: metabolised in the liver mainly by glucuronidation

Hepatic impairment: avoid in severe impairment or hepatic failure; in mild to moderate impairment maximum daily dose no more than 60 mg/kg/day (max 2g/day) in people with body weight <50kg or chronic liver disease

Renal impairment: caution in severe impairment if eGFR < 30 mL/min/1.73m^2 – increase dose interval

Interactions:
- *increased toxicity of paracetamol* may occur with ***alcohol***
- *increased anticoagulant effect* of ***warfarin*** may occur if given with concurrent paracetamol regularly for a long time so monitor INR
- *increased absorption of paracetamol* may occur with ***metoclopramide*** and ***domperidone***
- *increased risk of hepatotoxicity* may occur with concurrent ***carbamazepine, phenytoin***

Dosing:

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

Syringe driver: not used subcut due to high volume

Mechanism of action: thought to have a central effect on pain pathways preventing transmission of nociceptive signals from peripheral tissues to the spinal cord; it may reduce prostaglandin production resulting in reduced pain sensation. Anti-pyretic effect but is not anti-inflammatory

Onset: 0.5 hours

Duration: 4 hours

Notes:
- give regularly rather than if required
- available in tablets, oral liquid & suppositories
- combination preparations are not recommended
- liver damage is likely to occur in overdose
- useful analgesic when given regularly in combination with opioids

Phenobarbitone

Class: anticonvulsant – barbiturate

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

Contraindications/cautions: acute intermittent porphyria, severe respiratory depression or pulmonary insufficiency, elderly, renal/hepatic failure

Adverse reactions: ***common:*** drowsiness, headache, hypotension, respiratory depression; ***less common:*** GI upset, paradoxical excitement, pain, hypocalcaemia,hallucinations

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

Interactions:

- *increased clinical effect/toxicity of phenobarbitone* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. ***fluconazole, fluoxetine, ketoconazole***
- *decreased clinical effect/toxicity of phenobarbitone* (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. ***phenytoin, rifampicin***
- *decreased clinical effect/toxicity of some drugs* (due to decreased blood concentrations of them) may occur with phenobarbitone due to metabolising enzyme induction by phenobarbitone e.g. ***aprepitant, buspirone, carbamazepine, clonazepam, dexamethasone, diazepam, domperidone, fentanyl, itraconazole, ketoconazole, methadone, midazolam, NSAIDs (e.g. diclofenac), phenytoin, prednisone, quetiapine, triazolam, warfarin***
- *additive CNS effects* with other CNS depressants e.g. ***benzodiazepines (e.g. lorazepam), phenothiazines (e.g. chlorpromazine), opioids, alcohol***
- Refer to PCF8 or NZF for full interactions

Dosing:

terminal agitation

oral:	60 to 180 mg per day (not often given orally)
subcut:	600 to 1,200 mg/24 hours – loading dose 200 mg can be given; increase dose in syringe driver progressively over 24 hours if required. Can be given IV or IM
rectal:	not available

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

Mechanism of action: depresses activity of all excitable tissue perhaps via GABA

Notes:

- risk of respiratory depression in overdose

Phenytoin

Class: anticonvulsant – hydantoin

Indications (NB some may be unlicensed): epilepsy, prophylaxis in neurosurgery, arrhythmias

Contraindications/cautions: low albumin, diabetes, elderly (reduced clearance)

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

Metabolism/clearance: metabolised by metabolising enzyme CYP2C8/9 mainly in the liver

Interactions:

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

Dosing:

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

Syringe driver: not applicable

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

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

Notes:

- monitor plasma concentrations
- small dose increases may result in large plasma concentration increases
- if the patient has NG feeds these will affect phenytoin concentrations

Prednisone

Class: corticosteroid – glucocorticoid

Indications (NB some may be unlicensed): allergy, asthma, rheumatic disease, inflammatory conditions, nausea/vomiting, inflammation in gastrointestinal obstruction, sweating, itch, hypercalcaemia, hiccup, pain, dyspnoea (lymphangitis), liver capsule pain, tenesmus, appetite

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

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

Metabolism/clearance: metabolised by the metabolising enzyme CYP3A mainly in the liver

Interactions:

- *increased clinical effect/toxicity of prednisone* (due to increased blood concentrations) may occur with some CYP metabolising enzyme inhibitors (see above) e.g. ***aprepitant, clarithromycin, fluconazole, fluoxetine, grapefruit juice, itraconazole, ketoconazole, valproate***
- *decreased clinical effect/toxicity of prednisone* (due to decreased blood concentrations) may occur with some CYP metabolism enzyme inducers (see above) e.g. ***carbamazepine, phenobarbitone, phenytoin, rifampicin, St John's wort***
- *increased risk of GI bleed/ulceration* when given with ***NSAIDs (e.g. diclofenac)***

Dosing:

oral:	5 to 60 mg usually once a day – dexamethasone used more commonly in palliative care
subcut:	not available
rectal:	not available

Syringe driver: not available

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

Notes:

- 0.75 mg dexamethasone has an equivalent anti-inflammatory effect to 5 mg prednisone or 20 mg hydrocortisone
- on discontinuation decrease dose slowly (taper) unless the patient has been taking it for less than 5 days in which case dose tapering is not necessary
- alteration in mood not usually seen below 40 mg prednisone (6 mg dexamethasone) per day
- corticosteroid induced insomnia responds to benzodiazepines (e.g. temazepam)
- corticosteroid induced mood disorder is usually depression and rarely mania
- metabolised to prednisolone

Pregabalin

Class: anticonvulsant – gabapentinoid

Indications (NB some may be unlicensed): neuropathic pain, anxiety, focal seizures, pruritis, sweating, hot flushes, refractory hiccup, restless legs syndrome, spasticity, refractory cough (PCF8)

Contraindications/cautions: renal disease (reduce dose – see below)

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

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

Interactions:

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

Dosing:

oral:	neuropathic pain/epilepsy	150 to 600 mg/day in 2 divided doses (start with lower dose 75 mg twice daily and increase)
subcut:	not available	
rectal:	not available	

Syringe driver: not available

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

Notes:

- reduce dose in renal impairment:
  - CrCl> 60 mL/min – starting dose 75 mg bd; maximum dose 300 mg bd
  - CrCl 31 to 60 mL/min – starting dose 25 mg tds; maximum 150 mg bd
  - CrCl 15 to 30 mL/min – starting dose 25 to 50 mg od; maximum 150 mg once daily
  - CrCl 15 mL/min – starting dose 25 mg od; maximum 75 mg once daily (PCF8)
- if stopping, withdraw dose gradually (over weeks)

Quetiapine

Class: antipsychotic – atypical, second generation

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

Contraindications/cautions: liver dysfunction, cardiovascular and cerebrovascular disease, hypotension, seizures, Parkinsons, DLB; caution with other drugs causing QT prolongation eg domperidone

Adverse reactions: ***common:*** drowsiness, dry mouth, GI effects (constipation), tachycardia, dizziness, headache, agitation, insomnia, weight gain, dyspepsia; ***less common:*** neuroleptic malignant syndrome, tardive dyskinesia, cholesterol changes, thyroid hormone changes, peripheral oedema, diabetes, extrapyramidal adverse effects, hepatotoxicity, blood disorders, postural hypotension, seizures, dyspnoea, sweating, rash

Metabolism/clearance: metabolised almost completely mainly in the liver by the metabolising enzyme CYP3A. Elimination renal (75%) and faecal (25%) – caution in renal impairment

Interactions:

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

Dosing:

oral:	anxiety, depression, psychosis	start with 12.5 to 25 mg bd – increase in 12.5 to 25 mg increments over 3 to 4 days. Typical effective dose – anxiety 50 to 150 mg/24 hours; depression – 150 to 300 mg/24 hours; psychosis 300 to 450 mg/24 hours
	mania	initially 50 mg bd increasing daily to 200 to 800 mg per day in 2 divided doses; increase in 50 mg dose increments
	delirium	start with 12.5 mg bd; increase in 12.5 to 25 mg increments – mean effective dose 75 mg/24 hours (range 25 to 300 mg/24 hours) (PCF8)
subcut:	not available	
rectal:	not available	

Quetiapine (CONTINUED)

Syringe driver: not available

Mechanism of action: antagonises serotonin, dopamine, 5-HT, alpha-adrenoreceptor and histamine-1 receptors in the CNS

Bioavailability > 75%

Onset of action: *delirium:* hours to days *psychoses:* 1 to 2 weeks

Time to peak plasma conc: 1.5 hours

Duration of action: 12 hours (PCF8)

Notes:

- 12.5 mg dose = halve a 25 mg tablet. Some references recommend commencing on 25 mg dose – lower does in elderly, renal or hepatic impairment
- lower potential for neurological adverse effects (e.g. extrapyramidal effects) than conventional antipsychotics
- can be used in acute delirium and behavioural disturbances associated with brain tumours

Risperidone

Class: antipsychotic – atypical

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

Contraindications/cautions: Parkinson's disease, DLB, epilepsy, cardiovascular/cerebrovascular disease, diabetes; caution in renal & hepatic impairment

Adverse reactions: ***very common:*** (>10%) – parkinsonism; ***common:*** insomnia, anxiety, headache, extrapyramidal symptoms; ***less common:*** drowsiness, dizziness, GI upset, sexual dysfunction, constipation, dry mouth, postural hypotension

Metabolism/clearance: metabolised by metabolising enzyme CYP3A and 2D6 mainly in the liver

Interactions:

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

Dosing:

oral:	dementia	initially 0.25 mg twice a day increasing to a max. of 1 mg twice a day
	delirium	Start with 0.5 to 1 mg at bedtime and prn; if necessary increase by 0.5 to 1 mg after 2 days Mean effective dose 1.5 mg/24 hours (range 0.5 to 3 mg)
	Psychosis & mania	Start with 2 mg at bedtime; can increase by 2 mg at bedtime on successive days to 6 mg. Halve dose in elderly and those with severe renal/hepatic impairment
subcut/rectal:		not available

Syringe driver: not available

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

Onset: ***psychosis:*** 1 to 2 weeks

Risperidone (CONTINUED)

Notes:

- lower potential for neurological adverse effects e.g. extrapyramidal effects than conventional antipsychotics
- increasingly used in acute delirium and behavioural disturbances associated with brain tumours
- at high dose (> 6 to 8 mg a day) or in the cerebrally compromised patient extrapyramidal side effects may occur
- doses can be given once daily at bedtime

Senna

Class: laxative – stimulant

Indications: constipation

Contraindications/cautions: acute abdominal pain, intestinal obstruction

Adverse reactions: ***common:*** abdominal cramps, diarrhoea, perianal irritation; ***less common:*** atonic colon (with prolonged use), hypokalaemia, discolouration of urine (brown or pink)

Metabolism/clearance: not absorbed to a great extent

Interactions:

- *decreased antispasmodic effects* of ***antispasmodics*** e.g. ***hyoscine butylbromide*** may occur

Dosing:

oral:	2 to 4 tabs (14 to 28 mg) at night with docusate 1 to 2 tabs at night (max. 4 tabs)
subcut:	not available
rectal:	not available

Syringe driver: not available

Mechanism of action: stimulates colonic activity via nerves in the intestinal mucosa. May also have stool softening properties

Onset: 6 to 12 hours

Notes:

- may be useful in opioid induced constipation.
- usually used with docusate (Laxsol)

Spironolactone

Class: diuretic – aldosterone antagonist, potassium sparing diuretic

Indications (NB some may be unlicensed): peripheral oedema associated with portal hypertension and hyperaldosteronism resistant hypertension, congestive heart failure, hirsutism, primary hyperaldosteronism, malignant ascites

Contraindications/cautions: moderate/severe renal dysfunction, hyperkalaemia, hyponatraemia; avoid concurrent use with K supplements

Adverse reactions: ***common:*** GI upset, drowsiness, dizziness, hyperkalaemia; ***less common:*** rashes, headache, confusion, impotence, gynaecomastia, hyponatraemia

Metabolism/clearance: metabolised in liver to active metabolites which are excreted partially by the kidneys

Interactions:

- *increased risk of hyperkalaemia* with ***NSAIDs (e.g. diclofenac), ACE inhibitors (e.g. cilazapril, quinapril), potassium*** supplements
- *increased clinical effect/toxicity* of ***digoxin*** may occur via increased digoxin concentrations

Dosing:

oral:	malignant ascites	start with 100 mg mane; increase by 100 mg mane every 3 to 5 days if required (max. 400 mg daily)
subcut/rectal:	not available	

Syringe driver: not available

Mechanism of action: inhibits aldosterone causing naturesis and potassium retention

Peak response: ***aldosterone antagonism:*** 6 to 8 hours
reduced ascites: 10 to 25 days

Notes:

- paracentesis may be necessary in malignant ascites
- monitor body weight and renal function
- take with food to minimise gastric irritation
- halve dose in patients with ascites and moderate renal impairment (eGFR 30 to 59 mL/min/1.73m^2)

Tramadol

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

Indications: step 2 on the WHO analgesic ladder – moderate to severe pain

Contraindications/cautions: epilepsy, drug abuse, respiratory depression; genetic polymorphism in CYP2D6 affects metabolism of tramadol; renal or hepatic impairment

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

Metabolism/clearance: metabolised by metabolising enzyme CYP2D6 mainly in the liver to an active metabolite – individual variability due to being poor or ultra-rapid metabolisers

Interactions:

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

Dosing:

oral:	normal release	50 to 100 mg 4 hourly (max. 400 mg/24 hours)
	slow release	100 to 200 mg twice a day
subcut:	up to 600 mg/24 hours	
rectal:	not available	

Syringe driver: give separately as compatibility as yet unknown

Mechanism of action: Tramadol is an agonist at opioid receptors resulting in inhibition of ascending pathways in the brain and spinal cord, altering the perception and response to pain. Tramadol also inhibits reuptake of noradrenaline and serotonin which may contribute to its analgesic activity. Enhances effect on descending inhibitory pathways

Peak effect:	***oral:*** normal release	0.5 to 1 hour
Duration:	***oral:*** normal release	3 to 7 hours

Notes:

- place in palliative therapy still to be established
- may be useful in patients who are constipated on codeine as it is less constipating generally
- start with low dose to minimise adverse effects
- it is not a controlled drug
- halve the starting dose in severe renal impairment

Tranexamic acid

Class: antifibrinolytic, haemostatic

Indications: haemorrhage – surface bleeding from tumours, nose and other organs (some indications are unlicensed)

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

Adverse reactions: *common:* GI upset (nausea,vomiting,diarrhoea) – reduce dose; *less common:* dizziness (iv), thrombocytopenia, headache, restlessness, impaired colour vision

Interactions:

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

Dosing:

Haemorrhage:

oral:	1 to 1.5 g 3 to 4 times a day
subcut:	can be used in 50ml WFI or saline by short infusion
topical:	the injection has been used topically on bleeding wounds
iv:	0.5 to 1 g 2 to 3 times a day

Control of surface (mucosal or epidermal) bleeding:

Oral:	1.5 g stat then 1 g tds – discontinue 1 week after bleeding stops or reduce to 500 mg tds
Mouthwash:	dissolve one 500 mg tablet in 10 mL of water and use as a mouthwash qid – rinse mouth then swallow

Syringe driver: 1000 mg to 2000 mg in WFI or saline over 24 hours

Mechanism of action: interacts with plasminogen to cause antifibrinolysis

Peak effect: 3 hours

Notes:

- tablets are large and many patients may have difficulty swallowing them
- tablets are dispersable in water & can be used to make a mouthwash
- in palliative care, a benefit versus risk assessment should be applied to cautions and contra-indications when making prescribing decisions
- evidence for use subcut & in syringe driver in the UK
- 1 g PO = 500 mg subcut
- reduce dose if eGFR < 50 mL/min/1.73 m^2

Valproate (sodium)

Class: anti-epileptic (muti-modal action)

Indications (NB some may be unlicensed): epilepsy, mania associated with bipolar disease, neuropathic pain; hyperactive delirium, intractable hiccup

Contraindications/cautions: liver dysfunction; renal impairment (may need to reduce dose)

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

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

Interactions:

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

Dosing:

neuropathic pain

oral:	Start with 150 to 200 mg at night; increase by 150 mg-200 mg /24 hours every 2 to 3 days – give as bd dose. (max. 2,000 mg per day, start low)
subcut:	available in injectable form, not commonly used
rectal:	not available

Syringe driver: available in 100 mg/mL injection – has been used in syringe driver in the UK (range 400 mg-1800 mg/24 hours) – WFI as diluent; Oral: subcut dose 1:1

Mechanism of action: Valproate is a sodium-channel blocker, an NMDA-receptor channel blocker, it increases potassium conductance, alters glutamate, GABA, dopamine and serotonin transmission. Role in pain

Bioavailability: 95% (oral)

Onset of action:	within 24 hours for neuropathic pain
Peak effect:	not known but peak concentrations reached in 4 to 8 hours
Duration of action:	12 to 24 hours

Notes:

- co-analgesic sometimes used with opioids in the treatment of neuropathic pain although gabapentin or pregabalin have become common alternatives
- valproate is not first line for neuropathic pain or hyperactive delirium
- may be used in neuropathic pain when tricyclic antidepressants have failed or in combination with tricyclic antidepressants
- when switching from carbamazepine to valproate watch for toxicity from other drugs as carbamazepine induces the metabolism of several drugs while valproate inhibits the metabolism of several drugs
- don't discontinue abruptly as risk of rebound seizures
- therapeutic drug monitoring is usually available but is of limited value
- monitor LFTs

Venlafaxine

Class: antidepressant – SNRI – serotonin and noradrenaline reuptake inhibitor

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

Contraindications/cautions: renal/hepatic failure, volume depletion, epilepsy, mania, heart disease; risk of QT prolongation

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

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

Interactions:

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

Dosing:

oral:	slow release	Elderly – start on 37.5 mg od; others start on 75 mg od; increase by 75 mg once daily every 2 weeks – maximum 375 mg od
subcut:	not available	
rectal:	not available	

Syringe driver: not available

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

Notes:

- take with or after food to improve tolerability
- in severe renal or mild-moderate hepatic impairment, reduce dose by 50% and give once daily
- monitor bp at commencement and dose increases
- neuropathic pain – 37.5 to 75 mg od – can increase gradually to max 375 mg od
- hot flushes – 37.5 mg od – can increase to 75 mg od if necessary

Warfarin

Class: anticoagulant (coumarin)

Indications: thrombotic disorders prophylaxis

Contraindications/cautions: potential haemorrhagic conditions; caution in hepatic and renal impairment

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

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

Interactions:

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

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

Dosing:

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

Syringe driver: not available

Mechanism of action: interferes with vitamin K synthesis

Warfarin (CONTINUED)

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

Treatment in DVT and PE	INR	Duration
Pre and perioperative anticoagulation	1.5 to 2.0	days
Treatment of calf DVT	**2.0 to 3.0**	**4 to 6 weeks**
Treatment of provoked DVT	**2.0 to 3.0**	**12 to 26 weeks**
Treatment of provoked PE or massive DVT	2.0 to 3.0	26 to 52 weeks
Treatment of unprovoked PE or DVT	2.0 to 3.0	life long
Treatment of recurrent PE or DVT*	3.0 to 4.0	life long
Atrial Fibrillation	2.0 to 3.0	life long
Mechanical heart valves		
Aortic valve replacement	2.0 to 2.5	life long
Mitral valve replacement	2.5 to 3.0	life long
Arterial disease	3.0 to 4.0	life long

*recurrence despite prothrombin ratio between 2 and 3

Table from Management Guidelines for Common: Medical Conditions, 15th Edition 2013, Canterbury District Health Board, New Zealand

Zoledronic acid

Class: bisphosphonate – calcium regulator

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

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

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

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

Interactions:

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

Dosing:

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

Syringe driver: not applicable

Mechanism of action: inhibits bone resorption

Onset: ***hypercalcaemia:*** 2 to 3 days

Duration: ***hypercalcaemia:*** 32 to 39 days
bone pain: 4 to 6 weeks

Zoledronic acid (CONTINUED)

Notes:

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

Malignancy

- in tumour-induced hypercalcaemia if creatinine clearance less than 30 mL/minute seek specialist advice
- in advanced malignancies involving bone:
  - if creatinine clearance greater than 60 mL/minute no dose adjustment required;
  - if creatinine clearance 50 to 60 mL/minute reduce dose to 3.5 mg every 3 to 4 weeks;
  - if creatinine clearance 40 to 50 mL/minute reduce dose to 3.3 mg every 3 to 4 weeks;
  - if creatinine clearance 30 to 40 mL/minute reduce dose to 3 mg every 3 to 4 weeks;
  - avoid if creatinine clearance less than 30 mL/minute;
  - if renal function deteriorates in patients with bone metastases, withhold dose until serum creatinine returns to within 10% of baseline value; see also Cautions above

Syringe drivers

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

Indications

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

Diluent

- most drugs and drug combinations used in a syringe driver need to be made up to a certain number of millimetres or volume with a diluent
- "Either normal saline or WFI may be used as a diluent. Most drugs are able to be diluted with either diluent with the exceptions being cyclIzine which must be diluted with WFI and Levomepromazine which must be diluted with NS
- Both diluents. have advantages and disadvantages...."
  - water for injection
    - has few ions present and therefore is less likely to cause precipitation of drugs out of solution
    - BUT may be more irritant to subcutaneous tissue
  - normal saline
    - contains ions and so is more likely to cause precipitation of drugs
    - BUT may be more like interstitial fluid and therefore less irritant to subcutaneous tissue

Compatibility

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

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

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.

To download a colour or grey-scale version of the Syringe Driver Compatability Chart visit www.hospice.org.nz/resources

Further Reading

Books

Ahmedzai S, Baldwin DR, Currow DC (eds) (2012) Oxford Textbook – Supportive care in respiratory disease. Oxford University Press, Oxford

Australian Wound Management Association. Pan Pacific Clinical Practice Guideline for the Prevention and Management of Pressure Injury. Cambridge Media Osborne Park, WA: 2012.

Ayonide OT et al (2000) The rediscovery of methadone for cancer pain management. Med J Aust. 2000 173:536-540

Cherny N, Fallon M, Kassa S, Portenoy R, Currow, D (eds) (2015). Oxford Textbook of Palliative Medicine (5th ed). Oxford; Oxford University Press.

Chochinov HM, Brietbart W (eds) (2012) Handbook of Psychiatry in Palliative Medicine. Oxford; Oxford University Press

Chochinov HM (2012) Dignity Therapy; final words for final days. Oxford; Oxford University Press

Farrell B (2010) Oxford Textbook of Palliative Nursing (3rd ed) Oxford; Oxford University Press

Faull C, Blankley K (2015) Palliative Care (2nd ed) Oxford; Oxford University Press

Goldman A, Hain R, Liben S (eds) (2015) Oxford Textbook of Palliative Care for Children. Oxford; Oxford University Press

Lipowski ZJ (1980) Delirium: acute brain failure in man. Springfield; Charles C Thomas

Lishman WA (1998) Organic Psychiatry: the psychological consequences of cerebral disorder.3rd Edition. Oxford; Blackwell

Lloyd-Williams M (ed) (2008) Psychosocial issues in palliative care (2nd ed). Oxford; Oxford University Press

Lucas C (2009) Oxford Handbook of Palliative Care (2nd ed) Oxford; Oxford University Press

Maddocks I, Brew B, Waddy H, Williams I (2006) Palliative Neurology. Cambridge; Cambridge University Press

Macleod AD (2011) The Psychiatry of Palliative Medicine – The dying mind (2nd ed) Oxford; Radcliffe Publishing

Mitchell G (2007) Palliative Care: A patient-centered approach. Oxford; Radcliffe Health

Morgan-Jones P, Colombage E, McIntosh D, Ellis P (2014) Don't give me eggs that bounce: 118 cracking recipes for people with Alzheimer's. Sydney; HammondCare Media

Morgan-Jones P, Greedy L, Ellis P, McIntosh D (2016) It's all about the food not the fork! 107 easy to eat meals in a mouthful. Sydney; HammondCare Media

Morgan-Jones P, MacLeod RD, Ellis P, Lynch J (2018) Lobster for Josino: Fabulous food for our final days. Sydney; HammondCare Media

Palliative Care Expert Group (2010) Therapuetic Guidelines: palliative care. Version 3. Melbourne: Therapeutic Guidelines Limited.

Read S (2006) Palliative care for people with learning disabilities. London; Quay Books.

Sandler J, Dare C, Holder A (1972) The Patient and the Analyst: The basis of the psychoanalytic process. New York; International Universities Press

Thomas, B, Bishop, J (2009) Manual of dietetic practice 4th edition, Oxford; Blackwell

Twycross, R.G., Wilcock A, Howard P. (2015) PCF5: Palliative care formulary (8th ed.) www.palliativedrugs.com. Oxford, New York; Radcliffe Publishing

Voltz R, Bernat JL, Borasio GD et al. (eds) (2004) Palliative Care in Neurology. Oxford; Oxford University Press

Journal Articles

American Psychiatric Association Guidelines (2004) Practice Guideline for the treatment of patients with acute stress disorder and posttraumatic stress disorder. American Journal of Psychiatry. 161:11, Supplement, 3-23

Auret K, Schug SA (2013) Pain management for the cancer patient – Current practice and future developments. Best Practice & Research Clinical Anaesthesiology 27: 545–561

Australian Wound Management Association. (2012) Pan Pacific Clinical Practice Guideline for the Prevention and Management of Pressure Injury. Cambridge Media Osborne Park, WA

Baker J, Dickman A, Mason S, Ellershaw J.(2018) The current evidence base for the feasibility of 48-hour continuous subcutaneous infusions (CSCIs): A systematically-structured review. PLoSOne. 13(3):e0194236. doi: 10.1371/journal.pone.0194236. PMID: 29538455; PMCID: PMC5851608.

Broadbent A, Khor K, Heaney A (2003) Palliation and chronic renal failure: opioid and other palliative medications – dosage guidelines. Progress in Palliative Care. DOI 10.1179/096992603225002627

Calman KC (1984) Quality of life in cancer patients: an hypothesis. Journal of Medical Ethics 10: 124-27

Chochinov HM (2000) Psychiatry and terminal illness. Canadian Journal of Psychiatry. 45:143-150

Clark K, Lam L, Currow D. (2009) Reducing gastric secretions--a role for histamine 2 antagonists or proton pump inhibitors in malignant bowel obstruction? Support Care Cancer.17(12):1463-8. doi: 10.1007/s00520-009-0609-3. Epub2009 Mar 17. PMID: 19290549.

Clayton JM, Hancock KM, Butow PN, Tattersall M, Currow DC (2007) Clinical practice guidelines for communicating prognosis and end-of-life issues with adults in the advanced stages of a life-limiting illness, and their caregivers. Medical Journal of Australia 186 (12); S77-108

Cochinov H, Wilson K, Enns M, et al. (1997) “Are you depressed?” Screening for depression in the terminally ill. American Journal of Psychiatry. 151:674-676

Dein S (2005) Working with the patient who is in denial. European Journal of Palliative Care. 12:251-253

Egan R, MacLeod R, Jaye C, McGee R, Baxter J, Herbison P (2011) What is spirituality? Evidence from a New Zealand hospice study. Mortality, 16(4): 307-324

Finnerup, D et al (2015) Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis Lancet Neurology. 162–73

Gibbs, M (2019) Clinical Guideline. Subcutaneous infusion of Tranexamic acid, Ashtons Hospital Pharmacy Services, SITA1 (v.2.0)

Goodarzi Z et al (2017) Depression case finding in individuals with dementia: A systematic review and meta-analysis. Journal of the American Geriatrics Society. 65:937-948

Grant L, Murray S A, Sheik A (2010) Spiritual dimensions of dying in pluralist societies. British Medical Journal. 341:c4859

Higgs CMB Vella-Brincat J (1995) Withdrawal with transdermal fentanyl. Journal of Pain and Symptom Management. 10(1): 4-5

Kissane DW, Clarke DM, Street AF (2001) Demoralisation syndrome – a relevant psychiatric diagnosis for palliative care. Journal of Palliative Care. 17:12-21

Krajnik M, & Zylicz Z (2001) Understanding pruritus in systemic disease. Journal of Pain and Symptom Management. 21(2), 151-168.

Kristjanson LJ, Aoun SM, & Oldham L (2006) Palliative care and support for people with neurodegenerative conditions and their carers. International Journal of Palliative Nursing. 12(8): 368-377

Lawler PG. (2002) The panorama of opioid-related cognitive dysfunction in patients with cancer: a critical literature appraisal. Cancer. 94:1836-1853

Lim K-M, Smith M, Ortiz V (2001) Culture and Psychopharmacology. Psychiatry Clinics of North America. 24:523-538

Lim LC, Rosenthal MA, Maartens N, et al. (2004) Management of brain metastases: review. Internal Medicine Journal. 34:270-278

Littlejohn C, Baldacchino A, Bannister J. (2004) Chronic non-cancer pain and opioid dependence. Journal of the Royal Society of Medicine. 97:62-65

Macleod AD (2002) Neurogenic pulmonary edema in palliative care. Journal of Pain and Symptom Management. 23(2):154-156

Macleod AD (1998) Methylphenidate in terminal depression. Journal of Pain and Symptom Management. 16(3):193-198

Macleod AD (2006) Delirium: the clinical concept. Palliative and Supportive Care. 4:305-12

Macleod AD, Vella-Brincat J, Frampton C (2003) Swallowing capsules Palliative Medicine. 17(6):559

MacLeod RD (2005) Dyspnoea – management: psychosocial therapies in Ahmedzai S, Muers M (eds) Oxford Textbook – Supportive care in respiratory disease. Oxford University Press, Oxford p227-237

MacLeod R, Rowland P (2008) Online Resource (CD and Web), Diagnostic Toolkit: Pain Assessment Made Easy, Goodfellow Unit, University of Auckland, http://pame.auckland.ac.nz/

Mancini AD, Griffin P, Bonanno GA. (2012) Recent trends in the treatment of prolonged grief. Current Opinions in Psychiatry. 25:46-51

Milton J. (2006) The impact of complementary therapy on mainstream practice. International Journal of Palliative Nursing, 12(3); 121-122

Moller H-J (1999) Effectiveness and safety of benzodiazepines. Journal of Clinical Psychopharmacology 19(Suppl 2):2S-11S

Noble H, & Kelly D (2006) Supportive and palliative care in end stage renal failure: the need for further research. International Journal of Palliative Nursing, 12(8), 362-364, 366-367

Puchalski C, Ferrell B, Virani R, Otis-Green S, Baird P, Bull J, et al. (2009) Improving the quality of spiritual care as a dimension of palliative care: the report of the Consensus Conference. Journal of Palliative Medicine. (10):885-904

Qaseem A et al (2015) Risk Assessment and Prevention of Pressure Ulcers: A Clinical Practice Guideline From the American College of Physicians Ann Intern Med. 2015;162:359-369. doi:10.7326/M14-1567 www.annals.org

Rhee C, Broadbent AM (2007) Palliation and liver failure: palliative medications dosage guideline. Journal of Palliative Medicine. 10:3; 677-685

Seden K, Dickinson L, Khoo S, Back D (2010) Grapefruit-drug interactions Drugs, 70, 18, 2373-2407

Senthil, K.P., Krishna, P., Kamalaksha, S. & Manisha, R. 2014, "Role of Nutrition and Dietetics in Palliative Cancer Care: A Special Perspective", International Journal of Food, Nutrition and Dietetics, vol. 2, no. 1, pp. 41-44.

Sirios F. (2003) Steroid psychosis: a review. General Hospital Psychiatry 25:27-33

Skevington SM, Pilaar M, Routh D, MacLeod RD (1997) On the Language of Breathlessness. Psychology and Health 12: 677-689

Sutherland (2021). Subcutaneous Tranexamic acid: a novel approach to managing bleeding. Annals of Hematology & Oncology 8(7):1356.

Toombs J (2008) Oral methadone dosing for chronic pain. A practitioner's guide. Pain Treatment Topics March:1-12

Smith HS. (2003) Management of hiccups in the palliative care population. American Journal of Hospice and Palliative Care, 20(2); 149-154

Solano JP, Gomes B, & Higginson I. (2006) A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. Journal of Pain and Symptom Management, 31(1), 58-69

Twycross R, Greaves MW, Handwerker H, et al. (2003) Itch: scratching more than the surface. Quarterly Journal of Medicine 96:7-26

Vella-Brincat J, Macleod AD (2007) Adverse effects of opioids on the central nervous systems of palliative care patients. Journal of Pain and Palliative Care Pharmacotherapy. 21(1): 15-25

Vella-Brincat J, Macleod AD (2004) Haloperidol in palliative care. Palliative Medicine. 18(3): 195-201

William L, MacLeod RD (2008) Therapy in Practice: Management of Breakthrough Pain in Patients with Cancer. Drugs 68(7): 913-924

Zhukovsky D (2002) Fever and sweats in the patient with advanced cancer. Hematology/ Oncology Clinics of North America, 16(3): 579-588

Websites

Advance Care Planning: https://www.myacp.org.nz/

Medsafe: https://www.medsafe.govt.nz/profs/PUArticles/September2022/Opioids-and-serotonergic%20medicines-risk-of-serotonin-syndrome.html

New Zealand Medicine Formulary: https://nzf.org.nz/interactions/stockleys/of/10118501000116109

Drug Index

Notes

Hospice New Zealand gratefully acknowledges
the Blue Sky Community Trust for their contribution
to the costs of printing the
Palliative Care Handbook New Zealand - First Edition

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