CHAPTER 24
MEDICINES USED IN PALLIATIVE CARE

PALLIATIVE CARE

Palliative care is an approach that improves the quality of life of patients and their families facing problems associated with life-threatening illness, regardless of whether or not they also receive life-prolonging treatment.

Palliative care requires a multidisciplinary approach and aims to address physical, psychosocial, and spiritual problems.

Life threatening illnesses are where death is expected to be a direct consequence of the specified illness.
Analysis of available evidence suggested 11 common symptoms occurring in the advanced stages and end of life stages: anorexia, anxiety, constipation, delirium, depression, diarrhoea, dyspnoea, fatigue, nausea and vomiting, pain and respiratory tract secretions.
All symptoms should be managed by a multi-disciplinary team to ensure a holistic approach.

Note: Please be advised that the recommendations in this chapter are directed at treating common symptoms alongside disease directed care and symptoms associated with end-of-life care.

The SPICT^{TM}-SA is a generic tool (https://www.spict.org.uk/the-spict/spict-sa/), designed for the South African setting, to help identify adults with advanced life-limiting illnesses when the best available and appropriate treatment has been given and their condition continues to deteriorate.

LoE:IVb[i]

Always refer to the latest National Guidelines on Palliative Care.

For management of pain in palliative care see Chapter 26: Pain.

24.1 GASTROINTESTINAL CONDITIONS

24.1.1 ANOREXIA AND CACHEXIA

R63.0/R63.4/R64 + (Z51.5)

DESCRIPTION

Anorexia/cachexia syndrome is a complex metabolic process found in many end-stage illnesses. It is characterised by loss of appetite, weight loss and

muscle wasting, and cannot be fully reversed by conventional nutritional support. It may impact significantly on the quality of life of patients, leading to increased anxiety and distress for both patients as well as family.

GENERAL MEASURES

Reduced food and fluid intake is expected at the end of life, and treatment of anorexia and weight loss may not be appropriate if these symptoms are not having a direct impact on quality of life. This should be explained to caregivers and family.

Management of anorexia and weight loss includes identification and, if appropriate, treatment of possible underlying cause(s). It may include the use of pharmacological and non-pharmacological treatment approaches.

Identify reversible problems that may contribute to or exacerbate anorexia/ cachexia including:

- Pain, nausea, heartburn, dyspnoea, gastritis, depression, constipation anxiety dysphagia, medication and fatigue
- Oral problems e.g. dry mouth, ulcers, candidiasis, etc.
- Odours e.g. fungating lesions, cooking smells, incontinence etc.
- Delayed gastric emptying due to local disease, autonomic neuropathy with early satiety and vomiting of undigested foods

If appropriate, moderate exercise must be encouraged, along with pacing of activities and good sleep hygiene.

Nutritional advice includes eating small amounts of enjoyable food frequently.

MEDICINE TREATMENT

If the anorexia and/ cachexia contributes significantly to decreased quality of life and the patient has a short life expectancy.

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 0.5 mg/kg (e.g. 20–30 mg) daily.
  - The effect may be rapid but usually decreases after 3–4 weeks.
  - If there is no benefit after 1 week, stop the treatment.

LoE:IIb[ii]

If symptoms of reflux or gastritis: see section 1.1.3: Gastro-oesophageal reflux disease.

If gastroparesis is present, see section 8.7.1 Diabetic neuropathies.

24.1.2 CONSTIPATION

K59.0 + (Z51.5)

DESCRIPTION

Constipation is the passage of small, hard faeces infrequently and with difficulty. Individuals vary in the weight they give to the different components

of this definition when assessing their own constipation and may introduce other factors, such as pain and discomfort when defecating, flatulence, bloating or a sensation of incomplete evacuation. Constipation may also be secondary to other conditions e.g. dehydration, immobility poor diet, anorexia, tumour compressing bowel wall or hypercalcaemia.

GENERAL MEASURES

Ensure privacy and comfort to allow a patient to defecate normally.
Increase fluid intake within the patient's limits.
Encourage activity and increased mobility within the patient's limits.
Anticipate the constipating effects of pharmacological agents such as opioids, anticholinergic agents (e.g. tricyclic antidepressants), antacids, iron, 5HT3 antagonists and provide laxatives prophylactically.

MEDICINE TREATMENT

The combination of a softener and stimulant laxative is generally recommended, and the choice of laxatives should be made on an individual basis.

- Sennosides A and B, oral, 13.5 mg, 1 tablet at night.
  - In resistant cases increase to 2 tablets.

AND/OR *LoE:IIb[iii]*

Lactulose, oral, 15–30 mL 12–24 hourly.

LoE:IIb[iv]

Severe constipation in patients who are unable to swallow:

- Bisacodyl, rectal, 10 mg suppository daily.

OR *LoE:IVb[v]*

Glycerine (glycerol), rectal, 1.698 mL/2.4 g suppository when necessary.

LoE:IVb

If these therapies are not effective, other options could be considered.

Note: Manual removal should only be undertaken if the patient has received adequate pain relief and sedation, if relevant.

REFERRAL/CONSULTATION

If bowel obstruction is suspected refer/consult for appropriate radiological investigations and, if appropriate, surgical interventions.

24.1.2.1 TUMOUR-RELATED BOWEL OBSTRUCTION

K56.6

DESCRIPTION

Malignant bowel obstruction is a well-recognised complication of advanced cancer and is defined as symptoms, signs, and radiographic evidence of obstruction to the transit of gastrointestinal contents caused by cancer, or the

consequences of anticancer therapy including surgery, chemotherapy or radiation therapy. It occurs most commonly with ovarian or colorectal cancer.

LoE:IVb[vi]

GENERAL MEASURES

Consult a surgeon to discuss potential surgical interventions before restricting management to medicine treatment. Patients and families require in depth counselling around the cause, care, further nutrition, and nasogastric tubes. Parenteral nutrition generally has no role in patients with advanced cancer.

MEDICINE TREATMENT

These patients may be difficult to manage. Consult with a palliative care provider for advice on management of patient.

To identify and contact a palliative care provider if necessary, visit: https://palprac.org/palliative-care/find-a-provider/.

See Section 24.1.4 Nausea and Vomiting.

REFERRAL/CONSULTATION

All patients that might require surgical management must be discussed with a surgeon.
All patients who require medical management of bowel obstruction must be discussed with a palliative care provider.

24.1.3 DIARRHOEA

A09.0

See Primary Health Care chapter: Medicines for palliative care: section 22.1.2: Diarrhoea.

24.1.4 NAUSEA AND VOMITING

R11 + (Z51.5)

GENERAL MEASURES

Treat the underlying cause and rehydrate the patient.
Identify and manage reversible causes, which include medication, hypercalcemia, constipation, uraemia, gastritis, gastroenteritis, coughing and infections.
Manage odours e.g. cooking smells and fungating wounds.

MEDICINE TREATMENT

- Metoclopramide, oral/IM/IV, 10 mg 8 hourly, 30 minutes before a meal.

- In renal impairment start with a dose of 5 mg, 8 hourly.
- Increase according to clinical response using alternate 5 mg and 10 mg doses if required.

LoE:IVb[vii]

<u>If metoclopramide is ineffective or contra-indicated (e.g., inoperable bowel obstruction):</u>

- Haloperidol, oral, 1.5–5 mg daily.

OR *LoE:IIIb*[viii]

- Olanzapine orodispersible tablet, oral or IM injection
  - Initiate 5 mg at night (2.5 mg in frail and elderly patients).
  - Titrate in increments of 2.5 mg to a maximum dose of 10 mg daily.

Monitor vital signs and beware of oversedation, neuroleptic malignant syndrome, and acute dystonia. *LoE:IVb*[ix]

<u>Drug-induced parkinsonism:</u> *LoE:IVb*[x]

ADD

- Anticholinergic agent, e.g.:
- Orphenadrine, oral, 50–150 mg daily according to individual response
  - Usual dose: 50 mg 8 hourly.
  - Maximum dose: 150 mg daily.
  - Use with caution in the elderly as it may cause confusion and urinary retention.

Note: Anticholinergic medicines (e.g. orphenadrine) should not be added prophylactically to antipsychotics to prevent extrapyramidal side effects.

<u>If haloperidol is ineffective/ inoperable bowel obstruction:</u>

- Promethazine, IM/IV, 12.5–25 mg, 4–6 hourly. *LoE:IVbI*[xi]

Corticosteroids can decrease cerebral oedema: see section: 14.12.1 Brain oedema due to tumours and inflammation.

REFERRAL

see Section 24.1.2.1 Tumour-related bowel obstruction
Consult a palliative care trained doctor if the vomiting persists.

24.1.5 MANAGEMENT OF CLOSE CONTACTS OF PATIENTS WITH HBV INFECTED HEPATOCELLULAR CARCINOMA

For patients with hepatocellular carcinoma caused by hepatitis B who are not on hepatitis B antiviral therapy (tenofovir/lamivudine/emtricitabine):

Screen caregivers, who are or will be in contact with bodily fluids, for hepatitis B including hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody (HBsAb):

» Vaccinate non-immune individuals against hepatitis B (see Section 9.2 Adult vaccination)
» Link individuals who test positive for HBsAg to care (see Section 1.2.4.1: Hepatitis B, Acute and Sections 1.2.4.2 and 1.2.4.3: Hepatitis B, Chronic without or with HIV co-infection, respectively)
» Educate rest of family regarding the risk of infection from bodily fluids

Consult the most recent Hepatitis Guidelines from the National Department of Health

24.2 NEUROPSYCHIATRIC CONDITIONS

24.2.1 ANXIETY

F41.0-3/ F41.8-9+ (Z51.5)

DESCRIPTION

Anxiety is defined as the apprehensive anticipation of future danger or misfortune accompanied by a feeling of dysphoria or somatic symptoms of tension. Anxiety is characterised by excessive feelings of fear, apprehension, and worry. Anxiety may be associated with symptoms of depression, poor concentration, insomnia, irritability, panic attacks, sweating, tremor and nausea. It is a common symptom in palliative care and the complex multi-causative nature of anxiety in patients with life threatening illnesses always require a multimodal approach.

GENERAL MEASURES

Address any contributing factors such as pain and dyspnoea. Consider other underlying conditions that may mimic anxiety e.g. electrolyte imbalance, hyperthyroidism, hypoxia, arrhythmias and many medicine side effects.
Assess for depression or any other previous psychiatric illness.
Include the caregivers.
Ensure the patient and caregivers have received the desired amount of information around the nature of the disease, treatment, side-effects and outcomes.
A multi-disciplinary team approach is recommended (including a spiritual carer).

MEDICINE TREATMENT

Acute management of anxiety:
<u>For an acute episode or intense prolonged anxiety:</u>

- Benzodiazepine, e.g.:
- Diazepam, oral, 2.5–5 mg as a single dose.
  - Repeat if required up to 12 hourly.

LoE:IIb[xii]

- Avoid if liver function impaired.

OR *LoE:IVb*[xiii]

- Lorazepam, oral, 0.5–1 mg, immediately.
  - Repeat as necessary to control symptoms. *LoE:IVb*[xiv]
  - Tablets may be crushed and administered sublingually.

LoE:IIIb[xv]

CAUTION
Benzodiazepines, especially diazepam IV, can cause respiratory depression.
Patients with liver dysfunction require lower doses.
Monitor patients closely. *LoE:IVb*[xvi]
In the short-term, benzodiazepines can aggravate delirium.

» In frail and elderly patients or where respiratory depression is a concern, reduce the dose by half. *LoE:IVb*[xvii]
» The safest route of administration is oral with the IV route having the highest risk of respiratory depression and arrest.
» Monitor vital signs closely during and after administration.
» Use haloperidol instead of benzodiazepines in patients with respiratory insufficiency.
» To avoid inappropriate repeat dosing allow at least 15–30 minutes for the medication to take effect. Repeated IM doses of benzodiazepines may result in toxicity owing to accumulation.

Patient unable to take oral medication/ terminal sedation required:
see section 24.5: Sedation in palliative care.

Long-term treatment:

- SSRI e.g.:
- Fluoxetine, oral *LoE:IIb*[xviii]
  - Initiate at 20 mg every alternate day for 2 weeks
  - Increase to 20 mg daily after 2–4 weeks
  - Delay dosage increase if increased agitation/panicked feelings occur.
  - Note: Fluoxetine is contraindicated if eGFR < 10mL/min

LoE:IIb[xix]

OR

- Citalopram, oral.
  - Initiate at 10 mg daily for 2 weeks.
  - Then increase to 20 mg daily.

LoE:IVb[xx]

Note: Effects of SSRIs are only apparent after 2–3 weeks of treatment, so they should be reserved for patients where end-of-life is not imminent.

REFERRAL

Poor response to treatment.

24.2.2 DELIRIUM

F05.0-1/F05.8-9 + (Z51.5)

DESCRIPTION

Delirium (confusion) is very common in the terminal stages of advanced disease and is associated with a short prognosis. When treatment of the underlying cause(s) of delirium is not possible or unsuccessful, pharmacological management is necessary. Causal treatment may not be indicated in patients with limited prognosis and pharmacological symptomatic therapy has to be initiated without delay.

See Adult Hospital Level chapter: Emergencies and Injuries: section 20.8

GENERAL MEASURES

Assess for underlying causes e.g. infection or electrolyte imbalance.
Remove factors that can agitate the patient (e.g. full bladder, thirst, pain, constipation, medicines such as opioids, steroids, benzodiazepines, withdrawal of medicines, dehydration, liver or renal impairment and cerebral tumour).
Reduce polypharmacy.
Where appropriate, ensure adequate fluid and nutritional intake (not indicated in the pre-terminal stage).
Mobilise early when appropriate.
Monitor for sensory deficits and manage accordingly e.g. using hearing aids.
Keep the family involved and informed. Provide tools of care such as how to orientate and reassure the patient.

MEDICINE TREATMENT

For agitated and acutely disturbed patient:

- Olanzapine, oral dispersible tablet or IM, 2.5–5 mg.
  - This can be repeated in 30–60 minutes, if required and then 6 hourly to a maximum dose of 20 mg within 24 hours.
  - Monitor vital signs and beware of oversedation, neuroleptic malignant syndrome, and acute dystonia.

In hyper active delirium or severe agitation or where there is no response or resistance to olanzapine:

ADD

- Lorazepam, oral, 0.5–1 mg 2–4 hourly as required.
  - Tablets may be crushed and administered sublingually. *LoE:IIIb*[xxi]

OR *LoE:IVb*[xxii]

Patients unable to swallow:

- Midazolam, SC/IV, 0.5–5 mg immediately.
  - Titrate up slowly. *LoE:IVb*[xxiii]

- Lower doses are indicated for patients with liver dysfunction.

24.2.3 DEPRESSION

F32.0-3/F32.8-.9/F33.0-3/F33.8-9/F34.1 + (Z51.5)

DESCRIPTION

Depression is characterized by persistent feelings of extreme sadness and low mood associated with loss of interest in activities and inability to experience pleasure. There are often associated biological features of significant changes in appetite and weight, disturbed sleep, fatigue and poor concentration.

Diagnosis of major depression in a terminally ill patient often relies more on the psychological or cognitive symptoms (worthlessness, hopelessness, excessive guilt and suicidal ideation) than the physical/somatic signs (weight loss and sleep disturbance) described in depression in patients who are not terminally ill. The key indicators of depression in the terminally ill are persistent feelings of hopelessness and worthlessness and/or suicidal ideation.

Demoralisation is a phenomenon where hope and meaning is lost and where patients wish to hasten their death because they cannot foresee any future pleasure.

GENERAL MEASURES

Exclude physical reversible causes e.g. hypothyroidism, hyperthyroidism, or hypercalcaemia.

MEDICINE TREATMENT

- SSRI e.g.:
- Fluoxetine, oral — *LoE:IIb*[xxiv]
  - Initiate at 20 mg every alternate day for 2 weeks
  - Increase to 20 mg daily after 2–4 weeks
  - Delay dosage increase if increased agitation/panicked feelings occur.
  - Note: Fluoxetine is contraindicated if eGFR < 10mL/min

LoE:IIb[xxv]

OR

- Citalopram, oral.
  - Initiate at 10 mg daily for 2 weeks.
  - Then increase to 20 mg daily.

LoE:IVb[xxvi]

OR

<u>If sedation is required:</u>

- Amitriptyline, oral, at bedtime.

- Start with: 25 mg, increase by 25 mg/day at 3–4 day intervals.
- Dose range: 75–150 mg daily.

Note: Effect of SSRIs are only apparent after 2-3 weeks of treatment, so they should be reserved for patients where end-of-life is not imminent.

24.2.4 FATIGUE

R53 + (Z51.5)

DESCRIPTION

Fatigue is defined as a subjective feeling of tiredness, weakness or lack of energy. The pathophysiology is not fully understood but will be multifactorial in most palliative care patients, including disease- and treatment-related causes. Fatigue may be severe, distressing and persistent, regardless of adequate amounts of sleep and rest.

GENERAL MEASURES

Treat underlying causes such as anaemia, depression, and infections.
Encourage aerobic exercises, where appropriate.
Ensure that the multidisciplinary team assists with activity pacing, assisted devices where indicated, and diet.

MEDICINE TREATMENT

Note: Because of limited evidence, consideration of steroids in palliative care should be restricted to use in the terminally ill with fatigue and a specific short-term treatment goal.
Fatigue can also protect patients at the end of life from physical and emotional distress.

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 0.5 mg/kg (e.g.:15–30 mg) daily, for 1 week.

LoE:IIb[xxvii]

24.3 PAIN

See chapter 26: Pain.

24.3.1 CHRONIC CANCER PAIN

See section 26.1.2: Analgesia for chronic cancer pain.

24.3.2 NEUROPATHIC PAIN

See section 26.1.4: Neuropathic pain.

24.4 RESPIRATORY CONDITIONS

For Coronavirus Disease-19. See PHC Infections and related conditions Section 10.19.1: COVID-19: CORONAVIRUS DISEASE-19.

24.4.1 DYSPNOEA

R06.0+ (Z51.5)

DESCRIPTION

Dyspnoea is the subjective unpleasant sensation of being unable to breathe adequately (breathlessness). Dyspnoea is a complex multidimensional symptom with physical, psychological, and emotional dimensions, especially anxiety. The intensity of dyspnoea is generally not related to the oxygen saturation.

Look for reversible causes, e.g. infection, pulmonary embolism, pleural effusion, bronchospasm and anxiety

The aim should always be to address the cause. However, in end stage disease symptomatic treatment is indicated.

GENERAL MEASURES

Ideally, include a physiotherapist and occupational therapist for pulmonary rehabilitation and to teach patients pursed lip breathing, pacing of activities, relaxation techniques, and positioning.

The use of a fan may reduce the sensation of dyspnoea.

Treat the underlying cause (e.g. antibiotics for underlying respiratory infection) wherever possible.

MEDICINE TREATMENT

- Morphine syrup, oral.
  - Starting dose: 2.5–5 mg, 4 hourly as required, titrating up slowly.
  - In renal failure: start at 1-2 mg and observe patient closely before titrating up as required..

<u>Dyspnoea associated with hypoxaemia</u>

- Oxygen.

24.4.2 RESPIRATORY SECRETIONS

R06.8 + (Z51.5)

DESCRIPTION

Excessive respiratory tract secretions (also referred to as death rattle), is used to describe a rattling noise produced by accumulated secretions in the airway which oscillate in time with inspiration and expiration. Generally, respiratory secretions occur in patients who are extremely weak and close to death.

GENERAL MEASURES

Change position of the patient.

Explain to caregivers and relatives that the patient is not distressed by the secretion. Patients are not conscious that they are unable to clear secretions. Minimal oropharyngeal suctioning is required.

MEDICINE TREATMENT

- Hyoscine butylbromide, SC/IM, 20 mg.
  - Increase dose to effect to maximum of 120 mg.

LoE:IVb[xxviii]

24.5 SEDATION IN PALLIATIVE CARE

Z51.5

Sedation in palliative care has unique objectives, and tolerance for some adverse effects may be greater than in other situations. There is also an emphasis on avoiding parenteral medication. Palliative sedation should be undertaken by clinicians experienced in the process and the advice of an expert should be sought where necessary. Sedation should only be started after discussion with, and with the consent of, the patient and/or family (when the patient is unable to consent).

The aim of sedation in palliative care is to ameliorate refractory suffering and not to hasten death.
Palliative care medication addresses symptoms such as pain, dyspnoea, nausea and depression. Managing many of these symptoms involves the use of medications which may have sedative properties. Palliative sedation involves the additional use of medication where sedation is the primary objective, and is appropriate only after standard care has proven unsuccessful.

GENERAL MEASURES

Pain must always be the first symptom to be excluded.
Always look for reversible causes of symptoms prior to prescribing sedation such as dehydration, hypoxia, concurrent synergistic sedative medicines, hypercalcaemia, renal failure, or infection.
Caution should be exercised and palliative care prescription examined for possible drug-drug interactions, prior to commencing sedation (or escalating doses of sedative medicines).
Dose escalation may be considered only if there is evidence of inadequate sedation.

MEDICINE TREATMENT

Dosing in frail, elderly patients should be titrated to effect.

- Lorazepam, oral, 0.5 mg 4 hourly.
  - Tablets may be crushed and administered sublingually.

OR

LoE:IVb[xxix]

If hyper active delirium or severe agitation

- Olanzapine 2.5–5 mg orodispersible tablet or IM.
    - Repeat after 30–60 minutes if needed. *LoE:IVb*[xxx]

Note: Repeated doses may result in excessive sedation

Patient unable to take oral medication or terminal sedation required:

- Midazolam, SC/IV:
    - Initial dose: 1–5 mg as needed
    - Titrate to effect.

LoE:IIb[xxxi]

24.6 MALODOROUS FUNGATING WOUNDS/TUMOURS

DESCRIPTION

Non-healing fungating tumours that are often secondarily infected and smelly causing social ostracization and distress to the patient and family. Examples include exophytic retinoblastoma, infected bedsores, rhabdomyosarcoma, osteosarcoma or Kaposi's sarcoma.

GENERAL AND SUPPORTIVE MEASURES

» Supportive counselling.
» Set realistic goals: may not include wound healing but could include odour eradication.
» Regular wound cleaning and dressing changes.
» Adequate ventilation.
» Disguise smell by placing a bowl of vanilla essence in the room, burn incense or place kitty litter under the bed to absorb smell.
» Air-fresheners and perfumes do not work.
» Change bedding and clothing regularly.

MEDICINE TREATMENT

- Provide good procedural pain management (see Chapter 26 Pain Control) and use distraction/relaxation techniques before and during dressing changes.
- Irrigate wounds with warmed normal saline. Debride gently with gloved hand not sharp instruments.
- Consider formal surgical debridement in patient where end-of-life is not imminent.
- Topical metronidazole:
    - Irrigation and cleaning of wound: 2 L saline combined with 13 crushed metronidazole 400 mg tablets (2 L 0.9% sodium chloride: 5200 mg metronidazole). Discard any remaining solution after each treatment, utilising appropriate medical waste management principles.

- Metronidazole tablet topical: Metronidazole tablet 400 mg per 35 cm^2 area twice daily to ameliorate malodor.

LoE:IIIb[xxxii]

- Activated charcoal dressings also help to absorb odours.
- For wound pain consider using topical anaesthetics such as lidocaine/prilocaine.

LoE:IIIb[xxxiii]

24.7 END OF LIFE CARE

Z51.5

DESCRIPTION

Patients can be defined as being terminal when there is irreversible decline in functional status prior to death. It is essential during this time to ensure the ethical management of the dying phase and to minimise distress for the patient, family, and fellow health care professionals by using a biopsychosocial and spiritual approach.

Signs of dying:

» The patient may gradually spend more time sleeping during the day and at times will be difficult to rouse.
» There may be decreased need for food and drink.
» The patient may become increasingly confused about time, place and identity of friends and family.
» Arms and legs may become cool to the touch and the undersides of the body may become darker in colour.
» Loss of control of bowel and bladder may occur.
» Urine output may decrease.
» Saliva and mucus may collect at the back of the throat as the swallowing and cough reflexes diminish. This sometimes causes a noise known as the “death rattle”.
» Vision and hearing may decrease.
» Breathing patterns may become irregular, with longer intervals between breaths.

GENERAL MEASURES

Communication is at the centre of care. The following aspects should be addressed:

» Honest, direct, compassionate and culturally sensitive information about the prognosis.
» Evaluation of the patient and family resources and needs, especially spiritual needs.
» Decision making on place of death as many patients want to go home.
» Education about patient care.
» Emergency contact details, especially if the patient wants to go home.

» Compassionate information about symptoms that might develop and how to manage them.
» Nutrition and hydration.

Discontinue all non-essential, futile procedures and medicines e.g. discontinue 4-hourly blood pressure measurements and vitamin tablets.
Ensure medicines are prescribed for symptom management and prescribe medicine when needed to pre-empt common symptoms during the terminal phase using the appropriate route of administration:
» Pain (see section above)
» Nausea and vomiting (see section above)
» Respiratory secretions (see section above)
» Agitation /restlessness/delirium (see section above)

Discuss feeding and hydration with the family. If the decision is to hydrate and/ feed, ensure gentle hydration and monitor oedema, especially in patients with hypoalbuminaemia. Hydration does not improve quality of life, survival, or symptom burden at the end of life, and should not be given as routine management. Rather offer sips of water if the patient is able to swallow.

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SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 24: MEDICINES USED IN PALLIATIVE CARE
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2020-4)

The Primary Health Care (PHC) Level Medicines Used in Palliative Care chapter underwent detailed clinical editing and editorial changes for clarity.

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG) and supporting medicine reviews. All reviews and costing reports may be accessed at: https://www.health.gov.za/nhi-edp-stgs-eml/

Review of the palliative care chapters is an ongoing process as aspects of the chapters continue to be prioritized for review as a long-term priority of NEMLC.

A: NEW STANDARD TREATMENT GUIDELINES

SECTION	CONDITION	MEDICINE MANAGEMENT	MEDICINE ADDED
24.1.2	**TUMOUR-RELATED BOWEL OBSTRUCTION**	No	n/a
24.15	**MANAGEMENT OF CLOSE CONTACTS OF PATIENTS WITH HBV INFECTED HEPATOCELLULAR CARCINOMA**	No	Cross references provided to: • Section 9.2 Adult vaccination • Section 1.2.4.1: Hepatitis B, Acute, • Section 1.2.4.2 Hepatitis B, Chronic without HIV co-infection • Section 1.2.4.3: Hepatitis B, Chronic with HIV co-infection
24.6	**MALODOROUS FUNGATING WOUNDS/TUMOURS**	Metronidazole, topical	Added (aligned to Paediatric Hospital Level STG)
		Activated charcoal dressings	Added (aligned to Paediatric Hospital Level STG)
		Lidocaine/prilocaine	Added (aligned to Paediatric Hospital Level STG)

The Committee deliberated the addition of a note regarding the use of cannabinoids in the palliative care setting and the potential for drug-drug interactions. No note was added to the chapter regarding cannabinoids which are currently not registered; as other traditional and non-registered medicines may also be used by patients in this setting and are not specifically mentioned.

24.1.2 TUMOUR-RELATED BOWEL OBSTRUCTION

A proposal to include guidance on the management of tumour-related bowel obstruction was accepted. For the development of the STG for tumour-related bowel obstruction, evidence for prevalence[1] and symptomatic management was included. Practical guidance was recommended with the inclusion of the palliative care hotline number which was provided through inclusion of an online link for several contact numbers throughout South Africa.

An external comment received to consult an oncology specialist nurse/doctor instead of a palliative care provider for advice on management of a patient; as some districts might not have a palliative medicine provider was not accepted. The addition was not supported, as these patients might be too complex for nurses to handle alone and a link for the Association of Palliative Care Practitioners of South Africa (PALPRAC), to locate a palliative medicine provider, is already provided in this section, and covers the whole country.

[1] Cherny N, Fallon M, Kaasa S. Oxford Textbook of Palliative Medicine. Oxford: OUP Oxford; 2015. Available from: http://UOCT.eblib.com/patron/FullRecord.aspx?p=2012658.

The STG was updated as follows:

24.1.2.1 TUMOUR-RELATED BOWEL OBSTRUCTION
K56.6

DESCRIPTION
Malignant bowel obstruction is a well-recognised complication of advanced cancer and is defined as symptoms, signs, and radiographic evidence of obstruction to the transit of gastrointestinal contents caused by cancer, or the consequences of anticancer therapy including surgery, chemotherapy or radiation therapy. It occurs most commonly with ovarian or colorectal cancer.

GENERAL MEASURES
Consult a surgeon to discuss potential surgical interventions before restricting management to medicine treatment. Patients and families require in depth counselling around the cause, care, further nutrition, and nasogastric tubes. Parenteral nutrition generally has no role in patients with advanced cancer.

MEDICINE TREATMENT
These patients may be difficult to manage. Consult with a palliative care provider for advice on management of patient.

To identify and contact a palliative care provider if necessary, visit: https://palprac.org/palliative-care/find-a-provider/.
See Section 24.1.4 Nausea and Vomiting.

Referral/consultation
All patients that might require surgical management must be discussed with a surgeon.
All patients who require medical management of bowel obstruction must be discussed with a palliative care provider.

24.1.5 MANAGEMENT OF CLOSE CONTACTS OF PATIENTS WITH HBV INFECTED HEPATOCELLULAR CARCINOMA

Palliative care includes the management of hepatocellular carcinoma caused by viral hepatitis. Family members/care givers caring for patients with hepatocellular carcinoma are at high risk of Hepatitis B acquisition because of exposure to bodily fluids when caring for patients not on hepatitis B antiviral therapy. Therefore, an STG for hepatitis B screening of close contacts and linkage to preventative vaccination or treatment as appropriate was added to the chapter through cross references to appropriate STGs in the adult hospital EML and STGs as follows:

For patients with hepatocellular carcinoma caused by hepatitis B who are not on hepatitis B antiviral therapy (tenofovir/lamivudine/ emtricitabine):

Screen caregivers, who are or will be in contact with bodily fluids, for hepatitis B including hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody (HBsAb):

» Vaccinate non-immune individuals against hepatitis B (see Section 9.2 Adult vaccination)

» Link individuals who test positive for HBsAg to care (see Section 1.2.4.1: Hepatitis B, Acute and Sections 1.2.4.2 and 1.2.4.3: Hepatitis B, Chronic without or with HIV co-infection, respectively)

» Educate rest of family regarding the risk of infection from bodily fluids

Consult the most recent Hepatitis Guidelines from the National Department of Health

24.6 MALODOROUS FUNGATING WOUNDS/TUMOURS

Metronidazole, topical: *Added* (aligned to Paediatric Hospital Level STG)
Activated charcoal dressings: *Added* (aligned to Paediatric Hospital Level STG)
Lidocaine/prilocaine: *Added* (aligned to Paediatric Hospital Level STG)

An STG for malodorous fungating wounds/tumours was added as per the Paediatric Hospital Level STGs.[2,3,4,5]

Low certainty evidence: Systematic Review & RCTs: IIIb

A systematic review evaluating the efficacy of topical application of metronidazole for controlling wound odour identified 14 applicable studies including two double-blind randomised clinical trials.[6]

» Ashford et al., included 12 patients with malignant neoplastic wounds and compared topical metronidazole versus placebo. This study found that the metronidazole group had a significant odour reduction ($p<0.01$) and a reduction of microbial load ($p<0.005$).[7]
» Bower et al., included 9 adult patients with malignant neoplastic wounds and compared metronidazole gel to placebo. Odour reduction occurred in 5 days for the metronidazole group ($p < 0.001$).[8]

The systematic review concluded that metronidazole is recommended in clinical practice, and although there is some evidence to support efficacy, this evidence is not strong, and further robust studies are needed to firmly support this recommendation.

Kerihuel et al., compared activated charcoal dressings to hydrocolloid dressings for reduction of wound area of chronic wounds (n=66). Activated charcoal dressings were demonstrated to be more effective initially with better tolerability, however effects at 4 weeks were comparable between groups. [9] Activated charcoal was proposed as a better tolerated product.

Following external comment regarding the stability and expiry of the prepared metronidazole irrigation solution the Committee refined the STG wording to include guidance on how any remaining topical metronidazole irrigation solution should be discarded after use to emphasize good pharmacy practice and waste management principles.

The STG was updated as follows:

DESCRIPTION

Non-healing fungating tumours that are often secondarily infected and smelly causing social ostracization and distress to the patient and family. Examples include exophytic retinoblastoma, infected bedsores, rhabdomyosarcoma, osteosarcoma or Kaposi's sarcoma.

GENERAL AND SUPPORTIVE MEASURES

» Supportive counselling.
» Set realistic goals: may not include wound healing but could include odour eradication.
» Regular wound cleaning and dressing changes.
» Adequate ventilation.
» Disguise smell by placing a bowl of vanilla essence in the room, burn incense or place kitty litter under the bed to absorb smell.
» Air-fresheners and perfumes do not work.
» Change bedding and clothing regularly.

MEDICINE TREATMENT

- Provide good procedural pain management (see Chapter 26 Pain Control) and use distraction/relaxation techniques before and during dressing changes.

[2] Paediatrics: National Department of Health: Essential Drugs Programme. Paediatric Hospital level STGs and EML, draft. Chapter 21: Palliative Care
[3] Paediatrics: National Department of Health: Essential Drugs Programme. Paediatric Hospital level STGs and EML, draft NEMLC Report. Chapter 21: Palliative Care
[4] De Castro DLV, de Gouveia Santos VLC. Controlling wound odor with metronidazole: a systematic review. Rev Esc Enferm USP. 2015, 49 (5):851-856.
[5] Minutes of the Primary Health Care and Adult Hospital Level Expert Review Committee meeting of 8 December 2022
[6] De Castro DLV, de Gouveia Santos VLC. Controlling wound odor with metronidazole: a systematic review. Rev Esc Enferm USP. 2015, 49 (5):851-856.
7 Ashford R, Plant G, Maher J, Teare L. Double-blind trial of metronidazole in malodorous ulcerating tumours. Lancet. 1984;1(8388):1232-3.
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[9] Kerihuel, Jean Charles. (2010). Effect of activated charcoal dressings on healing outcomes of chronic wounds. Journal of wound care. 19. 208, 210-2, 214. 10.12968/jowc.2010.19.5.48047.

- Irrigate wounds with warmed normal saline. Debride gently with gloved hand not sharp instruments.
- Consider formal surgical debridement in patient where end-of-life is not imminent.
- Topical metronidazole:
  - Irrigation and cleaning of wound: 2 L of saline combined with 13 crushed metronidazole 400mg tablets (2 L 0.9% sodium chloride: 5200 mg metronidazole). Discard any remaining solution after each treatment, utilising appropriate medical waste management principles.
  - Metronidazole tablet topical: Metronidazole tablet 400mg per 35 cm^2 area twice daily to ameliorate malodor.
- Activated charcoal dressings also help to absorb odours.
- For wound pain consider using topical anaesthetics such as lidocaine/prilocaine.

B: PROPOSED AMENDMENTS

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/ NOT ADDED/ RETAINED
PALLIATIVE CARE	SPICT-SA Tool	SPICT-SA Tool added for identification of patients with palliative care needs
24.1.4 NAUSEA AND VOMITING	Metoclopramide, oral	Retained
	Metoclopramide, IM	Retained
	Metoclopramide, IV	Retained
	Haloperidol, SC	Deleted
-If metoclopramide is ineffective or contra-indicated (e.g., inoperable bowel obstruction)	Haloperidol, IM	Deleted
	Haloperidol, IV	Deleted
	Haloperidol, oral:	Retained
	Olanzapine, oro-dispersible	Added
	Olanzapine, oral	Added
	Olanzapine, IM	Added
24.2.2 DELIRIUM	Haloperidol, oral	Deleted
	Haloperidol, SC	Deleted
	Haloperidol, IV	Deleted
	Olanzapine, oro-dispersible	Added
	Olanzapine, IM	Added
- In hyper active delirium or severe agitation or where there is no response or resistance to olanzapine	Lorazepam, oral	Retained as part of terminal sedation
In hyper active delirium or severe agitation or where there is no response or resistance to olanzapine - ***For Patients unable to swallow:***	Midazolam, SC	Retained
	Midazolam, IV	Retained
24.4 RESPIRATORY CONDITIONS	Coronavirus Disease-19	Cross reference to PHC Infections and related conditions Section 10.19.1: COVID-19: CORONAVIRUS DISEASE-19.
24.5 SEDATION IN PALLIATIVE CARE	Lorazepam, oral,	Retained
	Olanzapine, oro-dispersible	Added
	Olanzapine, IM	Added
-Patient unable to take oral medication or terminal sedation required	Midazolam, SC	Retained
	Midazolam, IV	Retained

PALLIATIVE CARE

Editorial changes were made to the introduction noting that treatment does not differ from usual treatment in the earlier disease trajectory.

For earlier identification of patients with palliative care the *Supportive and Palliative Care Indicators TOOL (SPICT-SA* tool) was included and referenced with accompanying online link. SPICT™ "is used to help identify people with deteriorating health due to a new serious illness, and those with one or multiple advanced conditions so they benefit from holistic assessment, future care planning (advance/anticipatory care planning) and a palliative approach to care."[10]

[10] Palliative Care: SA Supportive and Palliative Care Indicators Tool (SPICTTM-SA). Available: file:///C:/Users/27798/Downloads/Version-2-SPICT-SA-Dec-2020%20(3).pdf.

Additionally, the STG has been amended to refer to end of life care rather than palliative care which in line with the SPICT^{TM}-SA tool

The following editorial updates were made to the introduction of the STG:

Palliative care is an approach that improves the quality of life of patients and their families facing problems associated with life-threatening illness, regardless of whether or not they also receive life-prolonging treatment.

~~It~~ **Palliative care** requires a multidisciplinary approach and aims to address physical, psychosocial, and spiritual problems.

Life threatening illnesses are where death is expected to be a direct consequence of the specified illness.
Analysis of available evidence suggested 11 common symptoms occurring in the advanced stages and end of life stages: anorexia, anxiety, constipation, delirium, depression, diarrhoea, dyspnoea, fatigue, nausea and vomiting, pain and respiratory tract secretions.
All symptoms should be managed by a multi-disciplinary team to ensure a holistic approach.

Note: Please be advised that the recommendations in this chapter are directed at treating common symptoms ~~associated with end-of-life care (acute and sub-acute) - a component of palliative care. The approach to end-of-life care may differ from supportive palliative care. Refer to relevant sections for supportive palliative care, e.g. section 15.3.1: Depressive disorders~~ **alongside disease directed care and symptoms associated with end-of-life care.**

The SPICT^{TM}-SA is a generic tool (https://www.spict.org.uk/the-spict/spict-sa/), designed for the South African setting, to help identify adults with advanced life-limiting illnesses when the best available and appropriate treatment has been given and their condition continues to deteriorate.

Level of Evidence: IVb – Guidelines

24.1.4 NAUSEA AND VOMITING

Metoclopramide, oral: *Retained*
Metoclopramide, IM: *Retained*
Metoclopramide, IV: *Retained*

If metoclopramide is ineffective or contra-indicated (e.g., inoperable bowel obstruction):

Haloperidol, oral: *Retained*
Olanzapine, oro-dispersible: *Added*
Olanzapine, oral: *Added*
Olanzapine, IM: *Added*

Following the discontinuation of haloperidol IM, an evidence review was undertaken on the use of olanzapine in adult palliative care patients with nausea and vomiting not responding to metoclopramide, as a replacement to haloperidol which is the standard of care for this indication. It was noted that while the use of olanzapine in the management of chemotherapy-related nausea and vomiting was well-documented in the literature, the use of olanzapine for the management of nausea and vomiting in palliative care is not supported by robust RCT evidence. Two systematic reviews were identified that reported on 2 small RCTs, which recruited participants with advanced cancer and malignant bowel obstruction, respectively and are summarised below.

Level of Evidence: Systematic Review: Critically low on appraisal with AMSTAR 2

For advanced cancer, a small randomised placebo controlled trial, (n=30) Navari et al (2020)[11] found that oral olanzapine 5mg reduced nausea scores by 8 (95% CI 7 to 8); p<0.001 compared to placebo, on an 11-point numerical rating scale (NRS) which rated nausea from 0 (no nausea) to 10 (severe nausea). Similarly, vomiting improved with a median of 2 fewer vomiting episodes per day (95% CI 2 fewer to 1 fewer vomiting episodes), p<0.001 Olanzapine exposure was not associated with excess sedation or other adverse effects (*very low quality evidence*).

For malignant bowel obstruction, a small, underpowered, open-label RCT (n=16), reported in a letter by Kaneishi et al (2020)[12], found similar reduction in nausea secondary to partial bowel obstructions, for a 3-day treatment course of olanzapine 5 mg/day compared to metoclopramide 20-30 mg/day. There was a change in score of −3.17 (NRS) for olanzapine and −2.38 (NRS) for metoclopramide, p=0.39 (*very low-quality evidence*).

Refer to the medicine review:

Olanzapine_Palliative NauseaVomiting_Adu

Recommendation:

Based on this review, the Adult Hospital Level Committee suggests that oral, oro-dispersable & IM olanzapine be used in adult palliative care patients with nausea and vomiting (N&V) not responding to metoclopramide, as a replacement to haloperidol.

Rationale: Haloperidol IM has been discontinued locally and an alternative for the management of N&V in palliative care patients is required. There is very little evidence to suggest that oral olanzapine may improve N&V and fatigue with no excessive sedation or adverse effects compared to placebo among adult patients with advanced cancer. Olanzapine may be as effective as metoclopramide in reducing N&V in malignant bowel syndrome.

Level of Evidence: Very low certainty evidence

NEMLC RECOMMENDATION – MEETING OF 23 FEBRUARY 2023:
NEMLC was in agreement with the recommendation by the Adult Hospital Level Committee & recommended oral, oro-dispersable & IM olanzapine be used in adult palliative care patients with nausea and vomiting (N&V) not responding to metoclopramide, as a replacement to haloperidol.

Additionally, an editorial update was made using inoperable bowel obstruction as one example, if metoclopramide is ineffective or contra-indicated, rather than the only indication.

The STG was updated as follows

MEDICINE TREATMENT
Treat the underlying cause.
- Metoclopramide, oral/IM/IV, 10 mg 8 hourly, 30 minutes before a meal.

If metoclopramide is ineffective or contra-indicated (**e.g.,** inoperable bowel obstruction):
- Haloperidol, oral, 1.5–5 mg daily.

~~**OR**~~

[11] Navari et al, 2020. Olanzapine for the treatment of advanced cancer-related chronic nausea and/or vomiting: a randomized pilot trial. JAMA Oncol 6(6):895–899 doi:10.1001/jamaoncol.2020.1052

[12] Kaneishi, 2020. Olanzapine versus Metoclopramide for Treatment of Nausea and Vomiting in Advanced Cancer Patients with Incomplete Malignant Bowel Obstruction. Journal of Palliative Medicine. 2020 Jul 1;23(7):880-881. doi.org/10.1089/jpm.2020.0101

~~Haloperidol, SC/IM/IV~~
- ~~Initiate 0.5 mg 12 hourly.~~

~~Titrate to a maximum dose of 5 mg 8 hourly~~

OR
- **Olanzapine orodispersible tablet, oral or IM injection, ~~5–10 mg~~.**
  - **Initiate 5 mg at night (2.5 mg in frail and elderly patients).**
  - **Titrate in increments of 2.5 mg to a maximum dose of 10 mg daily.**

Monitor vital signs and beware of oversedation, neuroleptic malignant syndrome, and acute dystonia.

A cross reference to Section 24.1.2.1 Tumour-related bowel obstruction was added under referrals.

The STG was updated as follows:

REFERRAL
<u>see Section 24.1.2.1 Tumour-related bowel obstruction</u>
Consult a palliative care trained doctor if the vomiting persists.

24.2.1 ANXIETY

In alignment with lorazepam dosing in the palliative care setting, tapering of diazepam dose was deleted from the STG.

The STG was updated as follows:

MEDICINE TREATMENT

Acute management of anxiety:
<u>For an acute episode or intense prolonged anxiety:</u>
- Benzodiazepine, e.g.:
- Diazepam, oral, 2.5–5 mg as a single dose.
  - Repeat if required up to 12 hourly.
  - ~~Duration of therapy: up to 2 weeks, taper off to zero within 6 weeks~~
  - Avoid if liver function impaired.

OR
- Lorazepam, oral, 0.5–1 mg, immediately.
  - Repeat as necessary to control symptoms.
  - Tablets may be crushed and administered sublingually.

24.2.2 DELIRIUM

Agitated and acutely disturbed patient:

<u>Haloperidol, oral: D</u>*eleted*
<u>Haloperidol, SC:</u> *Deleted*
<u>Haloperidol, IV:</u> *Deleted*
<u>Olanzapine, oro-dispersible:</u> *Added*
<u>Olanzapine, IM:</u> *Added*

The subheading for the indication *"<u>In the elderly or where there is no response or resistance to haloperidol"</u>* was revised to include all patients with hyper active delirium or severe agitation or where there is no response or resistance to olanzapine; which now replaces haloperidol.

In hyper active delirium or severe agitation or where there is no response or resistance to olanzapine:

*<u>Lorazepam, oral:</u> retained (*Tablets may be crushed and administered sublingually)
<u>Midazolam SC:</u> retained (for patients unable to swallow)
<u>Midazolam IV:</u> retained (for patients unable to swallow)

Haloperidol injection has been discontinued from the South African market. With the discontinuation of haloperidol injection, alternative options such as olanzapine and levomepromazine injection (phenothiazine commonly used for similar indications to that of haloperidol in European Guidelines, which can be used subcutaneously and is more sedative than haloperidol) were considered for review. However, levomepromazine is not SAHPRA registered[13].

Olanzapine oro-dispersable and Olanzapine, IM were reviewed for the management of aggressive disruptive behaviour in adults[14]. The STG on delirium in the medicines and palliative care chapter was reviewed and updated with the Adult Hospital Level Mental Health conditions & Emergencies and Injuries chapters, regarding olanzapine as an alternative to haloperidol in this clinical setting, for the agitated and acutely disturbed patient. A cross reference to the Emergencies and Injuries chapter was also added[15].

Refer to the medicine review:

Olanzapine_delirium_
PHC-AdultsReview_18/

Recommendation: The PHC/ Adult Hospital Level Committee suggests using olanzapine (oral, orodispersible and parenteral formulations) as an option to manage delirium where non-pharmacological management is not sufficient *(conditional recommendation).*
Rationale: Available low-quality evidence shows that haloperidol is comparable to olanzapine.
Level of Evidence: Low to very low certainty evidence
Review indicator: Evidence of harm, efficacy

NEMLC RECOMMENDATION (20 OCTOBER 2022 MEETING):
The NEMLC considered the recommendation, as proposed by the PHC/Adult Hospital Level Committee and concerns were raised regarding the feasibility of administering medication via NGT to a patient with delirium. Alternative agents were also discussed, noting the reported paucity of evidence for clotiapine and the safety concerns of droperidol (QT-prolongation).
NEMLC recommended olanzapine oro-dispersible tablet or IM for delirium with agitated and acutely disturbed behaviour Once the patient is able to swallow, to continue with oral haloperidol or olanzapine, until behaviour is contained.

In hyper active delirium or severe agitation or where there is no response or resistance to olanzapine lorazepam was retained as part of terminal sedation. Midazolam was retained in patients unable to swallow with hyper active delirium or severe agitation or where there is no response or resistance to olanzapine.

The STG was updated as follows:

DESCRIPTION
Delirium (confusion) is very common in the terminal stages of advanced disease and is associated with a short prognosis. When treatment of the underlying cause(s) of delirium is not possible or unsuccessful, pharmacological management is necessary. Causal treatment may not be indicated in patients with limited prognosis and pharmacological symptomatic therapy has to be initiated without delay.

See Adult Hospital Level chapter: Emergencies and Injuries: section 20.8

GENERAL MEASURES
Assess for underlying causes e.g. infection or electrolyte imbalance.
Remove factors that can agitate the patient (e.g. full bladder, thirst, pain, constipation, medicines such as opioids, steroids, benzodiazepines, withdrawal of medicines, dehydration, liver or renal impairment and cerebral tumour).
Reduce polypharmacy.
Where appropriate, ensure adequate fluid and nutritional intake (not indicated in the pre-terminal stage).
Mobilise early when appropriate.

[13] Minutes of the Primary Health Care and Adult Hospital Level Expert Review Committee meeting of 9 September 2021.

[14] Olanzapine, oral/oral dispersible tablet/IM/: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Olanzapine for delirium, 9 August 2022. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[15] Minutes of the Primary Health Care and Adult Hospital Level Expert Review Committee meeting of 9 February 2023.

Monitor for sensory deficits and manage accordingly e.g. using hearing aids.
Keep the family involved and informed. Provide tools of care such as how to orientate and reassure the patient.

MEDICINE TREATMENT

- ~~Haloperidol, oral/SC/IV, 0.5 mg 8 hourly.~~
  - ~~Titrate dosage up as required and use the minimum dose that controls the symptoms.~~

For agitated and acutely disturbed patient:

- **Olanzapine, oral dispersible tablet or IM, 2.5–5 mg.**
  - **This can be repeated in 30–60 minutes, if required and then 6 hourly to a maximum dose of 20 mg within 24 hours.**
  - **Monitor vital signs and beware of oversedation, neuroleptic malignant syndrome, and acute dystonia.**

~~In the elderly or where there is no response or resistance to haloperidol:~~

In hyper active delirium or severe agitation or where there is no response or resistance to olanzapine:

ADD

- Lorazepam, oral, 0.5–1 mg 2–4 hourly as required.
  - Tablets may be crushed and administered sublingually.

OR

Patients unable to swallow:

- Midazolam, SC/IV, 0.5–5 mg immediately.
  - Titrate up slowly.
  - Lower doses are indicated for patients with liver dysfunction.

24.4 RESPIRATORY CONDITIONS

For COVID-19 management relevant cross-referrals to the infections chapter were made.

The STG was updated as follow:

24.4 RESPIRATORY CONDITIONS

"For Coronavirus Disease-19. See PHC Infections and related conditions Section 10.19.1: COVID-19: CORONAVIRUS DISEASE-19.

24.5 SEDATION IN PALLIATIVE CARE

If hyper active delirium or severe agitation:

Olanzapine, oro-dispersible: *Added*

Olanzapine, IM: *Added*

The sedation in palliative care STG was aligned to the Adult Hospital Level Mental Health Chapter but starting with lower doses of olanzapine (2.5–5mg) as for elderly, frail, or medically unwell patients which would be more appropriate for the palliative care setting.

The STG was updated as follows:

MEDICINE TREATMENT

Dosing in frail, elderly patients should be titrated to effect.

- Lorazepam, oral, 0.5 mg 4 hourly.
  - Tablets may be crushed and administered sublingually.

OR

~~Haloperidol, oral, 0.5 mg 4 hourly.~~

If hyper active delirium or severe agitation

- Olanzapine 2.5–5 mg orodispersible tablet or IM.
  - Repeat after 30–60 minutes if needed.

Note: Repeated doses may result in excessive sedation

Patient unable to take oral medication or terminal sedation required:

- Midazolam, SC/IV:
  - Initial dose: 1–5 mg as needed
  - Titrate to effect.

South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Medicines for palliative care

MEDICINE REVIEW

1. Executive Summary

Date: November 2022
Medicine (INN): Olanzapine injection, orodispersible
Medicine (ATC): N05AH03
Indication (ICD10 code): Nausea and vomiting in palliative care R11 + (Z51.5)
Patient population: Adult palliative care patients with nausea and vomiting not responding to metoclopramide
Prevalence of condition: 62% to 71% (refs)
Level of Care: Hospital level (Adults)
Prescriber Level: Medical officer
Motivator/reviewer name(s): Trudy Leong, Dalene van Jaarsveld, Rene Krause
PTC affiliation: DVJ – Free State PTC; RK – Western Cape PTC

Key findings

- **Background:** Currently, haloperidol IM/SC/IV is the standard of care in the management of palliative nausea and vomiting where metoclopramide cannot be tolerated or is ineffective. Haloperidol injections have been discontinued from the South African market.
- We reviewed evidence for efficacy and safety of olanzapine in managing nausea and vomiting in adult palliative care patients.
- In a literature search conducted on 4 November 2022, we identified two systematic reviews that reported on 2 small randomised controlled trials (RCTs), which recruited participants with advanced cancer and malignant bowel obstruction, respectively. Both reviews were rated critically low on appraisal with AMSTAR 2.
- *Advanced cancer:* In a small randomised placebo controlled trial (n=30) Navari et al (2020) found that oral olanzapine 5mg reduced nausea scores by 8 (95% CI 7 to 8); p<0.001 compared to placebo, on an 11-point numerical rating scale (NRS) which rated nausea from 0 (no nausea) to 10 (severe nausea). Similarly, vomiting improved with a median of 2 fewer vomiting episodes per day (95% CI 2 fewer to 1 fewer vomiting episodes), p<0.001 Olanzapine exposure was not associated with excess sedation or other adverse effects (*very low quality evidence*).
- *Malignant bowel obstruction:* A small, underpowered, open-label RCT (n=16), reported in a letter by Kaneishi et al (2020), found similar reduction in nausea secondary to partial bowel obstructions, for a 3-day treatment course of olanzapine 5 mg/day compared to metoclopramide 20-30 mg/day. There was a change in score of −3.17 (NRS) for olanzapine and −2.38 (NRS) for metoclopramide, p=0.39 (*very low quality evidence*). Note that metoclopramide is a prokinetic and should therefore be avoided in patients with colic or abdominal pain.
- In summary, low to very low certainty evidence suggests that oral olanzapine may be considered in management of nausea and vomiting in advanced cancer or malignant bowel obstruction where metoclopramide is ineffective or not tolerated.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

Recommendation: Based on this review, the Adult Hospital Level Committee suggests that oral, oro-dispersable & IM olanzapine be used in adult palliative care patients with nausea and vomiting (N&V) not responding to metoclopramide, as a replacement to haloperidol.

Rationale: Haloperidol IM has been discontinued locally and an alternative for the management of N&V in palliative care patients is required. There is very little evidence to suggest that oral olanzapine may improve N&V and fatigue with no excessive sedation or adverse effects compared to placebo among adult patients with advanced cancer. Olanzapine may be as effective as metoclopramide in reducing N&V in malignant bowel syndrome.

Level of Evidence: Very low certainty evidence

Review indicator: New high-quality evidence of a clinically relevant benefit

NEMLC RECOMMENDATION – MEETING OF 23 FEBRUARY 2023:

NEMLC was in agreement with the recommendation by the Adult Hospital Level Committee & recommended oral, oro-dispersable & IM olanzapine be used in adult palliative care patients with nausea and vomiting (N&V) not responding to metoclopramide, as a replacement to haloperidol.

Monitoring and evaluation considerations

Research priorities

2. Name of author(s)/motivator(s)

Dalene van Jaarsveld, Rene Krause, Trudy Leong

3. Author affiliation and conflict of interest details

DvJ (University of the Free State), RK (University of Cape Town), and TL (Cochrane-SA, Medical Research Council-SA; Right-To-Care as Secretariat support to the PHC/Adult Hospital Level Committee) have no conflict of interests to declare related to olanzapine.

TL is partly supported by the Research, Evidence and Development Initiative (READ-It) project. READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies).

4. Introduction/ Background

Nausea and vomiting are regarded as one of the most distressing symptoms experiences by most palliative care patients (Leach, 2019). It is a common during the last days of life in patients with underlying cancer, heart failure, renal failure, AIDS, etc., and if not treated effectively, will cause deterioration in the patient's experience of quality of life and contribute to care giver distress.

Most palliative care symptom management guidelines, including the Adult Hospital Level Standard Treatment Guidelines (STGs) and Essential Medicine List STG (2019 edition), recommends metoclopramide as first line pharmacological therapy for nausea and vomiting in palliation. Currently, the STGs recommend haloperidol oral or administered intramuscularly or subcutaneously as a second-line option for those with retractable nausea and

vomiting with or without metoclopramide. Haloperidol injection has been withdrawn from the South African market and an alternative agent is required specifically in patients where the oral route is unsuitable.

Olanzapine is an atypical antipsychotic, and its antiemetic action is attributed to dopamine and serotonin antagonist properties. The palliative care formulary (7th edition, p 256) (3) recommends olanzapine as a second-line anti-emetic in patient where symptoms persist despite optimal first-line treatment. However, most RCT evidence is for olanzapine for chemotherapy-induced nausea and vomiting (Sutherland, 2018), and evidence for olanzapine as an antiemetic in palliative care settings (non-chemotherapy related nausea and vomiting in patients with advance disease) has been reported to be case series, case studies and observational studies (Saudemont, 2020).

An evidence review was conducted to study the safety and effectiveness of olanzapine in treating nausea and vomiting in adult palliative patients.

5. Purpose/Objective

Question: Is olanzapine safe and effective for the management of nausea and vomiting in adult palliative care patients compared to haloperidol?

-P: Adult palliative care patients with nausea and vomiting not responding to metoclopramide
-I: Olanzapine injection or orodispersible formulation for intractable nausea and vomiting (with or without metoclopramide)
-C: Haloperidol oral, parenteral
-O: Quality of life, numeric nausea and vomiting rating scores, other validated nausea and vomiting severity scales, number of emetic episodes during trial period, nausea and vomiting diaries, number of breakthrough nausea and vomiting, serious adverse events other adverse effects including somnolence or fatigue

Study designs: Systematic reviews of randomized controlled trials (RCTs) and RCTs, and if these are not available observational studies and guidelines

6. Methods:

a. Data sources

Systematic reviews were sought in PUBMED and Epistemonikos.

b. Search strategy

A search strategy was developed for PubMed and adapted to other databases (Appendix 1).

c. Screening, data extraction and evidence synthesis

Records were screened, followed by text screening by one reviewer (TL). A step-wise approach was taken, screening for systematic reviews, and if these were not available followed by RCTs, then observational studies. Any discrepancies were resolved by consensus. Eligible systematic reviews were appraised using the AMSTAR II Checklist (Shea, 2017). Risk of bias of RCTs were assessed using the Cochrane's RoB 2.0 Tool (Higgins, 2022). Data extraction for included reviews was done by one reviewer (TL) and data was extracted in Table 1. For dichotomous outcomes, risk ratios (RR) with 95% confidence intervals (CI) were reported and reported results from the review were described. Where available, the GRADE (level of certainty) of the evidence was reported (Guyatt, 2008).

d. Excluded studies

Rationale for excluding studies is described in Appendix 3.

7. Results:

a. Search results

PubMed and Epistemonikos was searched on 4 November 2022, and 29 records were identified for screening. Four duplicates were removed, and 8 were irrelevant. 17 full-text studies were assessed for eligibility; 15 studies were excluded. There were two systematic reviews selected for evidence synthesis. Refer to the Prisma Flow Chart in Appendix 2.

b. Description of systematic reviews

Two systematic reviews that informed Multinational Association for Supportive Care in Cancer guidelines were identified for inclusion:

1) *Davis et al, 2021*: Review within the "MASCC antiemetics in advanced cancer updated guideline" (Davis, 2021a)
2) *Davis et al, 2021*: Review within the "Medical management of malignant bowel obstruction in patients with advanced cancer: 2021 MASCC guideline update" (Davis, 2021b)

Davis, 2021a (advanced cancer): For the updated guideline for antiemetics in advanced cancer, Davis et al reviewed RCT evidence for the pharmacological management of nausea and vomiting in advanced cancer patients. Studies related to chemotherapy-related nausea and vomiting, non-pharmacological management of nausea and vomiting in advanced cancer and malignant bowel obstruction were excluded. The review was assessed to be of critically low quality using the AMSTAR 2 tool. See Table 1). Primary outcome was not stated in the review. Outcomes assessed were reduction in chronic generalized nausea and vomiting in advanced cancer and nausea and vomiting associated with opioid therapy

For haloperidol compared to olanzapine, the reviewers found limited RCT evidence, with a paucity of head-to-head studies. However, a single well conducted, small placebo-controlled RCT (n=30) showed that olanzapine 5 mg was superior to placebo, amongst patients with advanced cancer with nausea and vomiting unrelated to chemotherapy or radiation (Navari, 2020). At day 7, there was an 8-point reduction in nausea scores in the olanzapine-treated group (95% CI 7 to 8) compared to the placebo arm, $p<0.001$ (using an 11-point numerical rating score, NRS 0 no nausea, 10 severe nausea). Vomiting, fatigue, pain, and well-being improved, and there was no excessive sedation or other toxic effects associated with olanzapine that was reported. The study was assessed to be of moderate risk of bias as one study participant in the placebo group withdrew from the study at day 5, due to persistent nausea and vomiting. Authors suggested further research with larger studies. See Table 2)

Davis, 2021b (MBO): The systematic review within the "Medical management of malignant bowel obstruction in patients with advanced cancer: 2021 MASCC guideline update", focused on RCTs for the pharmacologic management of nausea and vomiting in malignant bowel obstruction (MBO) only. Studies on non-pharmacological management and surgical management of MBO were excluded.

The review was assessed to be of critically low quality using the AMSTAR 2 tool. One small placebo controlled RCT of olanzapine was included in the review. (Table 1 and 2)

The small RCT (n=16), reported in a letter (Kaneishi, 2020) showed that olanzapine may be as effective as metoclopramide in reducing nausea secondary to partial bowel obstructions (though, metoclopramide is a prokinetic and should be avoided if there is colic or abdominal pain). Patients with incomplete bowel obstruction and an average nausea score >4 (using NRS) were randomized to olanzapine 5 mg daily or metoclopramide 20–30 mg daily for 3 days. The primary outcome was mean nausea score for 3 days. There was no difference in the reduction in nausea, with a change in nausea score of −3.17 (NRS) for olanzapine vs −2.38 (NRS) for metoclopramide, p=0.39; assessed by systematic reviewers as low quality evidence due to lack of blinding and uncertainty about testing equi-effective doses. Because as the study was assessed as high risk of bias as open-label, study protocol was not available and most of the study details were not reported in the publication, the quality of the evidence was downgraded to very low quality. This was a small, underpowered open-label pilot trial and further research is needed.

Table 1: AMSTAR assessment of systematic reviews

Systematic review	Recommendation(s)	Appraisal AMSTAR 2
Davis et al, 2021a. MASCC antiemetics in advanced cancer updated guideline. Support Care Cancer. 2021 Dec;29(12):8097-8107. doi: 10.1007/s00520-021-06437-w	• Metoclopramide recommended as first-line antiemetic; *moderate quality evidence, consistent findings* • Haloperidol recommended as first-line antiemetic; *moderate quality evidence, consistent findings* • Olanzapine recommended as a second-line antiemetic; *moderate quality evidence, generally consistent findings*	Critically low-quality review. See Appendix 4
Davis, 2021b. Medical management of malignant bowel obstruction (MBO) in patients with advanced cancer: 2021 MASCC guideline update. Support Care Cancer. 2021 Dec;29(12):8089-8096 doi: 10.1007/s00520-021-06438-9	• Octreotide recommended as a front-line treatment for inoperable MBO; *high quality evidence, consistent findings* • Metoclopramide suggested as an active antiemetic in the management of MBO; *low quality evidence, generally consistent findings* • Olanzapine suggested as an active antiemetic in the management of MBO; *low quality evidence, generally consistent findings* • Haloperidol suggested as an active antiemetic in the management of MBO; *low to very low quality evidence, generally consistent findings*	Critically low-quality review. See Appendix 4

Haloperidol, conventionally has been used to treat breakthrough nausea and vomiting from MBO in randomized trials but has not be compared with other antiemetics (Davis, 2021b).

Table 2: Characteristics of included studies

Author, date	*Type of study*	Population (n)	Comparators	Primary outcome	Effect sizes	Comments
Davis et al, 2021a. MASCC antiemetics in advanced cancer updated guideline. Support Care Cancer. 2021 Dec;29(12):8097-8107. doi: 10.1007/s00520-021-06437-w	Systematic review of 1 SR and 3 RCTs, assessed as critically low quality. Only 1 RCT was related to olanzapine (Navari, 2020) – which is described below					
Navari et al, 2020. Olanzapine for the treatment of advanced cancer-related chronic nausea and/or vomiting: a randomized pilot trial. JAMA Oncol 6(6):895–899 doi:10.1001/jamaoncol.2020.1052	Double-blind, placebo-controlled, multi-center RCT *Inclusion criteria* - outpatients with advanced cancer with persistent nausea/vomiting without history of chemo- or radiotherapy in previous 14 days. - Chronic nausea present for at least 1 week (worst daily nausea score> 3 on a NRS 0-10 scale). *Funding:*	n=30 (n_1=15; n_2=15) Adults: 16 women, 14 men Mean age: 63 (39-79) years. Baseline median nausea scores: 9 out of 10 (range, 8-10).	*Intervention:* Olanzapine 5 mg/d, orally, days 1-7 (n_1=15) vs. *Placebo* (n_2=15)	Primary outcome: Reduction in nausea and vomiting (using NRS) Other outcomes: Nausea, appetite, fatigue, sedation, pain, well-being numeric rating scores; number of emesis episodes	**Olanzapine vs placebo:** Primary outcome: *Change in nausea scores (NRS):* –8 (95% CI –8 to –7), p<0.001 Other outcomes (difference between study groups): *Vomiting episodes/day:* Median –2 (95% CI –2 to –1), p<0.001 *Alternative antiemetic doses/day:* difference not reported *Appetite scores (NRS):* Median (range) 5 (95% CI 5 to 6), p<0.001 *Fatigue scores (NRS):* –3 (95% CI–4 to –1), p=0.004 *Sedation scores (NRS):* –1 (95% CI–2 to 0), p=0.08 *Pain sores (NRS):* –1 (–2 to 0), p=0.01 *Well-being scores (NRS):* 5 (4 to 5), p<0.01	Small pilot RCT, consistent with the results of other pilot studies (Passik, 2002; Harder, 2019; Macintosh, 2013) One study participant in the placebo group withdrew from the study at day 5, due to persistent nausea and vomiting Overall risk of bias assessment: **Some concerns** • *Randomisation:* **Low risk** • *Deviations from intervention:* **Low risk** • *Missing outcome data:* **Some concerns** • *Measurement of outcome:* **Low risk** • *Selection of the reported results:* **Low risk**

Davis, 2021b. Medical management of malignant bowel obstruction in patients with advanced cancer: 2021 MASCC guideline update. Support Care Cancer. 2021 Dec;29(12):8089-8096 doi: 10.1007/s00520-021-06438-9	Systematic review of 1 SR and 3 RCTs, assessed as critically low quality. Only 1 RCT was related to olanzapine (Kaneishi, 2020) – which is described below					
Kaneishi, 2020. Olanzapine versus Metoclopramide for Treatment of Nausea and Vomiting in Advanced Cancer Patients with Incomplete Malignant Bowel Obstruction. Journal of Palliative Medicine. 2020 Jul 1;23(7):880-881. doi.org/10.1089/jpm.2020.0101	Open-label pilot RCT *Inclusion criteria:* - advanced cancer - average nausea score of >4/10 due to incomplete malignant bowel obstruction (iMBO) *Funding:* Grant for Research Advancement on Palliative Medicine from the Japanese Society for Palliative Medicine	n=16 Number of participants per comparator group not reported	*Intervention:* Olanzapine 5 mg/d x 3days vs. Metoclopramide 20–30 mg/d x 3 days	Outcomes: -Change in mean nausea scores (NRS) for 3 days - rate of 30% reduction in NRS score - number of vomiting episodes - satisfaction rating of patients - preference to continue with the treatment - frequency of severe toxicities - adverse events	**Olanzapine vs placebo:** *Change in mean nausea scores over 3days:* -3.17 vs -2.38; p=0.39 *Rate of 30% reduction in NRS score:* 87.5% vs 50%; p = 0.11 *Mean difference in vomiting episodes/ day:* 2.25 vs 0.85; p=0.83 *Patient satisfaction rate:* 87.5% vs 75% *Preference to continue treatment:* 100% vs 50% *Frequency of severe toxicities:* Most symptoms were of low grade, and no patient chose to stop anti- emetic therapy *Adverse events:* Both olanzapine & metoclopramide caused drowsiness and dizziness	Lack of blinding and uncertainty about testing equi-effective doses; *low certainty evidence*. Study results reported in a letter to editor of a journal. Baseline demographics of comparator groups were not reported. Small pilot study, suggest the potential efficacy of olanzapine and metoclopramide against nausea and vomiting in patients with advanced cancer who have iMBO. Overall risk of bias assessment: **High risk** • *Randomisation:* Some concerns • *Deviations from intervention:* **High risk** • *Missing outcome data:* **High risk** • *Measurement of outcome:* **High risk** • *Selection of the reported results:* Some concerns

Conclusion

A review of available RCT evidence of low quality, suggests that oral olanzapine 5mg/daily may reduce nausea scores and vomiting episodes compared to placebo amongst adult patients with advanced cancer and is safe. Amongst patients with malignant bowel obstruction, very low quality evidence there was no difference in the reduction of nausea with olanzapine compared to metoclopramide. Currently, haloperidol injections (discontinued from the South African market), administered IM/SC/IV is the standard of care in the management of palliative nausea and vomiting where metoclopramide cannot be tolerated or is ineffective. Thus, based on low to very low certainty evidence (pilot studies conducted in high income countries), olanzapine oral may be considered as an alternative to metoclopramide in advanced cancer or malignant bowel obstruction. However, research is required to sufficiently address the question of olanzapine for palliation, noting that there is a need for evidence from low-income settings.

Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** *a.* *Nausea/vomiting in advanced cancer* High [ ] Moderate [ ] Low [ ] Very low [x]	*a.* *Nausea/vomiting in advanced cancer* **Olanzapine** (oral) **vs placebo:** Very low certainty evidence
	b. *Nausea/vomiting in MBO* High [ ] Moderate [ ] Low [ ] Very low [X] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	*b.* *Nausea/vomiting in MBO* **Olanzapine vs metoclopramide:** Very low certainty evidence
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** *a.* *Nausea/vomiting in advanced cancer* Large [ ] Moderate [X] Small [ ] None [ ]	*a.* *Nausea/vomiting in advanced cancer* **Olanzapine vs placebo:** • Nausea scores reduced (an 11-point numerical rating score, NRS: 0 no nausea, 10 severe nausea) by 8 (95% CI 7 to 8); p<0.001 vs placebo • Vomiting episodes improved with a median of –2 (95% CI –2 to –1), p<0.001
	b. *Nausea/vomiting in MBO* Large [ ] Moderate [ ] Small [ ] None [x]	*b.* *Nausea/vomiting in MBO* **Olanzapine** (oral) **vs metoclopramide:** • No difference in the reduction in nausea, with a change in score of −3.17 (NRS) for olanzapine vs −2.38 (NRS) for metoclopramide, p=0.39 • Vomiting episodes – not reported
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** *a.* *Nausea/vomiting in advanced cancer* High [ ] Moderate [ ] Low [ ] Very low [x]	*a.* *Nausea/vomiting in advanced cancer* **Olanzapine** (oral) **vs placebo:** very Low certainty evidence
	b. *Nausea/vomiting in MBO* High [ ] Moderate [ ] Low [ ] Very low [X]	*b.* *Nausea/vomiting in MBO* **Olanzapine vs metoclopramide:** Very low certainty evidence
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** *a.* *Nausea/vomiting in advanced cancer* Large [ ] Moderate [ ] Small [ ] None [X]	*a.* *Nausea/vomiting in advanced cancer* **Olanzapine** (oral) **vs placebo:** No sedation or adverse effects reported.
	b. *Nausea/vomiting in MBO* Large [ ] Moderate [ ] Small [ ] None [ ]	*b.* *Nausea/vomiting in MBO* **Olanzapine vs metoclopramide:** Not reported
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** *a.* *Nausea/vomiting in advanced cancer* Favours intervention [x] Favours control [ ] Intervention = Control *or* Uncertain [ ]	*a.* *Nausea/vomiting in advanced cancer* **Olanzapine** (oral) **vs placebo:** Favours intervention

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
	b. Nausea/vomiting in MBO Favours intervention: [ ] Favours control: [ ] Intervention = Control *or* Uncertain: [X]	*b. Nausea/vomiting in MBO* **Olanzapine vs metoclopramide:** Uncertain
THERAPEUTIC INTERCHANGE	n/a	
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes: [X] No: [ ] Uncertain: [ ]	Olanzapine is currently SAHPRA-registered (including generic products). Olanzapine has also been considered as an alternative to haloperidol injection for the management of aggressive disruptive disorders and delirium in adult patients (due to the current discontinuation of haloperidol injection from the South African market).
RESOURCE USE	**How large are the resource requirements?** More intensive: [ ] Less intensive: [ ] Uncertain: [ ]	**Price of medicines/ treatment course** Direct price comparison using maximum doses for 3 days AND patient cannot swallow: **A: Standard of care** — **Single dose** — **3-day course** Haloperidol IM/SC/IV — R 45,68 — R 411,12 *Haloperidol IM/SC/IV 5mg 8hrly x 3 days* *Previous S21 price* **B: Olanzapine alternative** **Single dose**: ***100% SEP*** R 8,91; ***60% SEP*** R 5,35 **3-day course**: ***100% SEP*** R26,74; ***60% SEP*** R16,04 Olanzapine orodispersible Olanzapine IM: ***100% SEP*** R 72,84; ***60% SEP*** R 43,71 **3-day course**: ***100% SEP*** R218,53; ***60% SEP*** R131,12 *Olanzapine alternative treatment: Olazapine ODT or IM 5 mg daily x 3 days*
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: [ ] Major: [ ] Uncertain: [X] **Is the option acceptable to key stakeholders?** Yes: [ ] No: [ ] Uncertain: [X]	
EQUITY	**Would there be an impact on health inequity?** Yes: [ ] No: [ ] Uncertain: [ ]	

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	November 2022	TL, DVJ, RK	NEMLC recommended oral, oro-dispersable & IM olanzapine be used in adult palliative care patients with nausea and vomiting (N&V) not responding to metoclopramide, as a replacement to haloperidol. Haloperidol IM has been

			discontinued locally and an alternative for the management of N&V in palliative care patients is required. Olanzapine may be as effective as metoclopramide in reducing N&V in malignant bowel syndrome.

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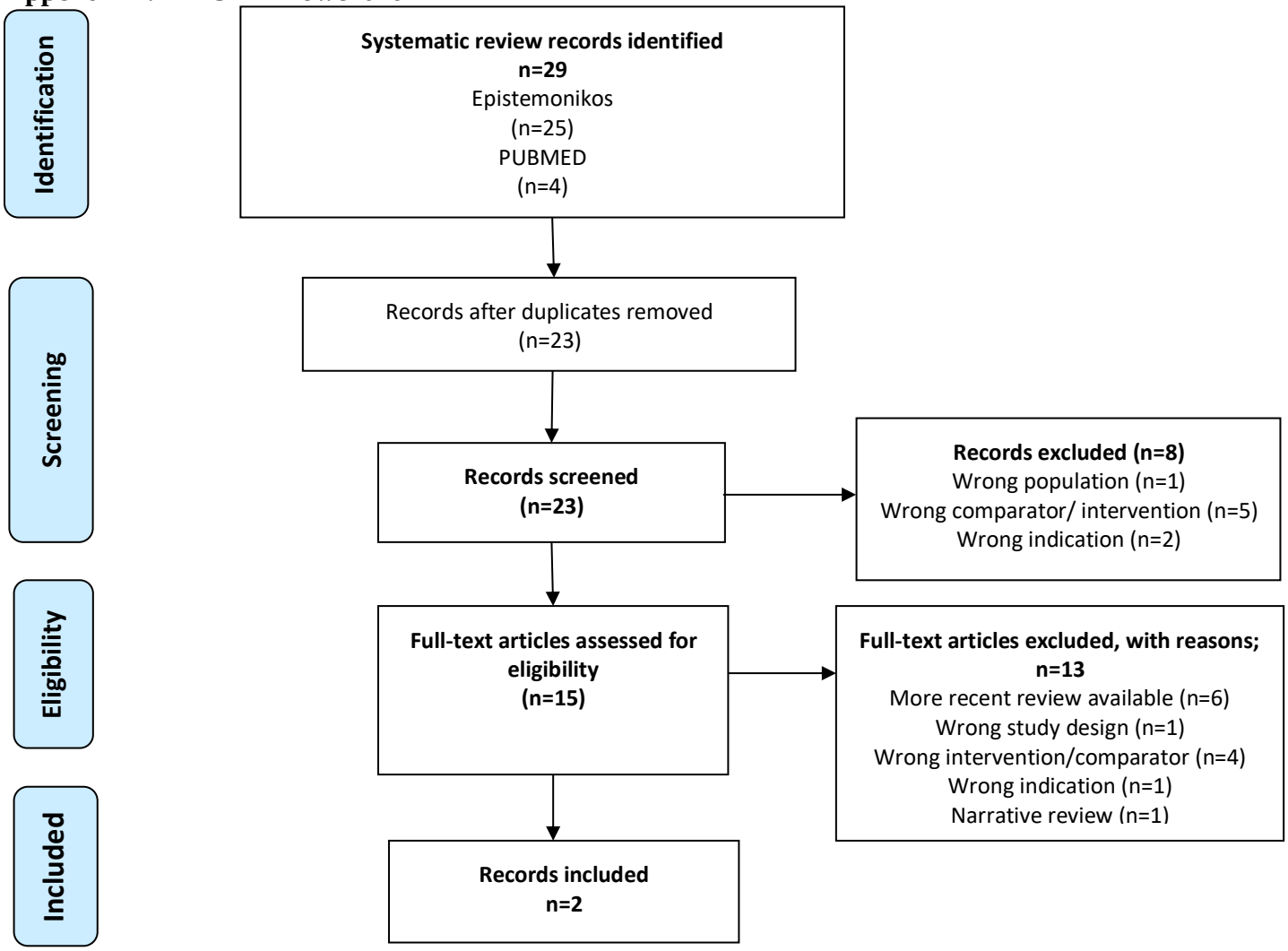
Appendix 1: Search strategy

A: PUBMED Date: 4 November 2022 Search strategy: (((olanzapine) AND (nausea)) AND (palliative care)) AND (vomiting) Filters applied: Systematic reviews Records retrieved: 4 Excluded: 2 Selected: 2
B: Epistemonikis Date: 4 November 2022 Search strategy: (title:((title:(olanzapine) OR abstract:(olanzapine)) AND (title:(nausea) OR abstract:(nausea)) AND (title:(vomiting) OR abstract:(vomiting))) OR abstract:((title:(olanzapine) OR abstract:(olanzapine)) AND (title:(nausea) OR abstract:(nausea)) AND (title:(vomiting) OR abstract:(vomiting)))) Filters applied: Systematic reviews, published last 5 years Records retrieved: 25 Excluded: 21 (6 records were duplicates)

Appendix 2: PRISMA flowchart



Appendix 3: List of excluded studies

Author, year	Study (systematic review)	Reason for exclusion
Chelkeba, 2017	Olanzapine for chemotherapy-induced nausea and vomiting: systematic review and meta-analysis. Pharm Pract (Granada). 2017 Jan-Mar;15(1):877	More recent review retrieved
Walsh, 2017	2016 Updated MASCC/ESMO consensus recommendations: Management of nausea and vomiting in advanced cancer. Support Care Cancer. 2017 Jan;25(1):333-340	More recent guidelines and supporting review retrieved
Saudemont, 2020	The use of olanzapine as an antiemetic in palliative medicine: a systematic review of the literature. BMC Palliat Care. 2020 Apr 22;19(1):56.	Wrong study designs (considered only if SRs of RCTs or RCTs are not available).
Chow, 2021	Olanzapine for the prophylaxis and rescue of chemotherapy-induced nausea and vomiting: a systematic review, meta-analysis, cumulative meta-analysis and fragility assessment of the literature. Support Care Cancer. 2021 Jul;29(7):3439-3459.	Control arm included other agents besides haloperidol, and did not stratify effect of olanzapine per comparator
Yoodee, 2017	Efficacy and safety of olanzapine for the prevention of chemotherapy-induced nausea and vomiting: A systematic review and meta-analysis. Crit Rev Oncol Hematol. 2017 Apr;112:113-125.	More recent review retrieved
Wang, 2021	The Balance Between the Effectiveness and Safety for Chemotherapy-Induced Nausea and Vomiting of Different Doses of Olanzapine (10 mg Versus 5 mg): A Systematic Review and Meta-Analysis. Front Oncol. 2021 Sep 30;11:705866. https://pubmed.ncbi.nlm.nih.gov/34660273/	Wrong comparator
Patel, 2022	Interventions for the prevention of acute phase chemotherapy-induced nausea and vomiting in adult and pediatric patients: a systematic review and meta-analysis. Support Care Cancer. 2022 Aug 12.	Intervention group not specific to olanzapine
Herrstedt, 2017	Updated MASCC/ESMO Consensus Recommendations: Prevention of Nausea and Vomiting Following High Emetic Risk Chemotherapy. Support Care Cancer. 2017 Jan;25(1):277-288.	More recent guidelines and supporting review retrieved
Qiu, 2021	Cost-Effectiveness of Aprepitant in Preventing Chemotherapy-Induced Nausea and Vomiting: A Systematic Review of Published Articles. Front Public Health. 2021 Aug 25;9:660514.	Wrong intervention
Yokoe, 2019	Effectiveness of Antiemetic Regimens for Highly Emetogenic Chemotherapy-Induced Nausea and Vomiting: A Systematic Review and Network Meta-Analysis. Oncologist. 2019 Jun;24(6):e347-e357.	Wrong indication
Zhou , 2020	Olanzapine combined with 5-hydroxytryptamine type 3 receptor antagonist (5-HT3 RA) plus dexamethasone for prevention and treatment of chemotherapy-induced nausea and vomiting in high and moderate emetogenic chemotherapy: a systematic review and meta-analysis of randomised controlled trials. ESMO Open. 2020 Feb;5(1):e000621.	Wrong intervention
Bai, 2020	Asian and North American patients with bipolar disorder have similar efficacy, tolerability, and safety profile during clinical trials with atypical antipsychotics? J Affect Disord. 2020 Jan 15;261:259-270.	Wrong indication
Sutherland, 2018	Olanzapine for the prevention and treatment of cancer-related nausea and vomiting in adults. Cochrane Database Syst Rev. 2018 Sep 21;9(9):CD012555.	More recent review retrieved
Yang, 2017	Efficacy of olanzapine for the prophylaxis of chemotherapy-induced nausea and vomiting: a meta-analysis. Br J Clin Pharmacol. 2017 Jul;83(7):1369-1379.	More recent 2021 review retrieved

Chiu, 2021	Secondary and cumulative meta-analysis of olanzapine for antiemetic prophylaxis for chemotherapy-induced nausea and vomiting: do we still need to study its effectiveness? Ann Palliat Med. 2021 Mar;10(3):2540-2547.	Control arm included other agents besides haloperidol, and did not stratify effect of olanzapine per comparator
Alhifany, 2020	Efficacy of olanzapine, neurokinin-1 receptor antagonists, and thalidomide in combination with palonosetron plus dexamethasone in preventing highly emetogenic chemotherapy-induced nausea and vomiting: a Bayesian network meta-analysis. Support Care Cancer. 2020 Mar;28(3):1031-1039.	Wrong comparator
Jahn, 2022	The Prevention and Treatment of Nausea and Vomiting During Tumor Therapy. Dtsch Arztebl Int. 2022 May 27;119(21):382-392.	Narrative review
Xiao, 2022	A pooled analysis of adding olanzapine to guideline-recommended antiemetic therapy for breast cancer patients treated with an anthracycline and cyclophosphamide in prospective and retrospective studies. Support Care Cancer. 2022 Mar;30(3):2445-2453. 34775535.	Wrong population group (specific to breast cancer patients), wrong study design
Zhang, 2018	Olanzapine-Based Triple Regimens Versus Neurokinin-1 Receptor Antagonist-Based Triple Regimens in Preventing Chemotherapy-Induced Nausea and Vomiting Associated with Highly Emetogenic Chemotherapy: A Network Meta-Analysis. Oncologist. 2018 May;23(5):603-616.	Wrong intervention
Bahbah, 2019	Should Olanzapine be Advocated Over Conventional Anti-Emetics for the Prevention of Chemotherapy-Induced Nausea and Vomiting? An Updated Meta-Analysis of Randomized Control Trials. Current Enzyme Inhibition. 2019;	Control arm included other agents besides haloperidol, and did not stratify effect of olanzapine per comparator
Solmi, 2020	Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: a large scale systematic meta-review of 78 adverse effects. World Psychiatry. 2020 Jun;19(2):214-232.	Wrong indication

Appendix 4: AMSTAR 2 assessment

		Yes/ Partial Yes/ No	
No	**Criteria**	**Davis, 2021a**	**Davis, 2021b**
1	Research questions and inclusion criteria for the review included the components of PICO	Partial yes	Partial yes
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	No, not explicit	No, not explicit
3	Review authors explained selection of the study designs for inclusion in the review	No	No
4*	Review authors used a comprehensive literature search strategy	Partial yes	Partial yes
5	Review authors perform study selection in duplicate	Yes	Yes
6	Review authors perform data extraction in duplicate	Yes	Yes
7	Review authors provided a list of excluded studies and justify the exclusions	No	No
8*	Review authors described the included studies in adequate detail	Yes	Yes
9	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	No	No
10*	Review authors reported on the sources of funding for the studies included in the review?	No	No
11	For meta-analyses, review authors used appropriate methods for statistical combination of results	n/a	n/a
12*	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	n/a	n/a
13	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	No	No
14*	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	n/a	n/a
15	For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	No	No
16*	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	Yes	Yes

** Critical domains*

• *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
• *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review
• *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest
• *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies
(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

OVERALL ASSESMENT: Critically low
Rationale: More than one critical flaw (# 2,10)
Conclusion: The AMSTAR assessment suggests that both reviews have more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.