Managing nausea and vomiting in the last days of life

Nausea and vomiting in the last days of life are often a cause of significant distress for patients and their family/whānau. A range of pharmacological and non-pharmacological interventions can be trialled to minimise the negative impact of these symptoms.

KEY PRACTICE POINTS:

- The causes of nausea and vomiting in the last days of life are often multifactorial and regular review is required to assess severity of symptoms, food and fluid intake, hydration status and any contributing factors
- Modifiable causes of nausea and vomiting should be addressed first, where appropriate, and discontinue preventative medicines that are no longer required, e.g. statins, oral hypoglycaemics
- Discuss non-pharmacological management strategies with the patient and their family/whānau, e.g. maintaining oral hygiene, relaxation or distraction techniques, complementary or alternative remedies
- If pharmacological treatment is required, subcutaneous haloperidol is the preferred first-line option in patients with no contraindications; metoclopramide and cyclizine can also be considered
  - Increase the dose if there is a small but insufficient improvement in symptoms
  - Establish regular dosing early to appropriately manage symptoms
  - Switch to an alternative antiemetic if there is no response to treatment
- Levomepromazine (methotrimeprazine) is the next option for patients with persistent nausea or vomiting despite maximum recommended doses of first-line antiemetics. N.B. Patients may experience sedation even at low doses.
- Occasionally, a combination of antiemetic medicines may be required to provide the patient sufficient symptom relief in the last days of life. Discuss with your local hospice or palliative care team if symptoms are complex.

This article is part of a series on managing symptoms in the last days of life. It is recommended to read this article in conjunction with the other articles in the series, particularly: "**Navigating the last days of life: a general practice perspective**".

Nausea and vomiting in the last days of life

Nausea and vomiting can be particularly distressing and significantly impact quality of life of a person in their final days.[1] Nausea and vomiting commonly occur in people with cancer, heart failure, liver disease or end stage renal disease.[2] Related symptoms include reduced appetite, weight loss, abdominal bloating/distention and constipation.[2]

Nausea and vomiting in the last days of life occurs due to a combination of factors, including:[1–3]

- Gastroparesis, constipation or functional bowel obstruction
- Medicines, e.g. opioids, NSAIDs, antibiotics, anticonvulsants or withdrawal from corticosteroids
- Upper gastrointestinal irritation, e.g. excessive secretions, infection, gastro-oesophageal reflux disease
- Electrolyte imbalances, e.g. hypercalcaemia, hyponatraemia, uraemia
- Anxiety, fear or pain
- Intracranial disorders, e.g. vestibular dysfunction, ototoxicity, raised intracranial pressure*

* Increased pressure inside the skull resulting from brain tumours or metastases, bleeding or swelling can compress structures in the brainstem involved in the vomiting reflex.[4] Common symptoms include nausea, vomiting, headaches and papilloedema, and are often more severe in the morning.[2]

The pathophysiology of nausea and vomiting is complex

The biological pathways that induce nausea and vomiting are complex (Figure 1).[5] The nucleus tractus solitarius (NTS, or vomiting centre) is a cluster of neurons in the brainstem that mediates the vomiting reflex. These neurons receive input from various sources, including:[5, 6]

The cerebral cortex, amygdala and limbic system – sensory input from higher centres relating to cognition and emotion, e.g. sights or smells that induce vomiting

The chemoreceptor trigger zone (CTZ) – located in the medulla oblongata, near the fourth ventricle, sitting outside of the blood brain barrier. This region detects circulating abnormalities, e.g. medicines, bacteria or electrolyte imbalances in the blood and cerebrospinal fluid.

The vestibular system – histamine-mediated signals resulting from inner ear dysfunction, e.g. motion sickness

The gastrointestinal system – mechanoreceptors stimulated by gastric distension and chemoreceptors that detect bacteria, toxins, medicines in the gastrointestinal lumen

In response to information from the above pathways, the NTS sends signals via the vagal nerve to increase gastric contraction and relax the oesophageal sphincter leading to emesis.[6, 7]

The exact pathophysiology of nausea is less well understood but it likely involves the NTS receiving input from similar sites as listed above and then sending signals to the cerebral cortex to produce the sensation of nausea.[5, 6]

Practice point: Clinicians should consider the likely pathophysiology of a patient's nausea and vomiting when deciding on the most appropriate antiemetic to prescribe (Table 1).

Assessing patients with nausea and vomiting

In patients with nausea or vomiting, consider the following factors during the baseline assessment (and ongoing reviews):[1–3]

The onset, duration and severity of symptoms

Potential triggers, e.g. smells from food preparation or those related to bodily functions

Whether any of the patient's medicines (for long-term conditions) are commonly associated with nausea or vomiting

Whether the adverse effects of these medicines outweigh any potential benefit at this stage

The presence of constipation or signs of faecal impaction, e.g. abdominal distension or mass, absence of bowel sounds

Current hydration status and food and fluid intake

The patient's thoughts and emotions concerning their symptoms, e.g. fear, anxiety, anticipation

Management of nausea and vomiting in the last days of life

Discuss with the patient and their family/whānau that nausea and vomiting is not unexpected, why it occurs, and the treatment options that are available for them. Knowing what to expect can alleviate distress. Reassure family/whānau that food and fluid requirements reduce in the last days of

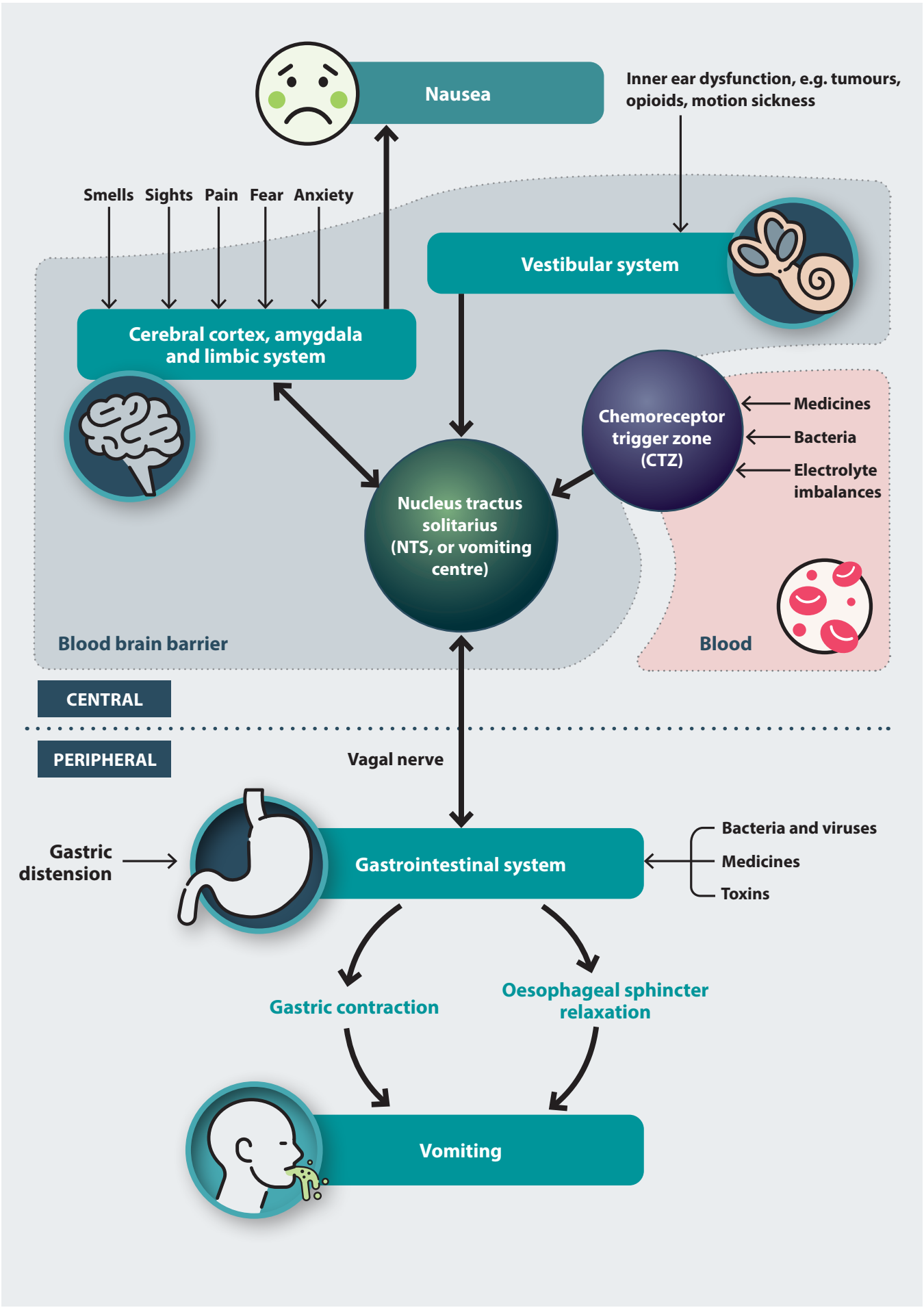


Figure 1. A simplified overview of the pathophysiology of nausea and vomiting.[5–7]

Table 1. Antiemetic medicines for managing nausea and vomiting in the last days of life.

Medicine	Dose	Considerations	Availability
Haloperidol* Dopaminergic (D_2) receptor antagonist (at chemoreceptor trigger zone reducing the effects of circulating abnormalities)[2, 10] In practice, the first-line antiemetic choice as lower adverse effect profile than alternatives, especially in frail or older people Effective for opioid-induced nausea and vomiting, nausea as a result of end stage renal disease or hypercalcaemia[10, 16]	*Patients not currently receiving an antiemetic:* 0.5 mg, subcutaneously every four hours, as needed (usually do not exceed 3 mg/24 hours) *Patients already receiving oral haloperidol should be switched to:* 0.5 – 1 mg, subcutaneously at night, or twice daily, as needed OR 1 – 3 mg/24 hours, via CSCI. Patients whose symptoms are not adequately controlled with 3 mg haloperidol over 24 hours are usually switched to levomepromazine (occasionally a higher dose of haloperidol, e.g. up to 5 mg over a 24-hour period, may be beneficial).	Contraindicated in Parkinson's disease, prolonged QT-interval (gastrointestinal obstruction is a relative contraindication in the last days of life)[8, 16] Avoid in patients with Lewy body dementia due to an increased risk of neuroleptic malignant syndrome[19]	5 mg/mL solution for injection (1 mL ampoules) PSO and prescription
Metoclopramide* D_2 and $5HT_3$ antagonist and $5HT_4$ agonist (at chemoreceptor trigger zone and peripherally promotes gastric emptying and motility)[2, 5] Appropriate for nausea and vomiting caused by gastroparesis, functional bowel obstruction (due to opioid use) and gastro-oesophageal reflux disease[2]	*Patients not currently receiving an antiemetic:* 10 mg, subcutaneously every six hours, as needed (maximum dose 40 mg/24 hours) *Patients already receiving oral metoclopramide should be switched to:* 10 mg, subcutaneously three to four times daily, as needed OR 30 – 60 mg/24 hours, via CSCI[8] however, in practice, patients whose symptoms are not adequately controlled with 40 mg metoclopramide, over 24 hours should be switched to levomepromazine N.B Higher doses of metoclopramide, e.g. 60 mg over a 24-hour period, should be reserved for managing nausea and vomiting that is likely caused by delayed gastric emptying (without obstruction)	Contraindicated in Parkinson's disease, prolonged QT-interval, or if complete bowel obstruction[10, 20] Monitor for extrapyramidal adverse effects, e.g. tardive dyskinesia (more common at doses greater than 30 mg/24 hours) May worsen abdominal cramps in some patients Do not co-prescribe with anticholinergics (e.g. cyclizine, hyoscine butylbromide) if delayed gastric emptying is the clear cause of nausea and vomiting[3]	5 mg/mL solution for injection (2 mL ampoules) PSO and prescription
Cyclizine* H_1 receptor antagonist with anticholinergic actions (at vomiting centre [NTS] and vestibular system)[2] Recommended for nausea and vomiting resulting from raised intracranial pressure (due to brain tumours or secondary metastases), bowel obstruction and vestibular disease[16]	75 – 150 mg/24 hours, via CSCI[16]	Do not co-prescribe with metoclopramide if the likely cause of nausea and vomiting is delayed gastric emptying (without obstruction)[3] Not recommended to be given as a subcutaneous bolus due to injection site reactions	50 mg/mL solution for injection (1 mL ampoules) PSO and prescription
Levomepromazine (methotrimeprazine)† Antagonistic action at dopamine, serotonin, cholinergic and histamine receptors[18] Second-line, broad spectrum antiemetic[16]	3.125 – 6.25 mg, subcutaneously every four to six hours, as needed OR 25 mg/24 hours[8]	Monitor for postural hypotension and excessive sedation[18]	25 mg/mL solution for injection (1 mL ampoules) Only prescription**

CSCI = continuous subcutaneous infusion

* Unapproved route

† Unapproved indication

** Three brands of levomepromazine injections are available on prescription: Levomepromazine (Wockhardt), Levomepromazin-Neuraxpharm (Section 29) and Nozinan (Section 29)

life. Food and fluids should be offered but reducing portion sizes or modifying the consistency may be required (see: "Non-pharmacological management strategies for nausea and vomiting").

Address modifiable causes early

Any modifiable causes of nausea and vomiting should be addressed first:[8]

Long-term medicines associated with nausea and vomiting include cardiac medicines (e.g. digoxin), NSAIDs and anticonvulsants.[2,3] Abrupt discontinuation of corticosteroids can result in adrenal insufficiency which may manifest as nausea.[2] Non-essential medicines should be discontinued (if they have not been already),[3] e.g. statins, oral hypoglycaemics. Possible exceptions include anticonvulsants or other medicines used to control symptoms, e.g. diuretics for heart failure, that could impact comfort or cause distress if withdrawn.[9,10]

Constipation in the last days of life may be caused by medicines, dehydration, reduced food intake, limited movement or bowel obstruction.[11] The benefit of pharmacological treatment may be limited at this time and is often not given, but if constipation is causing significant discomfort and thought to be contributing to nausea and vomiting, pharmacological treatment may be considered. Suppositories (e.g. bisacodyl, glycerol) or enemas (e.g. sodium citrate, phosphate) are preferred as oral medicines may no longer be appropriate.

N.B If constipation is causing distress and treatment is not successful, a rectal examination may be appropriate to rule out faecal impaction or bowel obstruction resulting from a rectal tumour.[10]

Switching opioids in the last days of life may not be practical

Opioids are regularly prescribed for patients receiving end of life care.[12] In some cases, the opioid may be able to be changed or the dose reduced if the usual adverse effects of opioids are intolerable, i.e. nausea, vomiting. However, in the setting of managing a patient in the community in the last days of life, often this is not practical, e.g. due to fixed doses established in syringe drivers, and higher doses needed to manage pain, therefore patients are usually managed by adding an antiemetic rather than withdrawing or changing the opioid. Patients who are vomiting and are currently taking oral opioids should be changed to subcutaneous delivery.[13]

Non-pharmacological management strategies for nausea and vomiting

Patient comfort is the main goal of management for nausea and vomiting. Non-pharmacological strategies to reduce nausea and vomiting include:[1]

- Positioning the patient upright when eating or drinking to reduce the likelihood of choking or aspiration
- Removing sights or smells that are known to trigger symptoms, e.g. certain foods, cooking aromas, deodorants/perfumes, air fresheners
- Adequate ventilation – open windows for fresh air, use of a fan
- Offering small quantities of food if the patient can still eat
  - Some patients may want their favourite food while others may prefer bland foods
  - Provide a variety of fluid options, e.g. water, juice, clear soup
  - Using a straw may make fluid intake easier
  - Offer ice blocks or ice chips if unable to tolerate oral fluids
  - Occasionally, a nasogastric tube may be appropriate for patients with persistent vomiting.[14] Discuss with the local hospice or palliative care team.
- Maintaining good oral hygiene – patients may benefit from regular mouth rinsing, brushing of teeth or cleaning of dentures
  - Mouthwash can be made at home by mixing half a teaspoon of baking soda and half a teaspoon of table salt in 250 mL of water
- Relaxation and distraction techniques, e.g. listening to music, spending time with family/whānau
- Visualisation or guided imagery – allows patients to distance themselves from their symptoms; suggest they imagine themselves in a place associated with happy memories, e.g. favourite holiday spot
- Complementary or alternative remedies for nausea, e.g. ginger ale or peppermint tea
  - Some patients may wish to include Rongoā Māori or other traditional remedies in their care, e.g. bark of the karamu plant (*Coprosma robusta*) for vomiting[15]
- The use of acupressure, either via family/whanau applying pressure to specific points or the use of wrist bands

Pharmacological management of nausea and vomiting

Pharmacological treatments are usually required in addition to non-pharmacological techniques to manage nausea and vomiting (Figure 2). Consider the most likely causes of a patient's nausea or vomiting and the mechanisms of action of available antiemetics when deciding on the most appropriate treatment (Table 1 and see: "The pathophysiology of nausea and vomiting is complex").[10] Patients with multiple possible causes of nausea or vomiting may benefit from a combination of antiemetics;[10] discuss with the local hospice or palliative care team.

Patient is already prescribed one or more antiemetic?

Yes

Convert current oral antiemetic medicines to subcutaneous doses and these can be administered as either regular bolus doses via subcutaneous line or 24-hour CSCI. Examples of subcutaneous antiemetic doses:

- **Haloperidol** 0.5 – 1 mg at night or twice daily (or 1 – 3 mg/24 hours). Patients whose symptoms are not adequately controlled with 3 mg haloperidol over 24 hours are usually switched to levomepromazine (occasionally a higher dose of haloperidol, e.g. up to 5 mg over a 24-hour period, may be beneficial); and/or
- **Metoclopramide** 10 mg three to four times daily (or 30 – 60 mg over a 24-hour period*, however, in practice, patients whose symptoms are not adequately controlled with 40 mg metoclopramide, over 24 hours should be switched to levomepromazine); and/or
- **Cyclizine** 75 – 150 mg, over a 24-hour period†

"Breakthrough" doses of antiemetic medicines should also be prescribed

No

Prescribe (via subcutaneous line) either:

- **Haloperidol** 0.5 mg, every four hours, as needed (maximum dose of 5 mg over a 24-hour period, however, in practice, patients whose symptoms are not adequately controlled with 3 mg haloperidol, over 24 hours should be switched to levomepromazine); or
- **Metoclopramide** 10 mg, every six to eight hours, as needed (maximum dose of 40 mg over a 24-hour period)

Consider switching to CSCI in patients who experience a sufficient improvement in symptoms

Depending on response, patients may require only one antiemetic medicine or a combination of medicines‡

"Breakthrough" doses of antiemetic medicines should also be prescribed

Review the patient within six hours of initiating antiemetic:
For persistent nausea and vomiting in patients taking maximum doses of (or cannot tolerate) first-line antiemetics, clinicians should prescribe levomepromazine (3.125 – 6.25 mg, every four to six hours, as needed). This can either replace or be added to the current antiemetic regimen.

- Consider switching to CSCI up to a maximum dose of 25 mg over a 24-hour period in patients who experience a sufficient improvement in symptoms

"Breakthrough" doses of levomepromazine should also be prescribed.

If nausea or vomiting remains or is worsening, or if additional support is required, contact the local hospice or palliative care team for advice

* Higher doses of metoclopramide, e.g. 60 mg over a 24-hour period, should be reserved for managing nausea and vomiting that is likely caused by delayed gastric emptying (without obstruction)

† Subcutaneous cyclizine should not be given as a bolus dose due to adverse reactions at the injection site

** Cyclizine and metoclopramide should not be prescribed together if the likely cause of nausea and vomiting is delayed gastric emptying

Figure 2. Anticipatory prescribing for patients with nausea and vomiting. Adapted from *South Island Palliative Care Workstream, 2020*.[8, 16]

CSCI = continuous subcutaneous infusion

First-line treatment options for nausea and vomiting

If the patient is not currently taking an oral antiemetic, subcutaneous haloperidol (unapproved route) is an appropriate first-line pharmacological treatment option, unless contraindicated e.g. Parkinson's disease, prolonged QT-interval.[8, 16] Subcutaneous metoclopramide (unapproved route) or cyclizine (unapproved route) are alternative first-line antiemetics for patients who cannot take haloperidol.[8] In practice, haloperidol is preferred in the last days of life as it has a lower risk of adverse effects in people who are frail compared to other first-line options and may have multiple indications, therefore reducing polypharmacy, e.g. it is also used to treat delirium.

Recommended doses:

- 0.5 mg haloperidol, subcutaneously every four hours, as needed (maximum dose 5 mg in 24 hours).[8] N.B. The decision to switch to levomepromazine (see below) is usually considered if symptoms are not adequately controlled with 3 mg haloperidol, subcutaneously over 24 hours.
- 10 mg metoclopramide, subcutaneously every six to eight hours, as needed (usually recommended not to exceed 40 mg in 24 hours)[8]
- 75 – 150 mg cyclizine over 24 hours, via subcutaneous infusion (subcutaneous bolus doses are not recommended due the risk of injection site reactions[17])[16]

Patients who are already taking an oral antiemetic should have their current regimen converted to subcutaneous doses which can be given either as bolus doses or over a 24-hour period using a continuous subcutaneous infusion (Table 1).[8]

Ideally, patients should be reassessed for treatment effectiveness and adverse effects within six hours.[8] It is recommended to convert "as needed" doses to a 24-hour dose for continuous subcutaneous infusion in patients who experience an improvement in symptoms.[8] Additional "breakthrough" subcutaneous doses of the antiemetic should also be prescribed.[8]

Practice point: Ondansetron is not generally recommended to manage nausea and vomiting in patients receiving palliative care as it may exacerbate opioid-related constipation.[2]

Levomepromazine is a second-line treatment option for nausea and vomiting

Levomepromazine* is the most suitable option for patients with persistent nausea or vomiting (unapproved indication) despite taking the maximum tolerable doses of first-line antiemetics.[8] It acts on multiple different receptors, making it suitable for patients with nausea and vomiting due a combination of causes.[10]

The previous antiemetic can be stopped and the patient switched to levomepromazine or it can be added to their regimen if there has been a partial effect from the previous medicine. The recommended initial dose is 3.125 – 6.25 mg of subcutaneous levomepromazine, every four to six hours, as needed (maximum dose 25 mg in 24 hours).[8] If the patient requires more than two "as needed" doses in a 24-hour period, increase the dose.[1] There is a risk of excessive sedation when higher doses of levomepromazine are used.[18]

* Previously known as methotrimeprazine

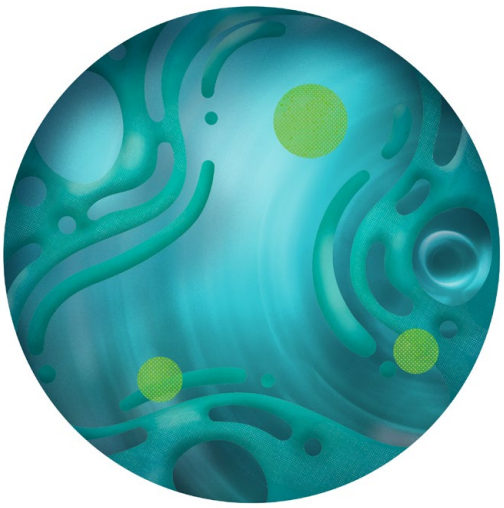
A combination of antiemetic medicines may be required for some patients

Nausea and vomiting often has multiple causes, making symptom management difficult.[3] Patients who do not have a sufficient clinical response to a single antiemetic medicine may benefit from a combination of antiemetic medicines that act via different mechanisms of action (Figure 2).[10] It is recommended to discuss patients with refractory nausea and vomiting with your local hospice or palliative care team.

Practice point: Avoid prescribing anticholinergic medicines (e.g. cyclizine, hyoscine butylbromide) concomitantly with prokinetic medicines (e.g. metoclopramide) in patients with nausea and vomiting attributed to delayed gastric emptying as the anticholinergic effects may reduce the beneficial effects on gastric motility.[3]

Prescribing benzodiazepines for nausea and vomiting

Benzodiazepines, e.g. midazolam, should be considered in patients whose nausea and vomiting may be related to fear or anxiety, e.g. administer beforehand if anticipation of a treatment or procedure is a likely cause of symptoms.[3, 10]



Acknowledgement: Thank you to the following experts for review of this article:

- **Dr Kate Grundy**, Palliative Medicine Physician, Clinical Director of Palliative Care, Christchurch Hospital Palliative Care Service and Clinical Lecturer, Christchurch School of Medicine
- **Vicki Telford**, Clinical Nurse Specialist, Nurse Maude Hospice Palliative Care Service, Christchurch
- **Dr Helen Atkinson**, General Practitioner and Medical Officer, Harbour Hospice
- **Dr Robert Odlin**, General Practitioner, Orewa Medical Centre
- **Fraser Watson**, Extended Care Paramedic Clinical Lead, Hato Hone St John

Article supported by Te Aho o Te Kahu – Cancer Control Agency

N.B. Expert reviewers do not write the articles and are not responsible for the final content. bpac^{nz} retains editorial oversight of all content

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This article is available online at:
www.bpac.org.nz/2023/last-days-of-life/nausea.aspx