# Management of nausea and vomiting in palliative care

***Nausea and vomiting are common symptoms in palliative care and can be highly distressing to patients. This review discusses the mechanisms by which nausea and vomiting are triggered, using case studies to highlight the most common scenarios and how to manage these.***

Nausea and vomiting are common symptoms in palliative care with prevalence reported as up to 70% of patients with advanced cancer, and up to 50% with non-malignant palliative conditions (Harris, 2010). They are particularly distressing symptoms, impacting on patients' quality of life, and can be difficult to treat (Harris, 2010). This article discusses common causes of nausea and vomiting in these patients and the modes of action of commonly used anti-emetics. It uses patient cases to improve understanding of the mechanisms behind nausea and vomiting, enabling readers to select the most appropriate treatment strategy.

## What is nausea and vomiting?

An important part of history taking is to differentiate between the nausea and vomiting as these are two distinct symptoms, although they may be linked. Nausea is an unpleasant feeling in the throat or stomach of needing to vomit, associated with autonomic symptoms. Vomit is expulsion of contents from the stomach through the mouth.

## What causes nausea and vomiting?

The pathogenesis of nausea and vomiting is complex. It is centred on a functional area in the brainstem called the vomiting centre. The vomiting centre receives emetogenic signals from four main areas (Palazzo and Strunin, 1984):

- Chemoreceptor trigger zone in the base of the fourth ventricle
- Cerebral cortex
- Vestibular nuclei
- Gastrointestinal tract (*Figure 1*).

### Chemoreceptor trigger zone

This is activated by various receptors, e.g. dopamine, serotonin. The chemoreceptor trigger zone sits outside the blood–brain barrier. Therefore, dopamine receptors are stimulated by high blood concentration levels of emetogenic substances, e.g. calcium ions, opioids, urea.

### Cerebral cortex

The cerebral cortex is thought to be stimulated via histamine and acetylcholine receptors. These are triggered by emotion or anxiety, raised intracranial pressure or meningeal irritation.

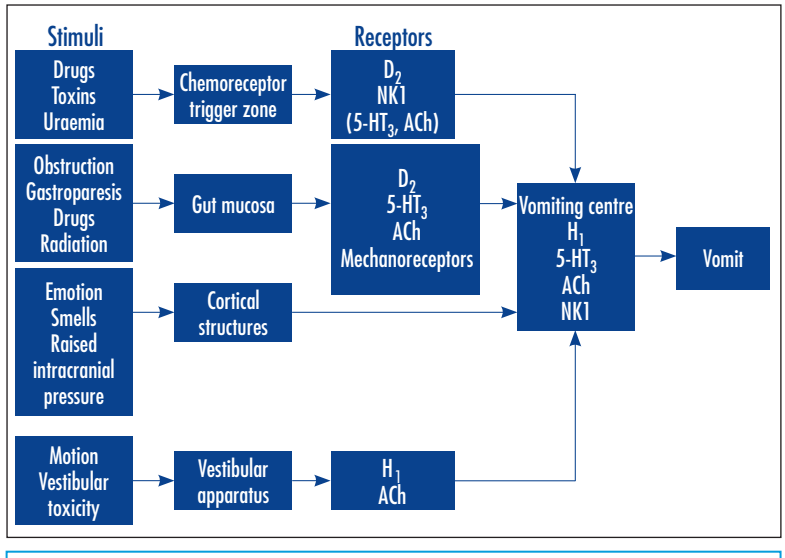
### Vestibular nuclei

The vestibular system is also mediated by histamine receptors which are triggered by movement in the inner ear.

### Gastrointestinal tract

Peripheral stimuli of the vomiting centre are mainly found in the gastrointestinal tract. Serotonin (5-HT) is released from cells in the gastrointestinal mucosa in response to drugs, radiotherapy and bacterial exotoxins. Mechanical distortion of the bowel or other viscera also stimulates histamine-1 receptors and acetylcholine receptors. This is fed back via the vagus and spinal sympathetic nerves to the vomiting centre (Becker, 2010).

***Figure 1. Pathogenesis of nausea and vomiting. Adapted from Palazzo and Strunin (1984).***

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## Common anti-emetics

*Table 1* outlines commonly used anti-emetics, recommended dose and route of administration, and key facts including which causes of nausea or vomiting the drug should target. The case studies will give examples of when to use each medication.

### Other anti-emetics

Areprepitant is an NK1 antagonist approved for prevention of acute and delayed nausea and vomiting associated with moderately and highly emetogenic chemotherapy (Joint Formulary Committee, 2013); it is currently not widely used in palliative care as its usefulness in this setting is unclear. Clinical use and randomized controlled trials have focused on highly emetogenic chemotherapy. It is also relatively more expensive (Rangwala et al, 2012). A dose of 125 mg is given 1 hour before chemotherapy then the dose is 80 mg a day for 2 days.

**Table 1. Common anti-emetics**

| Drug | Receptors | Dose | Comments |
|---|---|---|---|
| Metoclopramide | $D_2$ antagonist<br>5-$HT_4$ agonist | 10 mg three times a day<br>Can be given orally or subcutaneously<br>Up to 100 mg/24 hours via continuous subcutaneous infusion but doses above 30 mg/24 hours should only be initiated on specialist advice | Prokinetic, therefore useful for gastroparesis and partial bowel obstruction without colic<br>Dopamine antagonist therefore useful for chemical-induced nausea<br>In view of extrapyramidal side effects use the smallest dose for the shortest time<br>Monitor for Parkinsonian side effects and avoid in patients with Parkinsonism<br>Metoclopramide can affect the QT interval so use with caution in those with cardiac conduction disturbances and those on other agents which may prolong the QT interval<br>Doses above 10 mg three times a day are used off license. The Medicines and Healthcare products Regulatory Agency recommends a maximum dose in 24 hours of 30 mg, for 5 days because of the neurological side effects |
| Cyclizine | Acetylcholine antagonist (also referred to as a antimuscarinic), histamine antagonist | 50 mg three times a day up to 150 mg/24 hours<br>Can be given orally or subcutaneously at the same dose | In view of receptor action considered to be useful for cerebral cortex and vestibular nuclei-related causes, but trial evidence of this use is lacking.<br>Dry mouth and constipation are side effects which may limit its use |
| Haloperidol | $D_2$ antagonist | 0.5–1.5 mg as required<br>Up to 5 mg in 24 hours, can be given orally or subcutaneously at the same dose | Chemical nausea, i.e. via chemoreceptor trigger zone<br>Avoid in Parkinsonism. It can cause QT prolongation so caution in patients with cardiac conduction disturbances or already on other agents which may prolong the QT interval<br>Haloperidol can also lower seizure threshold so monitor those with known seizure risk or pre-existing seizures disorders |
| Ondansetron/ granisetron | 5-$HT_3$ antagonists | Ondansetron 4 mg as required, up to 16 mg in 24 hours orally or subcutaneously at the same dose, granisetron 1–2 mg as required, maximum 2 mg in 24 hours | Used in chemotherapy-related nausea and vomiting, consider as an alternative in obstruction<br>With longer term use is constipating |
| Levomepromazine | $D_2$ antagonist, histamine antagonist, acetylcholine antagonist (antimuscarinic), 5-$HT_2$ antagonist | 6.25 mg as required orally or subcutaneously<br>25 mg maximum dose in 24 hours (for nausea – has alternative indications) | 'Broad spectrum' anti-emetic as covers several receptors, but can be sedating which limits use |
| Domperidone | $D_2$ antagonist | 10–20 mg three times a day orally or per rectum<br>Maximum 60 mg in 24 hours | Used for chemical nausea and is a prokinetic<br>In comparison to metoclopramide and haloperidol, it does not cross the blood–brain barrier so is a suitable alternative where Parkinsonian side effects are a concern<br>Haloperidol has 10 times the affinity for $D_2$ receptors hence it is first choice in chemical-induced nausea. Domperidone's prokinetic effect comes from its $D_2$ antagonism whereas metoclopramide has additional $5HT_4$ activation, but randomized controlled trials have shown no advantage<br>Consider switching from subcutaneous metoclopramide to domperidone if a patient can take oral medication<br>Domperidone is only available in oral or rectal preparations<br>Caution, it is associated with QT prolongation |

From Ellidukuz and Kaya (2003), Hedges et al (2003), Camilleri et al (2012), Joint Formulary Committee (2013), Medicines and Healthcare products Regulatory Agency (2013). Also see *Palliative Care Formulary 4* (Twycross and Wilcock, 2011) for further details

### Beware polypharmacy

Some anti-emetics have opposing actions or additive toxicities. For example:

- Using a drug for prokinesis, e.g. metoclopramide or domperidone, with an antimuscarinic, e.g. cyclizine. Prokinetics act through a cholinergic pathway which is competitively blocked by antimuscarinic drugs (Schuurkes et al, 1986)
- Metoclopramide, levomepromazine and haloperidol are all centrally-acting antidopaminergic drugs and in combination increase the risk of extrapyramidal side-effects (Jackson et al, 2008)
- Haloperidol and domperidone are both associated with QT prolongation.

### Unlicensed use of medications

Several of the drugs used commonly in palliative care, e.g. haloperidol for nausea and the use of metoclopramide above 30 mg a day, are unlicensed indications for these drugs. This is acceptable when clinical need cannot be met by licensed versions (Joint Formulary Committee, 2013).

### Difficult to treat nausea and vomiting

Levomepromazine has a broad spectrum of action and should be considered if the patient's symptoms have not resolved with targeted therapies, if nausea and vomiting is multifactorial or the underlying causal mechanism cannot be identified.

Some combinations of anti-emetics can be useful if their mode of action targets different receptors. Levomepromazine plus a 5-$HT_3$ antagonist gives additional receptor coverage. A combination including any of cyclizine, a 5-$HT_3$ antagonist and haloperidol may also be useful.

## Approach to assessment and management of nausea and vomiting

The management of nausea and vomiting involves the treatment of reversible causes, the use of pharmacological and non-pharmacological measures, and the management of associated complications including hydration and nutritional support. Overall there is a paucity of robust trials supporting the use of individual anti-emetics in patients receiving palliative care (Glare et al, 2004). Cochrane reviews of two commonly used agents, haloperidol and levomepromazine, did not identify randomized controlled trials that met inclusion criteria (Perkins and Dorman, 2009; Darvill et al, 2013).

The authors describe a commonly used approach based on identification of the aetiology of nausea and vomiting and the neuropharmacology of the emetic pathway. Evidence from uncontrolled prospective studies supports this approach with complete amelioration of nausea in 56–82% and vomiting in 84–89% of cancer patients (Bentley and Boyd, 2001; Stephenson and Davies, 2006). However, randomized controlled trials in advanced cancer show lower response rates: 23–36% for nausea and 18–52% for vomiting with similar response rates for aetiology based and empirical drug selection (Glare et al, 2004). This highlights the need for:

- Individualization of treatment – selecting management options based on a patient's diagnosis, comorbidities, medication, lifestyle and preferences
- Establishment of realistic expectations
- Patient education
- Regular review of treatment efficacy.

The key to effective treatment of nausea and vomiting is diagnosis of the underlying cause(s) by means of a thorough assessment.

- Distinguish between nausea and vomiting
- May be multifactorial
- Triggers, e.g. medications, movement, recent chemotherapy and/or radiotherapy
- Frequency and timing of episodes
- Relation to meals
- Bowel frequency (treat constipation)
- Dysphagia – solids or liquids, intermittent
- Dyspepsia – patients can confuse this with nausea.

### Reverse the reversible

After a thorough history consider:

- Constipation: laxatives, suppositories and/or enema
- Treat oro-pharyngeal thrush and optimize mouth care
- Review medications: antimuscarinics (e.g. amitriptyline) and opioids can cause gastric stasis. Opioids and other medications can cause chemical-related nausea
- Antibiotics: antibiotics and the underlying infection can cause nausea and vomiting
- Biochemical: check and treat hypercalcaemia, uraemia
- Other symptoms: severe pain and cough can contribute to nausea and vomiting
- Pharmacological and behavioural management of anxiety.

### Route of administration

Oral anti-emetics may be ineffective if patients are vomiting or gastrointestinal absorption is impaired. Consider using subcutaneous administration initially to ensure medications are being absorbed. Once vomiting is controlled, and provided the gut is functioning, consider switching to the oral route.

## Case studies

The following cases illustrate commonly encountered nausea and vomiting scenarios in palliative care. Working through these will outline a logical approach to management.

### Case 1

Mrs Smith is a 77-year-old woman with metastatic ovarian cancer and known peritoneal disease. She reports a 2-week history of vomiting. Initially her vomiting had been once a day and she had managed to eat small

amounts. Now she has completely lost her appetite and has not opened her bowels for 3 days but is passing minimal flatus. She has large volume vomits approximately three times a day, does not have colicky abdominal pain but feels nauseous. She had already decided before this that she did not want to have any further invasive tests or treatment as her general condition has worsened.

On examination her abdomen is slightly distended and she has sparse bowel sounds. You diagnose her clinically with sub-acute bowel obstruction.

**Possible causes of obstruction**

Possible causes of obstruction can include the primary tumour or metastases (peritoneal metastases in this case), past treatment, e.g. adhesions or post-radiation fibrosis, or unrelated condition, e.g. strangulated hernia.

In patients with bowel obstruction there are two approaches:

**Complete obstruction:** If the bowel is completely obstructed, i.e. evidence of colicky abdominal pain, no flatus, no bowel sounds, then treatment should avoid prokinetics as these will worsen colic. The authors recommend getting expert oncology and/or palliative medicine advice if a patient with malignant bowel obstruction is not under the care of an oncology team. Consider procedural interventions for relief of obstruction or symptom management in selected patients, including stenting, surgical bypass or a venting gastrostomy.

Give anti-emetics subcutaneously as they will not be absorbed after oral administration and will therefore be ineffective. To treat vomiting by reducing gastrointestinal secretions, use hyoscine butylbromide or hydrobromide (both also treat colic). Octreotide, a somatostatin analogue which does not treat colic, may be of benefit if hyoscine has not adequately reduced the volume and/or frequency of vomiting. A trial of dexamethasone could be considered, on expert advice, if there is an inflammatory component to the obstructive lesion. If nausea is present use cyclizine or haloperidol first line, and then levomepromazine second line because of its broad action.

With obstruction above the distal small bowel it may not be possible to stop vomiting completely. Aim to reduce the frequency and volume as much as possible. If symptoms remain refractory to pharmacological treatment consider a wide bore nasogastric tube for symptomatic relief if acceptable to the patient.

Discuss the pros and cons of continuing to eat and drink and offer dietary advice. While oral food and fluids may provide pleasure they may contribute to the volume and frequency of vomiting. Ensure the patient receives adequate mouth care.

**Incomplete bowel obstruction:** If the patient has incomplete obstruction, i.e. no evidence of colic, some flatus, then treatment could initially focus on prokinesis with metoclopramide. Give anti-emetics subcutaneously. Address constipation with a stool softener such as sodium docusate if there is evidence of faecal loading. Monitor symptoms as it may progress into complete bowel obstruction, or resolve, and so need management changing.

## Case 2

Mrs Jones has metastatic breast cancer with multiple bony metastases. She has become nauseous and increasingly confused at home. She describes constant background nausea with no vomiting and the smell of food makes her symptoms worse. She has non-specific abdominal pain and worsening hip pain. She is admitted to hospital for further investigations and is found to be hypercalcaemic. She is started on fluids and will have a bisphosphonate after hydration. However, she is feeling very nauseated and you decide to start an anti-emetic.

This case describes a chemical cause for nausea – hypercalcaemia. While benefit from the treatment of her hypercalcaemia is awaited, anti-emetics can be started and regularly reviewed as they may only be needed for a short period. The first-line treatment should be haloperidol subcutaneously or orally to focus on the chemoreceptor trigger zone.

## Case 3

Mr Long has been diagnosed with an inoperable glioma. He has been suffering from headaches and blurred vision as well as nausea. His nausea is worse in the morning, lying flat, and when he rolls over in bed. He does vomit, usually in the morning. There is no other cause for nausea in his history.

This patient has raised intracranial pressure caused by a glioma. This triggers the receptors in his cerebral cortex, and therefore medications should be targeted at this area. The first-line treatment should be high-dose steroids (if not already on these) to reduce peri-tumour oedema and decrease intracranial pressure. Use a starting dose 8–16 mg and monitor for effect. Ensure a clear dose reduction regimen is in place, blood glucose levels are monitored and consider gastric protection. If there is no improvement with steroids after 48 hours then reduce and stop within a week. Second-line treatment is cyclizine in combination with steroids. Ensure this is prescribed as rescue medication if not given regularly.

## Case 4

Mrs Jones has pancreatic cancer with large volume liver metastases. She has found that over the past few weeks her oral intake has decreased and she is losing weight. She finds that on eating a very small amount she feels full (early satiety) and vomits shortly after. In between meals, and when she does not eat, she can feel slightly nauseous but does not tend to vomit, experiences dyspepsia, feels bloated and belches more frequently than usual.

Causes of gastric stasis can include:

- Constipation
- Drugs, e.g. opioids, antimuscarinics

- Tumours around gastric outlet, e.g. cancer of the head of the pancreas, large liver metastases
- Autonomic neuropathy (paraneoplastic or diabetic)
- Retroperitoneal disease
- Neurological disorders
- Post-surgical.

The aim in gastric stasis is to aid gastric emptying. First-line treatment should be metoclopramide or domperidone (prokinetics). Other advice for the patient includes eat little and often and avoid carbonated drinks. Consider use of $H_2$-receptor antagonists or proton pump inhibitors; both reduce gastric acid output and the former reduces the volume of gastric secretions (Clark et al, 2009).

## Conclusions

This article provides an approach to management of nausea and vomiting based on targeting the cause and application of the correct drug. A thorough history and examination is key, as well as treating reversible causes. An awareness of patients' comorbidities is essential to ensure safe prescribing. BJHM

### KEY POINTS

- Distinguishing between nausea and vomiting and establishing the cause of symptoms are the keys to successful treatment.
- The vomiting centre receives emetogenic signals from four main areas, trying to identify which area or areas have been triggered will guide anti-emetic selection.
- Reverse the reversible – even if these are not the sole cause of a patient's nausea or vomiting, treatment of these can have a profound effect on symptoms.
- Do not forget to give patients practical advice such as trying small meals and avoiding strong smells.
- Persistent nausea and vomiting requires regular anti-emetic treatment.
- Consider the route of administration and have a low threshold for using subcutaneous therapies. Apparent failure of medication given orally may reflect poor gastrointestinal absorption rather than a lack of pharmacological efficacy.
- Most hospitals have access to a specialist palliative care team who can be contacted for advice.

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