Nausea and Vomiting in Palliative Care

Nausea and vomiting are distressing symptoms in patients receiving palliative care for advanced cancer. Studies suggest, however, that they are less common than was once thought. Effective management can significantly improve the quality of life in these patients. An understanding of the likely causes of these symptoms is required for accurate assessment and treatment, resulting in better symptom control.

Epidemiology

Recent studies suggest that the prevalence of nausea and vomiting in patients receiving palliative care is less common than was once thought. A systematic review found that pain, breathlessness and fatigue were all more common. The review reported a prevalence of 30% in end-stage kidney disease patients, at least 17% of heart failure patients and at least 6% of cancer patients. Nausea was most commonly reported in late-stage AIDS patients (43%). The prevalence increases towards the end of life; one study reported a figure of 71% in the last 1-2 weeks of life.\(^1\)

15-30% of patients given morphine for chronic cancer pain experience long-term nausea.\(^2\)

Causes of nausea and vomiting\(^3\)

A greater understanding of the physiological mechanisms causing nausea and vomiting in the palliative care patient will help to select the most appropriate treatment. There are four main sites of activity:\(^4\)

- The vomiting centre (VC) - this is situated in the brainstem and has histamine (H1), acetylcholine (ACh) and 5-hydroxytryptamine 2 (5-HT2) receptors.
- The chemoreceptor trigger zone (CTZ) - located in an area of the brain that has no blood-brain barrier, which enables various drugs, toxins and metabolites to access the site. It has dopamine (D2) and 5-HT3 receptors.
- The cerebral cortex - there are multiple receptors which can be triggered by anxiety. Also, mechanoreceptors in the meninges are sensitive to changes in intracranial pressure.
- The vestibular system - changes in movement or diseases of the ear may stimulate the ACh or H1 receptors, triggering nausea or vomiting.
- Gut and serosal surfaces in the viscera - 5-HT3 receptors in the gut are stimulated by drugs, radiotherapy and bacterial exotoxins. H1 and ACh receptors in the gut and the serosal surfaces of other viscera are stimulated by mechanical distortion.

Blocking the receptors at various sites is the mainstay of the drug management of nausea and vomiting. In cancer patients, it is helpful to group the principal causative pathways into seven syndromes, based on receptor sites, clinical features and treatment.
<table>
<thead>
<tr>
<th>Underlying cause</th>
<th>Examples</th>
<th>Mechanisms leading to nausea and vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritation or stretching of the meninges.</td>
<td>Raised intracranial pressure caused by intracranial tumour.</td>
<td>Not known, may involve meningeal mechanoreceptors.</td>
</tr>
<tr>
<td>Bowel obstruction secondary to malignancy.</td>
<td>Mechanical - intrinsic or extrinsic by tumour. Functional - disorders of intestinal motility secondary to malignant involvement of nerves, bowel muscle or blood supply. Paraneoplastic neuropathy.</td>
<td>Stretching of mechanoreceptors.</td>
</tr>
<tr>
<td>Anxiety-induced.</td>
<td>Concern about diagnosis, treatment, symptomatology, social issues, anticipatory emesis with cytotoxics.</td>
<td>Multiple receptors in the cerebral cortex.</td>
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Assessment of the palliative care patient with nausea and vomiting

An accurate assessment of patients with nausea and vomiting will allow for appropriate management of the patient and better symptom control.

Assessment of the patient may include the following:

**History**
- Timing of symptoms - after meals (e.g., gastric stasis), on movement (e.g., vestibular disease), when lying flat (e.g., due to meningeal irritation or raised intracranial pressure).
- Food and fluid intake.
- Drugs, including over-the-counter ones and alternative therapies.
- Pain.
- Bowel habit.
- Urinary output.
- Affect on daily life.

**Examination**
- Assessment of hydration.
- Signs of infection - e.g., fever.
- Presence of jaundice.
- Neurological examination, including examination of the optic fundi to exclude papilloedema.
- Rectal examination.
- Abdominal examination - tenderness, distension, ascites, masses, hepatomegaly.
Depending on the findings of the history and examination, further investigations may be performed to look for the underlying cause of the symptoms - for example:

- Urea and electrolytes
- Serum calcium level
- LFTs
- FBC and differential
- Urine culture
- Abdominal ultrasound/X-ray
- Endoscopy
- CT/MRI scan

At the end of the assessment it should be possible to categorise the cause into one of the following syndromes:[4]

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Clinical features may include</th>
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</thead>
<tbody>
<tr>
<td>Irritation or stretching of the meninges.</td>
<td>• Headache and nausea on lying flat, focal neurological signs and papilloedema.</td>
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<tr>
<td></td>
<td>• May be confirmed by CT and MRI scans.</td>
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<tr>
<td>Pelvic or abdominal tumour.</td>
<td>• Nausea and vomiting may be caused by stretching of the mechanoreceptors. Poorly localised pain, with or without radiation, may also be present.</td>
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<tr>
<td></td>
<td>• Radiology is usually required to confirm diagnosis.</td>
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<tr>
<td>Malignant bowel obstruction.</td>
<td>• The onset is usually insidious and obstruction remains partial. This is reflected in the presentation.</td>
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<tr>
<td></td>
<td>• Abdominal pain is present in 90% of patients, with superimposed colic in 70%.</td>
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<td></td>
<td>• Abdominal distension is less usual if the bowel is stuck down by omental metastases or in high obstruction.</td>
</tr>
<tr>
<td></td>
<td>• Vomiting is an early symptom in high obstruction and may be copious. It is a later feature in large bowel obstruction.</td>
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<td></td>
<td>• Investigations are appropriate to confirm the diagnosis, and constipation should be excluded.</td>
</tr>
<tr>
<td>Gastric stasis.</td>
<td>Features may include:</td>
</tr>
<tr>
<td></td>
<td>• Fullness.</td>
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<td></td>
<td>• Epigastric pain.</td>
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<td>• Acid reflux.</td>
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<td></td>
<td>• Hiccups.</td>
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<tr>
<td></td>
<td>• Early satiety.</td>
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<td></td>
<td>• Large-volume vomiting with little preceding nausea.</td>
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<td>• All symptoms being relieved by vomiting.</td>
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<tr>
<td>Chemically/metabolically induced nausea.</td>
<td>• The onset of symptoms may coincide with starting medication.</td>
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<td></td>
<td>• Hypercalcaemia may be indicated by drowsiness (and in fact drowsiness may be the only feature in 50%).</td>
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<td>• Confusion is common.</td>
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<td>• Polyuria and nocturia may also be present but marked if there is coincidental dehydration.</td>
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<td></td>
<td>• Blood biochemistry will confirm the diagnosis.</td>
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<tr>
<td>Anxiety-induced nausea.</td>
<td>This is usually diagnosed by exclusion and suggested by the symptoms and signs of stress.</td>
</tr>
<tr>
<td>Movement-related nausea and vomiting.</td>
<td>These may be features of abdominal tumour, vestibular disease or recent commencement or increase of opioids.</td>
</tr>
</tbody>
</table>
Reversible causes of nausea and vomiting should be corrected first wherever possible:
- Hypercalcaemia may respond to rehydration and the use of bisphosphonates.
- Uraemia may be corrected by rehydration using intravenous (IV) fluids in some patients.
- Gastric ulceration or gastritis may respond to treatment with proton pump inhibitors or H2-receptor antagonists.
- Infection should be treated with appropriate antibiotics.
- Constipation may respond to the use of laxatives or enemas.
- Corticosteroids, such as dexamethasone, may reduce the size of the tumour or reduce oedema surrounding the tumour.
- Anxiolytics may have a role in some patients in whom anxiety is thought to be playing a part.

Treatment in specific scenarios[^4,^5]

First-line treatment should be tailored according to the identified clinical syndrome and likely receptors to be targeted. A non-oral route should be used for the first 48 hours, changing to an oral preparation once the symptoms have improved.

**Irritation or stretching of the meninges**
- If the patient has raised intracranial pressure, refer for consideration of radiotherapy.
- High-dose dexamethasone (maximum 16 mg daily for 4-5 days, subsequently reducing to 4-6 mg daily) may help.[^5]
- Add cyclizine 25-50 mg three times a day or levomepromazine once at bedtime (2.5-5 mg subcutaneously or 12.5 mg oral dose). Higher doses of levomepromazine can cause significant adverse effects (postural hypertension, dry mouth, sedation).[^1]

**Pelvic or abdominal tumour**
- Cyclizine is helpful, as it blocks ACh and histamine H1 receptors in the vomiting centre that are triggered by the mechanoreceptors in the abdominal and pelvic viscera.
- Try 25-50 mg oral tablets or subcutaneous injection first-line, including when vomiting is aggravated by movement.
- Add dexamethasone if vomiting persists.

**Malignant bowel obstruction**

**Functional or partial bowel obstruction**
- Preserving bowel motility needs to be balanced with the prevention of colic.
- Stop osmotic and stimulant laxatives.
- Docusate is minimally stimulated and should be titrated to produce a comfortable stool without colic. Avoid high-fibre foods and advise taking food and fluids at regular intervals and in small amounts.
- A prokinetic anti-emetic such as metoclopramide or domperidone should be given if the patient continues to pass flatus and does not have colic.
- Prokinetics block dopamine D2-receptor activity in the gut.
- Metoclopramide has a direct excitatory activity and may be better than domperidone for patients in this situation. It may be given as a 10 mg oral dose four times a day or as a 40-60 mg/24-hour continuous subcutaneous infusion.
- Domperidone has a long plasma half-life; a starting oral dose of 20 mg twice a day may be increased if necessary to a 30 mg oral dose, or a 90 mg rectal dose every eight hours.
- Prokinetic drugs should not be given with antimuscarinic drugs (eg, cyclizine, hyoscine), as they are competitively blocked by the latter. If colic develops, stop the prokinetic immediately and treat as obstruction.
- Haloperidol is another option for the management of persistent vomiting or nausea in the absence of colic. It is a specific dopamine D2-receptor antagonist that has a profoundly inhibitory effect on the CTZ. Small doses - eg, 2.5 mg haloperidol once at bedtime by subcutaneous injection - are normally effective.[^6]
- Olanzapine shows potential in the management of nausea in patients with partial bowel obstruction but is not yet licensed for this use.[^7]
Complete bowel obstruction

- The first-line treatment is cyclizine, as it blocks the stimulation of the vomiting centre via the vagal afferents, which happens in complete obstruction. If this fails, change to levomepromazine.
- Large-volume vomiting should be treated with an antisecretory drug.
- A nasogastric tube should be inserted to drain intestinal secretions if there is gastric outflow obstruction with rapid dehydration. This may be removed as soon as control is achieved with medication.
- IV hydration should be commenced or, if the patient is at home, 1000-1500 ml of saline can be given subcutaneously. Ranitidine should be used to reduce volume of gastric secretions.
- Complete distal obstruction may require hyoscine butylbromide or octreotide. One study, reviewing 20 years of experience with octreotide, reported a 60-90% success rate for this indication and recommends it as first-line use.\[8\]
- Consider referring for venting gastrostomy if there is an ongoing need for a nasogastric tube.
- If vomiting persists, consider referring for stent emplacement to overcome obstruction, or consider starting corticosteroids.
- Consider parenteral hydration of fluid to reduce the intensity of nausea in a dehydrated patient. This can be given subcutaneously at home.

Gastric stasis

- Prokinetics such as metoclopramide or domperidone are first-line drugs. See above for details of dosage.
- If prokinetics fail, consider adding therapies which reduce gastric secretions, such as ranitidine or octreotide.

Chemically/metabolically-induced nausea

- Haloperidol is the first-line drug for opioid-induced nausea, kidney disease and hypercalcaemia.\[3, 5\] Hypercalcaemia should also be treated with a bisphosphonate.\[6\]
- A prokinetic may be useful prophylactically when initiating and titrating morphine.
- If nausea develops secondary to cytotoxic therapy or radiotherapy, haloperidol should be used first-line, keeping levomepromazine in reserve should this fail.
- Another option is a specific 5-HT3 antagonist, such as granisetron or ondansetron, which blocks 5-HT3 receptors in the gastrointestinal tract and in the CNS. Palonosetron is licensed for the prevention of nausea and vomiting induced by moderately and severely emetogenic chemotherapy.\[5\]
- Aprepitant, a neurokinin-1 receptor antagonist, is licensed for the prevention of acute and delayed nausea and vomiting associated with cisplatin-cytotoxic chemotherapy. It is often used with dexamethasone and a 5-HT3 antagonist and this combination is being increasingly used as standard therapy in many patients receiving moderately or highly emetogenic chemotherapeutic agents.\[3\]
- A further option occasionally used under specialist care is nabilone, a synthetic cannabinoid with anti-emetic properties, although its use is limited by side-effects such as dizziness and drowsiness. It is particularly useful in patients with nausea and vomiting induced by cytotoxic chemotherapy who are unresponsive to other agents.\[3\]
- Chemotherapy-induced nausea and vomiting in children has been studied in a Cochrane review. This suggested that 5-HT3 antagonists with dexamethasone added were effective, although the risk-benefit profile of additional steroid remained uncertain. Cannabinoids were probably effective but induced more side-effects.\[10\]

Anxiety-induced nausea

- Anxiety is often generated by lack of information or by failure of communication and may be easily resolved with simple explanation and reassurance. More deep-seated anxiety may require the support of other members of the multidisciplinary team, such as psychologists, Macmillan nurses, or spiritual advisers.
- Ensure that all other physical causes of nausea and vomiting have been excluded before attributing the symptoms to anxiety.
- Avoid diazepam, which has a long plasma half-life and may cause excessive sedation when given to palliative care patients who may be elderly, debilitated, have hepatic impairment or be on other therapy such as strong opioids.\[4\]

Motion-Induced nausea

The first-line treatment is cyclizine 25-50 mg every eight hours. Another option is hyoscine hydrobromide, 300 micrograms orally or subcutaneously or 1000 micrograms/24 hours transdermally. Cinnarizine is worth trying second-line, if these fail.

Nausea and vomiting of uncertain origin

There will be cases where the cause of nausea or vomiting remains uncertain, or where the prognosis does not warrant subjecting the patient to further invasive investigations. In such patients the use of a broad-spectrum anti-emetic is appropriate. Levomepromazine blocks 5-HT2, histamine H1 and ACh receptors and is the most practical option.\[4\]

Further reading & references

- Nausea and vomiting: Macmillan Cancer Support
- Overview of chemotherapy nausea and vomiting, Bandolier
- Kulaš G, Managing Nausea
- Palliative care - nausea and vomiting: NICE CKS, July 2015 (UK access only)
- British National Formulary (BNF); NICE Evidence Services (UK access only)

3. Kulaš G, Managing Nausea
4. Palliative care - nausea and vomiting: NICE CKS, July 2015 (UK access only)
5. British National Formulary (BNF); NICE Evidence Services (UK access only)


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