Nausea and vomiting

Marcus Harbord

Suzanne Pomfret

Abstract

Nausea and vomiting originate from peripheral (gastrointestinal tract or middle ear) or central stimuli. Nausea is often precipitated by medication. Pregnancy, recent surgery and alcohol excess are also common causes. Rarely, endocrine disease, uraemia and psychiatric causes are contributing factors. Accurate history and examination usually direct the physician to the cause and allow a more tailored approach to anti-emetic therapy if necessary. Antagonists to dopamine, serotonin, or acetylcholine can all be used. Accurate assessment of fluid status is crucial in vomiting patients to prevent clinical deterioration and electrolyte disturbance. Specific investigation and treatment depends on the likely aetiology, but should be performed urgently if alarm features are present. Relief of nausea and vomiting is a mainstay of good palliative care.

Keywords anti-emetic; emesis; motility; nausea; vomiting

Nausea is a common symptom and, when accompanied by vomiting, usually self-limiting. Although there are numerous causes, originating from peripheral or central stimuli, the history should identify the cause in the vast majority of cases. This article provides a structured framework to simplify the management of nausea and vomiting.

Mechanism of vomiting

Vomiting is a reflex controlled by the 'vomiting centre' in the medulla oblongata. Afferent inputs to this centre originate in chemo- or mechano-receptors in the upper gastrointestinal tract; in the chemo-receptor trigger zone (CTZ), which is located adjacent to the area postrema; or from within the vestibular system (Figure 1).[1] The reflex results in a combination of reverse peristalsis and relaxation of both pylorus and lower oesophageal sphincters. The reverse contraction of the pylorus and gastric antrum leads to expulsion of intestinal contents via the oesophagus.

Nausea and vomiting can be an appropriate physiological response to stimuli, such as salmonella infection or neurotransmitter release in motion sickness. Pathological responses represent disruption to normal pathways, for example within the brain (e.g. a space-occupying or demyelinating lesion), within the autonomic nervous system (e.g. diabetic neuropathy), or within smooth muscle of the intestine (e.g. amyloid).

Marcus Harbord *BSc MBBS PhD FRCP is Honorary Senior Lecturer at Imperial College, London, UK, and Consultant Physician and Gastroenterologist at the Chelsea and Westminster Hospital, London, UK. Competing interests: none declared.*

Suzanne Pomfret *BA MBBS MRCP is a Speciality Registrar at Chelsea and Westminster Hospital, London, UK. Competing interests: none declared.*

Alarm symptoms

There are several red flag symptoms that should alert the clinician to possible serious organic pathology. For example, *anaemia* or *haematemesis* occur in patients with foregut malignancy and significant *weight loss* (defined as >5% unintentional weight loss) is present in a wide range of conditions. *Dysphagia* must be investigated urgently to exclude oesophageal malignancy. Nausea is a common symptom in patients with functional gastrointestinal (GI) disease (e.g. irritable bowel syndrome) but *vomiting* must alert the clinician to seek an alternative diagnosis. Generally, alarm features predicate urgent gastroscopy with or without cross-sectional imaging.

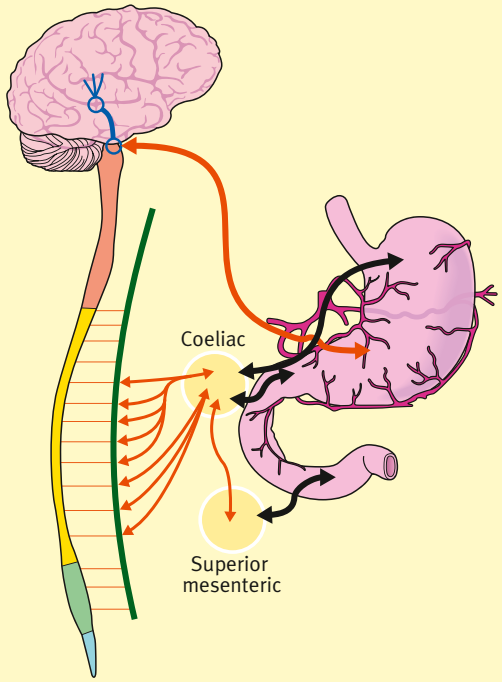
Aetiology

Nausea and vomiting usually result from problems within the central nervous system, middle ear or gastrointestinal tract. Pregnancy, postoperative nausea/vomiting and alcohol excess are other common causes. Rarer causes comprise endocrine diseases, uraemia and psychiatric illness. This can best be remembered by the rule of threes (three main systems, three other common causes, three rarer causes) (Figure 2).

Often the history and examination provide a clue to the diagnosis.

- Medication — the more medication a patient takes, the more likely this is the cause. Consider drug interactions, especially inducers or inhibitors of cytochrome P450, or excessive dosing in the context of renal/hepatic disease.
- Chemotherapy-induced nausea and vomiting.
- Postoperative nausea and vomiting are common.
- Toxins — either exogenous (e.g. alcohol, cannabis) or endogenous (e.g. uraemia).
- Endocrine causes include diabetic ketoacidosis, acute adrenal insufficiency and hypercalcaemia (usually secondary to malignancy or primary hyperparathyroidism).
- Gastroparesis is usually idiopathic but can be secondary to diabetic neuropathy; rarer causes include amyloid neuropathy or sarcoidosis.
- Pregnancy is a common cause, especially in the first trimester. Hyperemesis gravidarum, HELLP syndrome, pre-eclampsia and acute fatty liver disease of pregnancy are less common pregnancy-related causes.
- Severe pain (e.g. chest pain suggestive of myocardial infarction).
- Vestibular neuronitis.
- Cerebellar disease.
- Intracranial bleed.
- Infective gastroenteritis, particularly if friends/family are ill, when a history of fever or diarrhoea/abdominal cramping are present. The cause is usually viral.
- Cyclical vomiting describes intermittent episodes of vomiting lasting several days, usually separated by periods of normality lasting a few months. It is more common in marijuana users[2] and patients with diabetes mellitus.
- Constipation, especially in the elderly.
- Intra-abdominal inflammatory causes include appendicitis, cholecystitis, pancreatitis, inflammatory bowel disease,

Neurological control of the foregut



Sympathetic control of the foregut arises from the thoracic spinal cord. The sympathetic chain (green line) connects to the coeliac and superior mesenteric ganglia via the great and small splanchnic nerves (thin red arrows). Post-ganglionic fibres (black arrows) innervate the stomach, small bowel and proximal colon.
Efferent sympathetic nerves inhibit intestinal motility; afferent nerves transmit nociceptive stimuli.
Parasympathetic stimulation increase gastrointestinal motility, mediated by the vagus nerve. Afferent nerves (thick red arrows) synapse in the nucleus tractus solitarius in the medulla; thereafter fibres travel to the area postrema in the floor of the fourth ventricle (also known as the chemo-receptor trigger zone as it is sensitive to humoral factors such as drugs, neurotransmitters).[1] This connects with higher centres. Vomiting is initiated by efferent vagal nerve fibres.

Figure 1

cholangitis and peritonitis. Episodic right upper quadrant pain and vomiting suggest gallstone disease.

- Dyspepsia, often caused by *Helicobacter pylori* or anti-inflammatory drug use.
- Gastric outlet obstruction.
- Lower gastrointestinal obstruction — faecal vomiting may be present.
- Bulimia should be considered in patients with dental erosions, calluses on the dorsum of the hands, salivary gland hypertrophy or lanugo hair.[3]
- Rare causes include acute angle glaucoma, high-altitude sickness and Bouveret's syndrome (foregut obstruction due to gallstone impaction).

Investigations

Baseline investigations include full blood count, bone profile, liver function, and measurement of serum urea and electrolytes, magnesium and (venous) bicarbonate, and plasma glucose. Capillary blood glucose and a urine dipstix for ketones should be routine. Patients with significant vomiting often have a hypokalaemic metabolic alkalosis. Vomiting causes loss of hydrogen ions, raising plasma bicarbonate concentrations. Consequently, the sodium bicarbonate concentration is high within the collecting ducts. To maintain sodium balance, sodium is reabsorbed in exchange for potassium, which results in hypokalaemia. Urine chloride will be low (<25 mmol/litre) due to gastric losses.

A pregnancy test should be performed in women of childbearing age. Arterial blood gases should be measured in sick patients, a septic screen is necessary in febrile patients, and stool cultures should be obtained if there is co-existent diarrhoea.

A plain abdominal X-ray may demonstrate fluid-filled small bowel loops indicative of bowel obstruction, and an erect chest X-ray should be obtained if perforation of the bowel is suspected.

Subsequent investigations depend on the suspected aetiology.

- Peptic ulcer disease requires gastroscopy plus biopsies as indicated for *H. pylori* or malignancy. Note that *H. pylori* can be detected by stool antigen testing, which can be used for screening and follow-up.
- Gastric outlet obstruction should be investigated by gastroscopy, once the stomach has been decompressed (with a wide-bore nasogastric tube).
- Gallstones can usually be confirmed by an abdominal ultrasound scan.
- GI malignancy requires an abdominal/pelvic CT scan together with a gastroscopy or and colonoscopy.
- Pseudo-obstruction requires a water-soluble contrast follow-through or enema, usually in patients with obstruction in whom gastroscopy or abdominal CT scan has demonstrated no lesion, particularly if gas is present within the rectum. Intestinal dilatation may be present in chronic intestinal pseudo-obstruction in which nausea and vomiting are common.[4]
- Gastroparesis requires scintigraphic gastric emptying studies.
- 'Red flag' symptoms, such as headache, loss of consciousness or seizures, should lead to a low threshold for cerebral imaging.
- Vestibular neuronitis may require an ENT opinion.

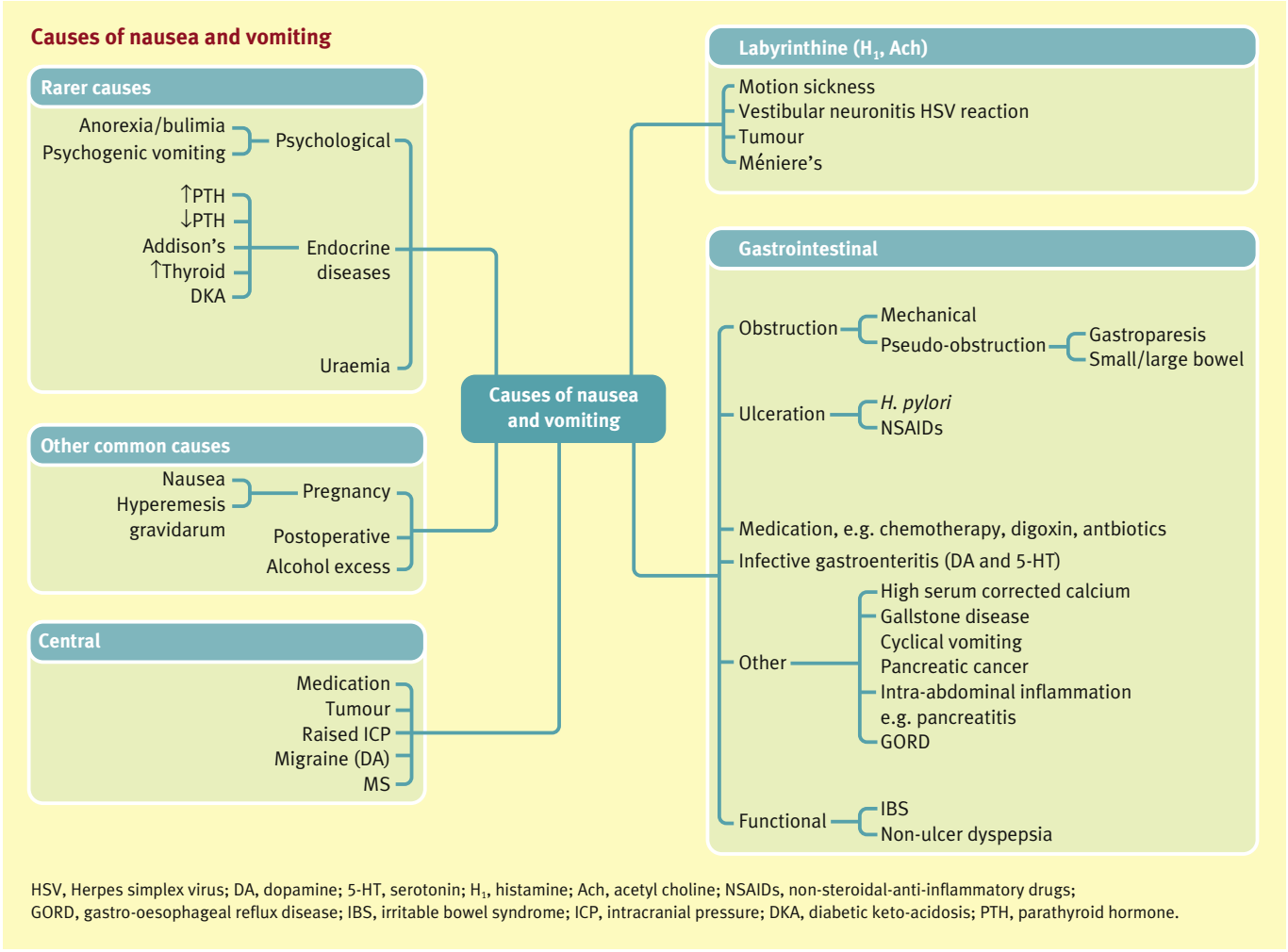
Complications

In addition to the problems directly related to the underlying pathology, patients with nausea and vomiting are at risk of dehydration and volume depletion as well as significant electrolyte disturbance; fluid and electrolyte status should be regularly monitored. In addition, aspiration or oesophageal rupture are serious complications. Haematemesis may occur with Mallory–Weiss tears of the oesophagus after vomiting. If vomiting is chronic, nutritional deficiencies may also appear. In the management of nausea and vomiting these complications should always be considered.

Management

Initial treatment

The mainstay of initial treatment comprises fluid replacement and anti-emetics (Figure 3). Consequently, it is important to assess the patient's volume status. The most sensitive indication



HSV, Herpes simplex virus; DA, dopamine; 5-HT, serotonin; H_1, histamine; Ach, acetyl choline; NSAIDs, non-steroidal-anti-inflammatory drugs; GORD, gastro-oesophageal reflux disease; IBS, irritable bowel syndrome; ICP, intracranial pressure; DKA, diabetic keto-acidosis; PTH, parathyroid hormone.

Figure 2

of volume depletion is a postural drop in blood pressure while standing or sitting. Other features such as skin turgor, degree of venous filling, presence of postural hypertension, pulse rate and the degree of thirst are less reliable. Most patients admitted to hospital with nausea and vomiting will require intravenous fluid replacement with crystalloid, usually sodium chloride 0.9% containing potassium chloride, guided by electrolyte status. The presence of pre-existing co-morbid conditions such as heart, renal or liver failure should be considered when prescribing fluids. If aspiration is likely, based on chest X-ray and clinical examination, antibiotics with anaerobic cover should be prescribed; co-amoxiclav is adequate in most cases. If an upper gastrointestinal bleed is suspected, prompt resuscitation and gastroscopy are indicated (see *MEDICINE* 2011; **39**(2): 94–100).

Anti-emetics

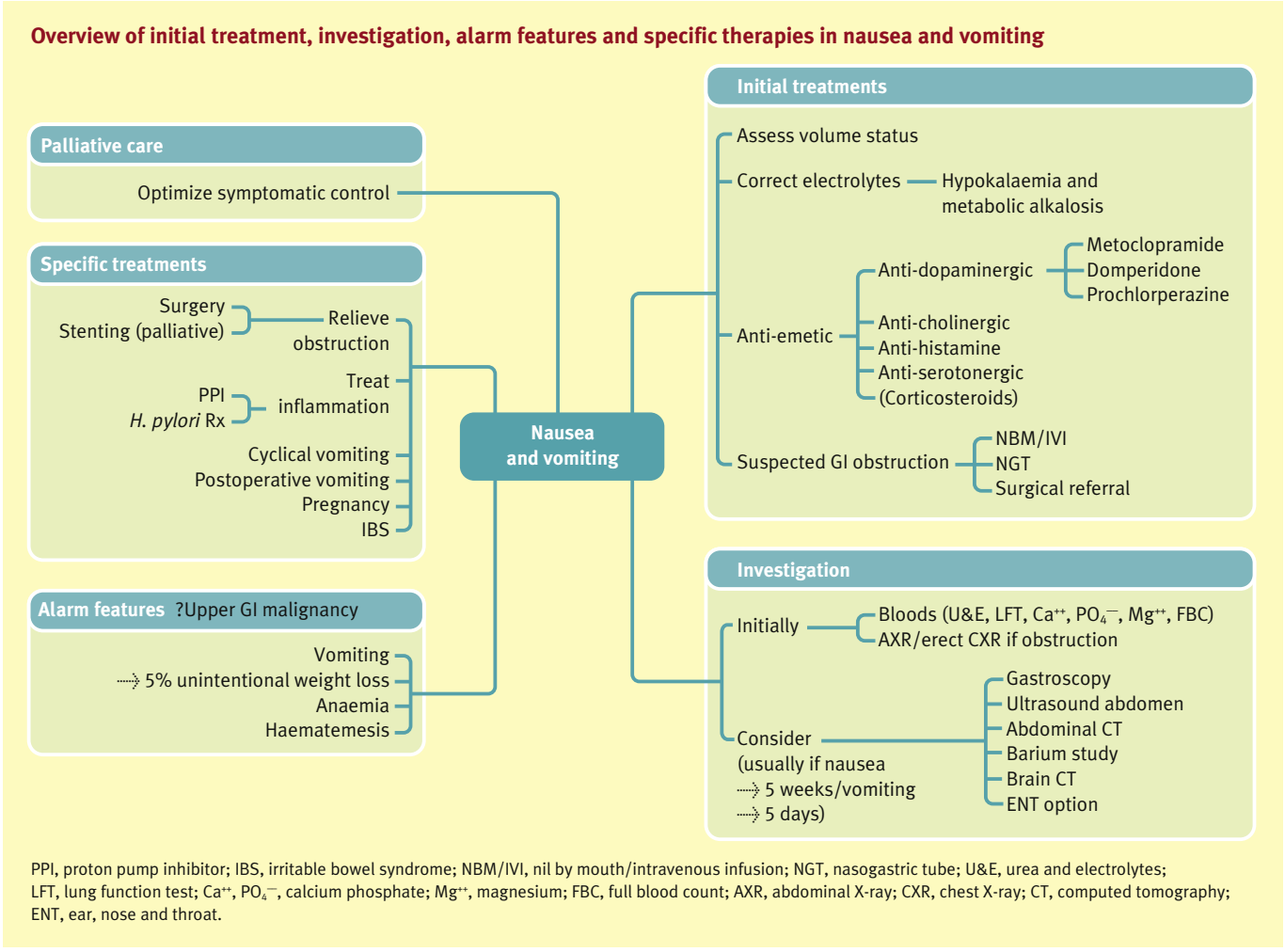
There are five neurotransmitter sites that are used in the pharmacological management of nausea and vomiting:

- M_1 – muscarinic acetylcholine
- D_2 – dopamine
- H_1 – histamine
- 5-HT_3 – hydroxytryptamine (serotonin)
- neurokinin-1 (NK-1) receptor – substance P.

The receptors are found mostly in the area postrema, except for H_1 receptors. H_1 receptors are present in the vestibular nucleus, and there is a concentration of 5-HT_3 receptors within vagal afferent neurones. The choice of anti-emetic depends on the likely cause of the symptoms.[5] Different anti-emetics or combinations can be used, especially if the symptoms are persistent or severe (Table 1).

Specific management points

- Review the patient's usual medication and consider stopping/substituting those drugs whose introduction coincided temporally with the onset of symptoms.
- Intravenous fluids are often required to replace fluid and electrolyte losses (including third-space losses into the GI tract).
- Acid suppression (e.g. omeprazole) often abolishes nausea/vomiting caused by dyspepsia or non-steroidal anti-inflammatory drugs (NSAIDs).
- *H. pylori*, if present, should be eradicated.
- In oncological and palliative patients, reversible factors such as excess opioid therapy, constipation, electrolyte abnormalities and raised intracranial pressure should be sought and corrected. Raised intracranial pressure can be



PPI, proton pump inhibitor; IBS, irritable bowel syndrome; NBM/IVI, nil by mouth/intravenous infusion; NGT, nasogastric tube; U&E, urea and electrolytes; LFT, lung function test; Ca^{++}, $PO_4^{—}$, calcium phosphate; Mg^{++}, magnesium; FBC, full blood count; AXR, abdominal X-ray; CXR, chest X-ray; CT, computed tomography; ENT, ear, nose and throat.

Figure 3

treated with high-dose dexamethasone 8—16 mg twice daily). In palliative cases gastric secretions can be inhibited with octreotide, and patients' comfort enhanced with sedatives such as midazolam.[7]

- Erythromycin has a prokinetic rather than anti-nausea action but its usefulness is limited by a low therapeutic index.
- In patients presenting with gastrointestinal obstruction:
  - keep nil by mouth and insert a nasogastric tube
  - seek a surgical opinion
  - prefer centrally acting anti-emetics, such as haloperidol, prochlorperazine, or levomepromazine, as they have fewer prokinetic effects.
- A 3-week reducing course of prednisolone is more effective than antiviral therapy in vestibular neuronitis, which is presumed to be due to a viral infection (specifically herpes simplex virus reactivation).[8] Physical therapy for vestibular rehabilitation may also have a role.
- Pregnancy-related nausea and vomiting requires reassurance and nutritional advice. The obstetric team must always be informed. In severe cases, metoclopramide and cyclizine are first-line medication. Regular pyridoxine has been shown to be effective.[9,10] Phenothiazines, antihistamines, selective 5-HT receptor antagonists and dopamine agonists are all safe in pregnancy.[11] Combinations are often required and corticosteroids may have a role for patients with hyperemesis resistant to conventional management.[12]
- Tricyclic antidepressants (e.g. amitriptyline) can be used in intractable cyclical vomiting syndrome. Drug-resistant cases can be referred for gastric pacing, using the Enterra™ system (a neuro-stimulator placed in the subcutaneous fat, with electrodes implanted into the stomach).
- Postoperative vomiting is common. A large, controlled trial has demonstrated that dexamethasone 4 mg and/or droperidol (antihistaminic, antiserotonergic and antidopaminergic actions) 1.25 mg at induction, or ondansetron 4 mg towards the end of surgery, both effectively reduce nausea.[12] A recent meta-analysis of randomized-controlled trials found that dexamethasone at doses more than 0.1 mg/kg is an effective adjunct in multimodal strategies to reduce postoperative pain and opioid consumption after surgery.[13]

For many patients, nausea and vomiting are self-limiting conditions that are effectively managed by patients themselves. In cases that require medical attention, assessing illness severity, determining a likely aetiology and prompt management are

Anti-emetic classification

Class	Receptor	Examples	Main uses	Important side effects
Anticholinergic agents	M_1	Procyclidine, scopolamine (transdermal)	Labyrinthine disorders	Dry mouth
Antihistamines	H_1	Cyclizine, promethazine	General plus labyrinthine disorders	Sedation
Benzamides	D_2, weak 5-HT_3	Metoclopramide, domperidone (poor CNS penetration, no parenteral preparation)	General especially migraine and gastroparesis	Tardive dyskinesia Domperidone — fewer extra-pyramidal effects
Butyrophenones	D_2	Haloperidol, Droperidol	Postoperative nausea and vomiting, preanaesthetic sedation	Sedation, QT prolongation, hypotension, acute dystonia
Phenothiazines	D_2, some M_1 and H_1	Prochlorperazine, chlorpromazine	Chemotherapy-induced emesis	Extra-pyramidal reactions, hypotension
Serotonin receptor antagonists	5-HT_3	Ondansetron	Chemotherapy-induced emesis	Mild headache, asthenia, constipation
Neurokinin receptor antagonists	NK-1	Aprepitant (used in conjunction with dexamethasone and 5-HT_3 receptor antagonist[6])	Chemotherapy-induced emesis	Hepatic impairment, many drug interactions
Glucocorticoids		Dexamethasone	Chemotherapy-induced emesis, palliative care	Multiple
Cannabinoids		Nabilone	Limited use, chemotherapy-induced emesis	Vertigo, xerostomia, hypotension, dysphoria, behavioural effects
Benzodiazepines		Lorazepam, diazepam	Weak anti-emetics	Sedation

Table 1

essential. Lifestyle advice — NSAID avoidance, smoking cessation and reduction in alcohol intake are an important part of the overall management plan and should not be forgotten. ◆

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