

Causes and treatment of nausea and vomiting

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Nausea and vomiting are associated with a range of underlying causes, and a full history and clinical examination are essential in order to yield a diagnosis and commence appropriate treatment. This article discusses the various causes of nausea and vomiting and the treatment options available.

Nausea is the subjective feeling of 'sickness' and is usually the term used to describe the sensation preceding vomiting. Vomiting is the physical ejection of gastric contents up the oesophagus and out through the mouth. Nausea and vomiting are protective mechanisms, and may present acutely or as a chronic condition. They are common and distressing symptoms with population-based data indicating that vomiting will occur once per month in 2–3% of the general population.¹ As such, rapid diagnosis and subsequent management of nausea and vomiting is essential; however, due to the multifactorial nature of the symptoms, this can be clinically challenging.

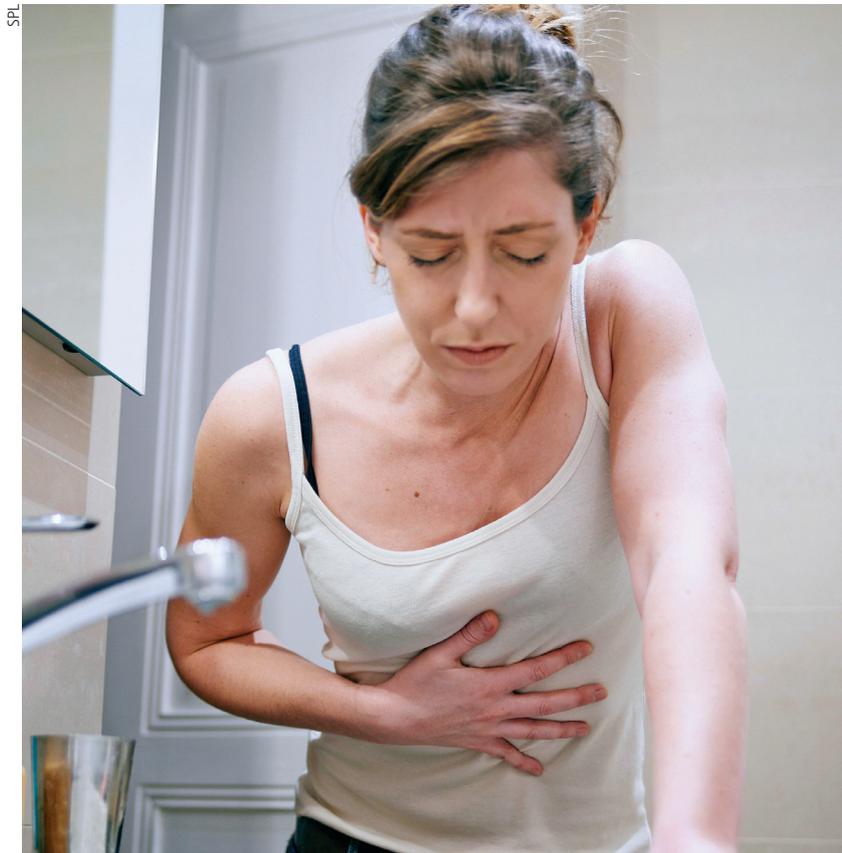
Dysphagia and rumination disorder are both conditions that may be confused with vomiting. Distinguishing these conditions can be difficult; however, the history is frequently indicative as food regurgitation is a key feature. Specifically, rumination is a motility disorder characterised by the effortless and involuntary regurgitation of recently ingested food, without the nausea and physical retching typically associated with vomiting. Dysphagia is difficulty swallowing (all or certain foods and liquids) and is usually a result of dysmotility or may have a neurological or structural cause.

Causes

Table 1 provides a summary of the causes of nausea and vomiting. The most commonly reported cause of acute nausea and vomiting in all age groups is gastroenteritis,² though with advancing age the proportion of organic to functional disease increases and this should be considered when making a diagnosis.³

Pathophysiology

The vomiting centre is located in the central medulla and this co-ordinates the complex events behind vomiting. It projects to the vagus nerve and spinal motor neurones, which innervate the abdominal muscles. The chemoreceptor trigger zone (CTZ)



Gastrointestinal causes
<i>Mechanical obstruction</i> Gastric outlet obstruction, small bowel obstruction, volvulus, intussusception
<i>Motility and functional disorders</i> Gastroparesis, irritable bowel syndrome, chronic pseudo-obstruction, functional dyspepsia, eosinophilic enteritis
<i>Other intra-abdominal and organic causes</i> Appendicitis, cholecystitis, hepatitis, mesenteric ischaemia, Crohn's disease, peptic ulcer disease, pancreatitis, malignancy, peritonitis, peritoneal carcinomatosis, superior mesenteric artery syndrome, retroperitoneal fibrosis
Medications
Aspirin and other NSAIDs, antibiotics, antidiabetic medications, anti-gout drugs, cancer chemotherapy agents, cardiovascular drugs, CNS medications, immunosuppressants, opiates, oral contraceptives
Infectious causes
Gastroenteritis, systemic infections
Endocrine causes
Acute intermittent porphyria, Addison's disease, diabetes mellitus, diabetic ketoacidosis, hypercalcaemia, hyperparathyroidism, hyperthyroidism, hyponatraemia, hypoparathyroidism, pregnancy, uraemia
CNS disorders
Autonomic disorders, demyelinating disease, epilepsy, hydrocephalus (high pressure, low pressure and congenital malformations), intracranial lesions with cerebral oedema (haemorrhage, infarction, abscess, tumour), meningitis, otitis media, epilepsy, migraine, vestibular and labyrinth disorders (labyrinthitis, Meniere's disease, motion sickness), visceral neuropathy
Miscellaneous
Depressive disorder, anxiety, alcohol and substance abuse, cardiac disease (myocardial infarction, heart failure, cardiac ablation), collagen vascular disorders (systemic lupus erythematosus, scleroderma), cyclical vomiting syndrome, cannabinoid hyperemesis syndrome, eating disorders, functional disorders, intense pain, paraneoplastic syndrome, postoperative state, postvagotomy, radiation therapy, starvation

Table 1. Causes of nausea and vomiting

is located in the area postrema in the floor of the fourth ventricle and is an important source of stimulation for the vomiting centre.

The vomiting centre contains muscarinic and histamine receptors while the CTZ is rich in dopamine (D₂) and 5-HT₃ receptors, thus explaining how drug antagonists provide their antiemetic effect. In addition, 5-HT₃ has a peripheral effect on

the gastrointestinal tract. The vomiting centre also receives afferent inputs from the sensory vestibular system and higher cortical centres such as the limbic cortex. Figure 1 shows the areas of the brain and the triggers involved in the vomiting reflex.

Diagnosis

Nausea and vomiting are common clinically identifiable symptoms. They are often acute and self-limiting and so often do not require investigation. However, where further investigation is required, a comprehensive clinical history, including detailed drug and alcohol history, often reveals the offending cause. Specific investigations should be guided by the preceding history and tailored rather than each patient empirically undergoing a blanket of clinical investigations.

Nausea and vomiting are encountered in both primary and secondary care and can, in severe cases, lead to serious complications, including hypovolaemic shock, renal failure, viscus perforation and severe electrolyte disturbance inducing cardiac dysrhythmia.

Clinical examination may reveal signs of dehydration (eg decreased skin turgor, cool peripheries) and can provide clues as to the underlying cause. Examination of the oral cavity may reveal eroded enamel indicating bulimia or severe reflux, and abdominal examination may reveal masses or abnormalities in bowel sounds suggesting bowel obstruction.

Vomiting can be a presenting feature of an acute intracranial event, especially traumatic cerebral haemorrhage. It is rarely the sole symptom but if the history is suggestive, CT imaging of the brain should be performed urgently.

Neurological and mental state assessment should be carried out if a CNS cause is suspected and if abnormal, or if there is evidence of raised intracranial pressure, brain imaging should be considered. A CT scan is usually sufficient but more detailed MRI scanning is used in the diagnosis of posterior fossa lesions and demyelinating disease, and may also be needed to further characterise CT findings. Vomiting can often occur in epilepsy, especially occipital lobe epilepsy; in this case, EEG would be the test of choice to exclude seizures.

The nature of the vomitus may provide a clue to the diagnosis, with food contents suggesting gastric outlet obstruction and bilious or faeculent vomit suggesting a more distal obstruction.

A comprehensive blood panel may help to identify causes of vomiting such as an inflammatory or infective process, pancreatitis or electrolyte abnormalities, as well as check for potential dehydration with a renal profile. Arterial blood gas sampling (including lactate measurement) may aid the diagnostic process, but will also help identify metabolic disturbance (such as metabolic alkalosis). An ECG should be performed to ensure that no dysrhythmias are present and also to assess the QT interval.

Gastroscopy can detect mucosal lesions including malignancy. Endoscopic investigation can also reveal gastric outlet obstruction such as the presence of food residue in the stomach indicating gastroparesis. To confirm the diagnosis,

contrast studies and/or gastric emptying studies can be considered.

Where subacute bowel obstruction is suspected (especially in the presence of other gastrointestinal symptoms such as abdominal distension and constipation), plain abdominal X-ray is a cheap, quick and relatively safe test to perform. However, despite being a first-line investigation in this scenario, abdominal radiographs are neither sensitive nor specific,^{4,5} and cross-sectional imaging such as computed tomography (CT) is preferred.

Pregnancy is another common cause of nausea and vomiting, with a prospective study of pregnant women showing that 28% experienced nausea only, while a further 52% had both nausea and vomiting.⁶ A urine pregnancy test should therefore be an essential part of the diagnostic work-up in any women of childbearing age presenting with symptoms. The precise underlying cause in pregnancy is not fully understood but it can be debilitating and severe (eg hyperemesis gravidarum), with a significant socioeconomic impact due to time away from the workplace.

Management

The focus of the management of nausea and vomiting lies in treating the underlying cause, as this will invariably alleviate symptoms.

The recommended management of vomiting secondary to gastric outlet obstruction is shown in Figure 2. In cases of vomiting secondary to bowel obstruction, a nasogastric tube should be inserted to help drainage of upper gastrointestinal contents and a surgical opinion sought as soon as possible. It is also important to correct dehydration and electrolyte abnormalities as a result of the vomiting, such as with intravenous fluid replacement.

Feeding and nutritional support should also be considered, especially in cases of persistent vomiting. This can be done either enterally (via nasogastric or nasojejunal tubes, depending on clinical context) or parenterally. In the presence of a functioning gut, the former is preferred as it helps gut remodelling (especially important in the context of inflammatory bowel disease) and also has a safer side-effect profile than parenteral

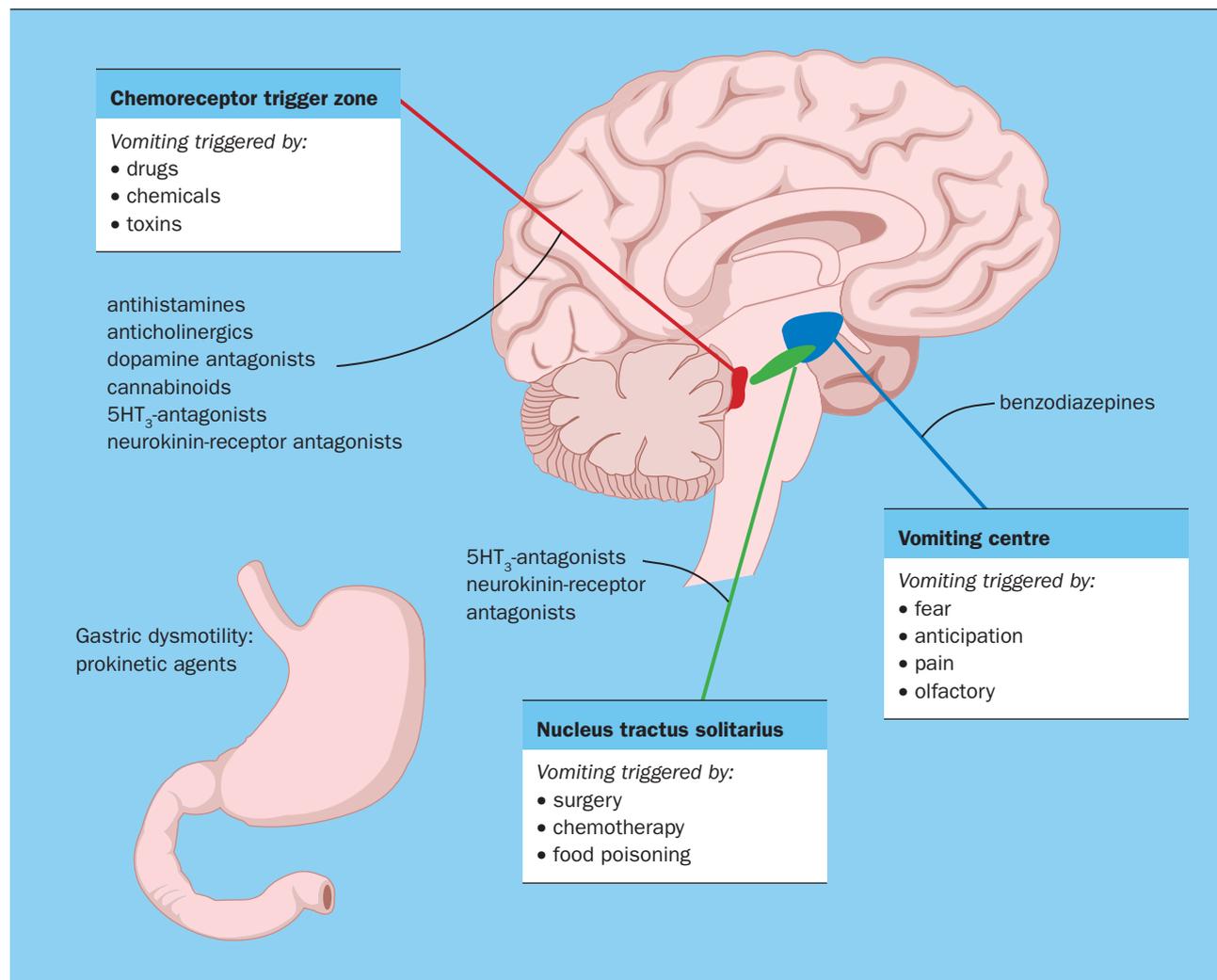


Figure 1. Areas of the brain and triggers involved in the vomiting reflex, with sites of action of antiemetic and prokinetic agents

nutrition. For those patients who are malnourished or who have had a prolonged period of starvation, nutritional supplements and vitamins (intravenous Pabrinex or oral Forceval capsules) should be given to replenish stores and minimise the risk of developing refeeding syndrome.

Numerous medications can contribute to nausea and vomiting, as has already been outlined, and sometimes the only management needed is simply to withdraw the offending agent.

In some conditions, it is not always easy to treat the underlying cause, or it may take time. Equally, emesis is a known side-effect of chemotherapy, but it is one where the potential benefit is likely to outweigh the risk of discontinuing treatment. In such situations, pharmacotherapy can be extremely beneficial in controlling symptoms and maintaining patient quality of life.

Pharmacological treatments

A direct head-to-head comparison of the efficacy of different treatments in nausea and vomiting is challenging, largely due to the wide range of aetiologies and individual pathophysiological responses. Most data is derived from situations where nausea and vomiting are common features, such as post-operative nausea and vomiting, and during treatment with chemotherapy.

Most agents have a central antiemetic action and some also act peripherally, *ie* have a prokinetic action (see Table 2). Second-line management usually entails using combinations of these agents. An important caveat is that in persistent vomiting, drugs will not be absorbed adequately in the oral form, and so other routes should be considered including buccal, intravenous, intramuscular and subcutaneous administration.

Dopamine antagonists

A summary of the most commonly used dopamine antagonists is provided in Table 3.

Phenothiazines act by blocking dopamine receptors in the chemoreceptor trigger zone. Prochlorperazine (5–10mg two to three times daily) is usually used first-line in this class of drugs as it is less sedating than its counterparts such as chlorpromazine. However due to extrapyramidal side-effects and also orthostatic hypotension, it is not as widely used. It is available in both oral and buccal forms, with the latter being less sedating.⁷

Prokinetic dopamine antagonists (*ie* metoclopramide and domperidone) are widely used; however, their use has been restricted in recent years following safety alerts.

Metoclopramide (10mg three times daily) is a D₂-receptor antagonist that acts as a gut prokinetic. It has high oral bio-availability (>90%) and can also enhance the absorption of other drugs, which can be useful in certain scenarios such as migraine treatment. It should be avoided in cases of gastrointestinal obstruction, perforation or haemorrhage. It generally has a good side-effect profile, but can be associated with extrapyramidal side-effects and has been known to cause severe dystonic reactions in young patients and in females. As such, due to the risk of these neurological side-effects (risk greater in children than adults), the European Medicines Agency (EMA) has limited its use to a maximum of five days and rec-

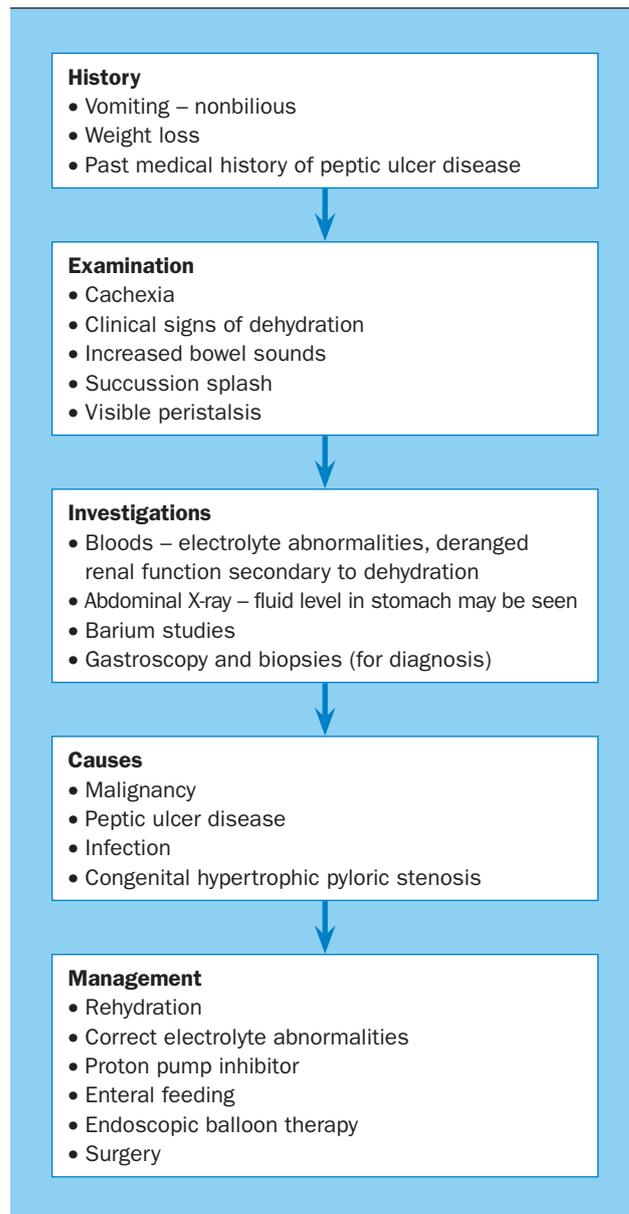


Figure 2. Management of gastric outlet obstruction

ommends dose reduction to 0.1–0.15mg per kg bodyweight in children age one year or older.⁸

Domperidone has a similar action to metoclopramide, but does not cross the blood-brain barrier so does not lead to extrapyramidal side-effects. However, in 2014 the Medicines and Healthcare products Regulatory Agency (MHRA) issued advice on the restricted use of domperidone due to the small increased risk of potentially life-threatening cardiac side-effects.⁹ Cardiac risk was found to be greater in those over 60 years old, and in those taking concomitant QT-prolonging medications (such as clarithromycin, citalopram or amiodarone) or CYP3A4 inhibitors (eg diltiazem or verapamil). The guidance stated it should also no longer be used in those with existing

Drug class	Examples	Mechanism of action	Uses	Side-effects
Dopamine antagonists	Prochlorperazine	Blocks dopamine receptors in the chemoreceptor trigger zone	Vertigo; nausea and vomiting including migraine-associated	See Table 3 for details
	Metoclopramide Domperidone	D ₂ -receptor antagonists and gut prokinetics	Restricted use following safety alerts (see text for details)	
Corticosteroids	Dexamethasone	Not entirely understood but endorphin release thought to be involved	Commonly used in palliative care	Immunosuppression, osteoporosis, impaired glucose control, adrenal insufficiency if withdrawn too abruptly
5-HT ₃ antagonists	Ondansetron Granisetron	Act centrally to block 5HT ₃ receptors	Chemotherapy-induced nausea and vomiting; postoperatively	Headache, dizziness, constipation, bradycardia
Antihistamines	Cyclizine	H ₁ -receptor antagonist	Motion sickness; postoperatively	Drowsiness, confusion (in the elderly), dry mouth, urinary retention, constipation
	Betahistine	H ₃ -receptor antagonist and H ₁ -receptor partial agonist; reduces endolymphatic pressure	Vestibular disorders	Headache

Table 2. Commonly used agents in the management of nausea and vomiting

liver or cardiac damage. This advice was based on previous European studies, which raised questions over domperidone's propensity to prolong the QT interval and increase the risk of ventricular arrhythmias. A study from the Netherlands reported a 44% increased risk of serious ventricular arrhythmias with domperidone usage (40mg once daily) compared with proton pump inhibitor use only.¹⁰ For these reasons, domperidone is very rarely used and if required, it should only be used sparingly and with caution.

5-HT₃ antagonists

There are a number of 5-HT₃-receptor antagonists available and these are usually used alongside chemotherapy or for postoperative nausea and vomiting, where up to 80% of patients may be affected.¹¹ Ondansetron is most commonly used (4–8mg up to three times daily). 5-HT₃-receptor antagonists act centrally and are highly effective. Their side-effects include bradycardia and headache. Granisetron is also commonly used in chemotherapy-induced nausea and vomiting and has been shown to be more effective than other 5-HT₃-receptor antagonists in preventing delayed symptoms in these patients.¹²

Corticosteroids

Dexamethasone is cheap and effective¹³ and can be used in palliative care. Its mechanism of action is not completely understood but it is postulated that it may act by releasing endorphins.¹⁴ However, as with any corticosteroid, it has

a large side-effect profile including immunosuppression, increased bone fragility and increased blood glucose levels. Corticosteroids are not suitable as a long-term option as they can lead to Cushing's syndrome. Additionally, the subsequent rapid withdrawal of steroid therapy can lead to adrenal insufficiency, thus necessitating therapy to be gradually tapered.

Antihistamines

Antihistamines are used as first-line therapy for motion sickness and nausea and vomiting in pregnancy. Cyclizine (50mg three times daily) can be administered via the oral, intramuscular and intravenous routes. It is a commonly used and inexpensive antiemetic, which acts by blocking H₁ receptors. Side-effects include confusion in the elderly as well as dry mouth, blurred vision and tachycardia.

Betahistine, a H₁-receptor partial agonist and H₃-receptor antagonist, is used as first-line treatment for vestibular disorders such as Meniere's disease and vertigo and works by reducing endolymphatic pressure.

Other agents

Proton pump inhibitors can be useful in nausea and vomiting associated with dyspepsia and gastro-oesophageal reflux. Although unlicensed, tricyclic antidepressants have been shown to be of some benefit in functional nausea and vomiting as well as abdominal pain, although more controlled trials are needed.¹⁵

Drug name	Usual oral dose and frequency	Oral bio-availability	Pharmacokinetics	Half-life	Drug interactions	Side-effects	Comments
<i>Prochlorperazine</i>	5–10mg, 2–3 times daily	<10%	Extensive first-pass metabolism	7h	Other drugs causing hypotension, lithium	Sedation, extrapyramidal reactions, hypotension	Available in several formulations including buccal tablets, oral liquid and injection
<i>Metoclopramide</i>	10mg, 3 times daily	>90%	Undergoes first-pass metabolism; clearance is by hepatic metabolism; only 20% is excreted in the urine unchanged	4h	Antipsychotics	Extrapyramidal reactions, restlessness, stimulation of prolactin release	Also available as an injection; can be used as a prokinetic agent; contraindicated in gastrointestinal patients with an obstruction, perforation or haemorrhage. Caution: can cause severe dystonic reactions (see main text for details)
<i>Domperidone</i>	10–20mg, 3–4 times daily	13-17%	Undergoes extensive presystemic metabolism	12–16h	None significant	Stimulates prolactin release, reduced libido	Less likely to cause extrapyramidal side-effects and sedation; also available as suppositories and oral liquid but not as an injection; also has prokinetic properties. Caution: can lead to increased cardiac side-effects (see main text for details)

Table 3. Dopamine antagonists most commonly used in nausea and vomiting and their properties

Pregnancy

Nausea and vomiting are very common symptoms of pregnancy and in severe cases, such as hyperemesis gravidarum, can require hospital admission for rehydration therapy. A stepwise approach to treatment is believed to be best. First-line therapy is usually with antihistamines such as cyclizine. The Royal College of Obstetricians and Gynaecologists advise that antihistamines (eg cyclizine, promethazine) should be used first-line, as many meta-analyses have commented on the safety and effectiveness of these agents with no adverse pregnancy outcomes reported.¹⁶ However, the summary of product characteristics (SPC) for cyclizine says that “in the absence of any definitive human data, the use of cyclizine in pregnancy is not advised,” and the SPC for promethazine says “not to be used in pregnancy unless the physician considers it essential.”

The use of 5-HT₃ antagonists in pregnant women remains controversial, though they are commonly prescribed. A recent systematic review concluded that the use of ondansetron in early pregnancy does not increase the risk of congenital malformations, but can increase the risk of cardiac abnormalities.¹⁷ Animal studies have indicated that it appears safe in pregnancy

and many women with hyperemesis find benefit from its use. It remains unlicensed for use in pregnancy and so patients should be counselled with regard to the available data, weighing up potential benefits versus risks in individual cases.

In fact, whichever antiemetic is chosen, the woman must be counselled on any potential risks documented in the literature before proceeding. If the woman fails to respond to a single agent, combinations of agents should be used, as they have varying mechanisms and synergistic effects.

Alternative therapies

Natural remedies such as ginger are thought to be helpful in the treatment of nausea and vomiting.¹ Acupuncture and hypnosis may also be options, especially for symptoms resistant to pharmacotherapy.

Conclusion

Nausea and vomiting are common, usually short-lived and self-limiting symptoms encountered in both the inpatient and outpatient setting. Thorough clinical history and physical examination is vital in establishing a cause for symptoms. Simple investigational tests

can also lead to a quick but essential diagnosis, such as urine pregnancy tests, which every woman of childbearing age presenting with vomiting should have. Once a cause has been identified, symptoms often respond well to treatment. However, in a small proportion of cases, chronic, persistent vomiting can be debilitating and severely impair quality of life.

It is important to treat not only the symptoms but also the consequences of nausea and vomiting, as intractable cases or severely affected patients will often present dehydrated and with electrolyte imbalances. Such cases should be referred for treatment in a hospital setting.

Many pharmacological agents are available for the treatment of nausea and vomiting but it is essential to tailor therapy to the individual to achieve optimal results. This requires a good understanding of the properties, indications and side-effect profiles of each of the classes of drugs.

Pharmacological agents are usually relatively cheap and widely available and cost should not be a barrier to treatment. The main development in pharmacotherapy over the last five years is the now cautious and restricted use of domperidone due to its cardiac side-effects.

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Declaration of interests

None to declare.

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