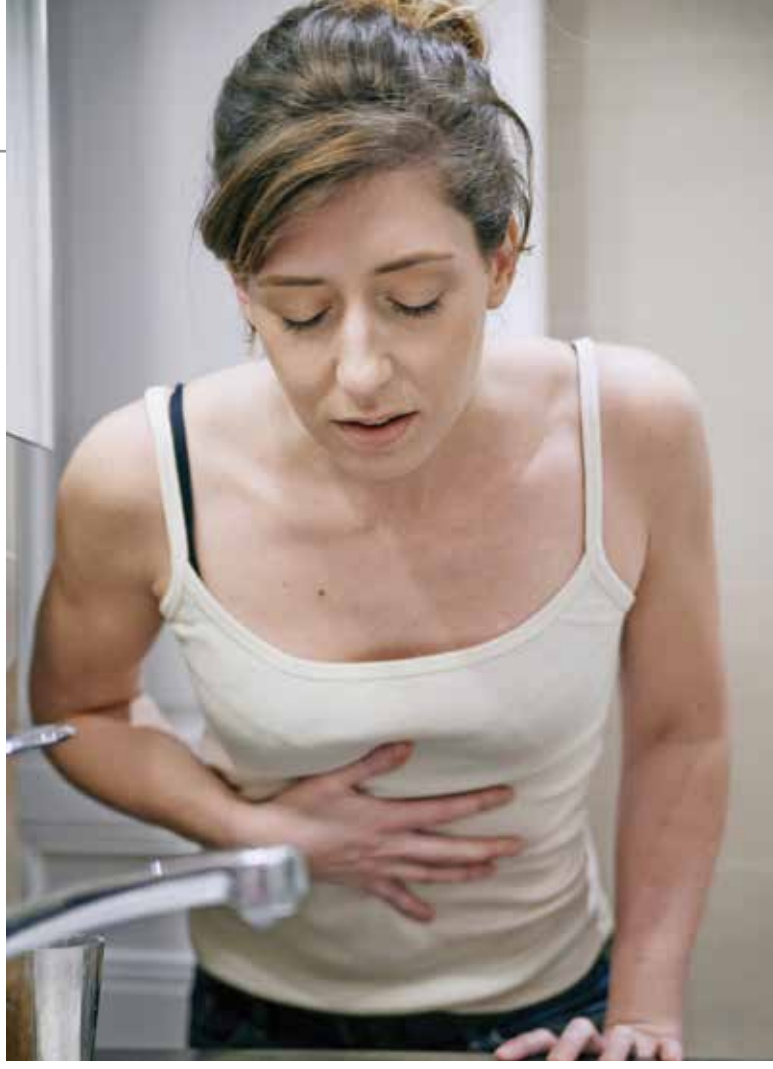
CLINICAL INVESTIGATIONS FROM THE RACP

Investigation of nausea

How far to go before referral

ELIOT ROACH MB BS(Hons), FRACP, GESA

In this series, we present authoritative advice on the investigation of a common clinical problem, especially commissioned for family doctors and written by members of the Royal Australasian College of Physicians.



© BSIP/ALICE S/DIOMEDIA.COM

KEY POINTS

- Nausea is a common presenting symptom and is often idiopathic or functional.
- Organic causes are usually apparent from a patient's history and physical examination.
- A few basic investigations will rule in or out most underlying causes.
- Referral of patients to a gastroenterologist should be considered when the diagnosis is in doubt, there is the suspicion of an underlying gastrointestinal cause or to reassure the patient.
- Consider anxiety as an underlying or contributing factor to nausea.

MedicineToday 2015; 16(7): 40-44

Dr Roach is a Gastroenterologist in private practice at Sydney Adventist Hospital, Sydney, NSW.
SERIES EDITOR: Christopher S. Pokorny, MB BS, FRACP, FRCP, FACG, is Conjoint Associate Professor of Medicine at the University of New South Wales, and Visiting Gastroenterologist, Sydney and Liverpool Hospitals, Sydney, NSW.

Nausea is the sensation of feeling sick or wanting to vomit. It should be distinguished from other symptoms such as fullness, satiety, bloating and dyspepsia, which the patient may interpret as nausea. Most cases of nausea do not have a serious cause but the symptom can be bothersome and in some cases debilitating. Treatment options are limited, have variable efficacy and in some cases are unsuccessful. Often the nausea will resolve without treatment.

Neurophysiology of nausea

Nausea may arise from the gut directly – for example, from food poisoning or gastritis – or from the central nervous system – for example, due to motion sickness or alcohol intoxication. The neural pathways involved in nausea are probably the same as those that cause vomiting. These include the chemoreceptor trigger zone in the brainstem, which is sensitive to chemical and neuropeptide stimulation, and the vomiting centre on the floor of the fourth ventricle of the brain, which receives input from the chemoreceptor trigger zone, vagal and sympathetic afferents from the gastrointestinal tract and the cortex, hypothalamus and limbic system. Efferent neural impulses travel from the vomiting centre via the vagus, phrenic and spinal nerves to cause retching and vomiting.

During nausea, gastric myoelectric activity is disturbed causing reduced gastric tone and peristalsis. Antinausea medications may act centrally, such as prochlorperazine, or

peripherally, such as domperidone, or sometimes at both sites, such as metoclopramide.

Clinical assessment of the patient with nausea

The patient with nausea may be of any age. The pattern of symptoms and clinical course provide the best clues to establishing whether the nausea is organic, functional or drug related.

Aetiologically, nausea can originate from the gastrointestinal tract, the central nervous system or from toxic, metabolic or medication-related causes. It is important to define the onset and periodicity of symptoms, whether they are persistent or intermittent, their variability, and precipitating or relieving factors.

Associated symptoms such as headache, dizziness, vertigo and diplopia would point to a neurological cause. Dyspepsia, abdominal pain, bloating, heartburn, dysphagia, diarrhoea, constipation and/or weight loss would indicate a gastroenterological diagnosis. Onset of nausea after starting a new medication would point to the drug being the cause.

Nausea may be the presenting symptom in a patient with anxiety or depression, so it is important to take a psychosocial history.

Differential diagnosis

The more common causes of nausea are listed in the Box. Many of the causes will be obvious from the patient's symptoms and signs.

Functional nausea

Most cases of chronic nausea have a functional aetiology. Chronic nausea is usually mild or moderate in severity, often worse in the morning and may improve during the day. It can be intermittent, with good and bad days or longer periods of remission between symptomatic episodes. Some patients develop nausea after eating but in many there may be no obvious precipitating factors. Nausea may be associated with or precipitated by anxiety and stress. Generally, weight loss is not a feature, unless there is avoidance of food and therefore reduced caloric intake. Patients with functional nausea will often have spontaneous remissions and exacerbations.

Patients with functional nausea may also have functional dyspepsia (i.e. early satiety, epigastric pain and bloating) and/or symptoms of irritable bowel syndrome. These may coexist or alternate at different times.

Drug-induced nausea

Any recently introduced medication should be suspected as the cause of the nausea. Table 1 shows a list of drugs that can induce nausea. Ceasing the medication for a trial period should be considered.

COMMON CAUSES OF NAUSEA

Functional nausea

Idiopathic, the patient looks well and examination is normal, may be associated with nonulcer dyspepsia or irritable bowel syndrome

Infections

Gastroenteritis, *Helicobacter pylori*, systemic infections

Gastrointestinal

Peptic ulcer, oesophagitis, gastric cancer, colitis/Crohn's disease, constipation, gastric outlet obstruction, gastroparesis, hepatitis, cholangitis, liver cancer, intra-abdominal carcinomatosis, cholecystitis, pancreatitis, intestinal pseudo-obstruction

Central nervous system

Labyrinthine disorders, tumours, elevated intracranial pressure, demyelination, cranial irradiation

Endocrine

Pregnancy, uraemia, hyperparathyroidism, hyperthyroidism, Addison's disease, diabetic ketoacidosis

Other

Abdominal radiotherapy, hepatic congestion (congestive cardiac failure), myocardial infarction

Anxiety

Drug-induced

See Table 1 for a list of drugs that can cause nausea

Investigation of patients with nausea

Functional nausea is idiopathic and is a diagnosis of exclusion, so the GP must decide how far to investigate. Younger patients require less investigation than older patients, in whom organic disease is more likely. Physical examination of patients with nausea typically has normal results, but clues to an organic aetiology are hepatomegaly or hepatosplenomegaly, an abdominal mass, lymphadenopathy, clubbing, significant weight loss, pallor, jaundice or skin pigmentation.

After assessing the patient clinically, the GP must decide whether to reassure the patient and take an expectant observational approach, to investigate further or to refer the patient to a specialist.

Blood tests

Basic blood tests will detect most inflammatory, metabolic and neoplastic disorders. These tests should include a full blood count, multiple biochemical analysis, coeliac serology, breath test for *Helicobacter pylori* and measurement of C-reactive protein, thyroid-stimulating hormone, calcium and blood sugar levels and erythrocyte sedimentation rate. Occasionally, a patient with hepatic metastases or systemic disease may have normal blood test results.

Testing for tumour markers is not recommended as the diagnostic and predictive value is low. These tests should be reserved for patients with known diseases or to help pinpoint tumours with an uncertain primary origin.

Imaging

Some x-rays and scans can help diagnose the cause of nausea.

- Plain abdominal x-ray may show faecal loading, colonic pseudo-obstruction or a dilated stomach.
- Abdominal ultrasound is noninvasive and is an excellent way of imaging the liver, gall bladder, spleen and pancreas (which is sometimes obscured by stomach gas); it does not detect intraluminal pathology (e.g. colorectal cancer or a peptic ulcer).
- Abdominal CT scan may be an alternative to ultrasound but is more expensive. This should be reserved for patients with a higher suspicion for organic disease, such as hepatomegaly, an abdominal mass, abnormal liver function, anaemia or Crohn's disease. Generally, CT scans should be avoided in younger patients because of the radiation risk.
- Brain CT or MRI scans should be performed in patients with neurological symptoms to assess for an underlying tumour or degenerative or inflammatory brain disorders.
- Abdominal MRI scans are not required to investigate patients with nausea except when CT is contraindicated or to further evaluate a lesion detected on ultrasound or CT scan; no Medicare rebate is available for this indication.
- Radionuclide gastric emptying scans are used to investigate patients with suspected gastroparesis and are only occasionally helpful in patient management.
- Hepatobiliary iminodiacetic acid (HIDA) scans are likely to be useful only if the patient has biliary features (right upper quadrant pain).
- Barium meals and enemas are likely to be helpful only in selected cases, and generally endoscopy and colonoscopy are preferable.
- Manometry is a rarely performed investigation restricted to specialty motility units; it is usually used for the work up of patients with gastroparesis in whom a gastric pacemaker is being considered.

When to refer

Some GPs will refer their patient with nausea immediately to a gastroenterologist and others will conduct a full work up of the patient and then refer the patient on if the problem remains unresolved. This is an individual judgement but referral of the patient to a gastroenterologist should be considered when the diagnosis is not clear, when there is suspected or proven organic disease, or when the patient or GP want another opinion about the diagnosis or treatment.

Endoscopy of the upper gastrointestinal tract is sometimes performed, especially in patients older than 40 years of age. Some patients will have unsuspected ulcerative oesophagitis, moderate-to-severe gastritis, an ulcer or rarely a tumour. A normal result can be reassuring for the patient. Negative results on investigations, including blood tests, ultrasound and endoscopy, would generally confirm the clinical suspicion of functional nausea, and the patient should be reassured that there is no need for further investigation unless their symptoms change.

TABLE 1. DRUGS THAT CAN INDUCE NAUSEA*

Class	Drugs
Antibiotic	Erythromycin, metronidazole, sulfonamide, tinidazole and most others
Anticonvulsants	Carbamazepine, phenytoin, sodium valproate
Anti-inflammatory	Colchicine, mesalazine, sulfasalazine
Anti-Parkinson	Bromocriptine, L-dopamine
Biguanide	Metformin
Cardiac	Antiarrhythmics, beta blockers, calcium channel blockers, digoxin, diuretics
Chemotherapy	Cisplatin, doxorubicin, etoposide, 5-fluorouracil, vinblastine
Hormones	Anti-androgens, oestrogens, oral contraceptive pill, tamoxifen
Immunosuppressive	Azathioprine, mercaptopurine, methotrexate
NSAIDs, COX-2 inhibitors	Aspirin, celecoxib, diclofenac, ibuprofen, meloxicam, naproxen
Opioids	Codeine, fentanyl, morphine, oxycodone, tramadol
Sulfonylurea	Glipizide

* Listed alphabetically by class.

Treatment of nausea

There are many drugs available for the treatment of patients with nausea. Table 2 lists some of these drugs, how they act and any side effects that may occur.

Metoclopramide and prochlorperazine are suitable for short-term use. Note that younger patients have a higher incidence of acute dystonia as a side effect of these drugs. They should not be used long term because of the risk of tardive dyskinesia.

Droperidol, haloperidol and chlorpromazine can be used in patients with nausea

TABLE 2. MEDICATIONS USED IN THE TREATMENT OF NAUSEA*

Drug	Class	Action	Side effects	Notes
Amitriptyline, nortriptyline	Tricyclic antidepressant	Antihistamine; anticholinergic; serotonin reuptake inhibitor	Dry mouth; lethargy; somnolence	Used to treat functional nausea/dyspepsia and anxiety
Aprepitant, fosaprepitant	Neurokinin receptor antagonist	NK1 blocker		Used to treat nausea associated with chemotherapy (with ondansetron and corticosteroids)
Cannabinoids		Possibly reduces central 5-HT release	Dysphoria; xerostomia; psychoactive effects; hypotension; drowsiness	Used to treat nausea associated with chemotherapy (not TGA approved)
Chlorpromazine or prochlorperazine	Phenothiazine	Central D2 inhibition (M1 and H1 inhibition)	Sedation; anticholinergic side effects; acute dystonia (young patients); hypotension; tardive dyskinesia (long-term use)	Used to treat acute nausea of any cause and migraine
Cisapride	Serotonergic	Peripheral 5-HT4 agonist; prokinetic	Cardiac arrhythmias; prolonged QT interval; drug interactions; diarrhoea; cramps	Only available through the TGA Special Assess Scheme; not available on the PBS
Diphenhydramine	Antihistamine	Central H1 blockade	Drowsiness	Used to treat motion sickness and vestibular nausea
Domperidone	Benzamide	Peripheral D2 inhibition (minimally crosses the blood–brain barrier)	Headache; prolonged QT interval; drug interactions; hyperprolactinaemia (rare)	Used to treat acute nausea of any cause and migraine
Droperidol, haloperidol	Butyrophenone (phenothiazine-like)	Central D2 inhibition	Side effect profile is high; same as for phenothiazines	Second-line treatment; short-term use
Ginger		Peripheral and central action of gingerols and shogaols		Used in pregnancy (can also use vitamin B_6) and to treat motion sickness
Hyoscine or scopolamine	Anticholinergic	Central M1 blockade	Drowsiness; dry mouth	Used to treat motion sickness
Metoclopramide	Benzamide	Central and peripheral D2 inhibition (weak 5-HT3 blocker); cholinergic stimulation of gastric muscle	Akathisia; anxiety; acute dystonia in young patients; extrapyramidal side effects (long-term use)	Used to treat acute nausea of any cause and migraine
Ondansetron	Antiserotonin	Serotonin (5-HT3) antagonist	Constipation; headache; asthenia	Used to treat nausea associated with chemotherapy (PBS restricted) and hyperemesis gravidarum
Promethazine	Antihistamine/ phenothiazine	Central H1 blockade	Same as for phenothiazines	Used to treat motion sickness and hyperemesis gravidarum; second-line treatment for nausea

* Listed alphabetically by drug name. Abbreviations: D2 = dopamine 2; H1 = histamine 1; 5-HT = 5-hydroxytryptamine; M1 = muscarinic 1; NK = neurokinin.

that proves resistant to treatment, but the side effect profile is high and includes Parkinsonism, sedation, postural hypotension and dyskinesia. These drugs should only be used in the short term.

Domperidone is a peripheral dopamine antagonist with poor blood–brain barrier penetration. It is generally safe, but there has been a recent warning regarding cardiac arrhythmias. These are uncommon but can occur in patients taking more than 30 mg/day or in those with cardiac conduction defects, and domperidone interacts with medications that prolong the QT interval.

The antihistamines promethazine and diphenhydramine can be effective second-line treatments for patients with nausea, but sedation can be a problem. They are useful for the treatment and prevention of motion sickness.

Ondansetron is used predominantly to treat patients with nausea from chemotherapy and those with other drug-induced nausea and vomiting. It is listed on the PBS with authority for the management of nausea and vomiting associated with radiotherapy being used to treat malignancy or nausea and vomiting associated with cytotoxic chemotherapy being used to treat malignancy which occurs within 48 hours of chemotherapy administration. However, it is not reimbursed on the PBS for other indications and is expensive.

If anxiety and insomnia are associated features of nausea, low-dose tricyclic antidepressants, such as amitriptyline or nortriptyline 10 to 25 mg at night, can occasionally be effective for treating patients with functional upper gut symptoms, including nonulcer dyspepsia and nausea. However, they should be considered second-line treatments. The anticholinergic side effects can limit the use of tricyclic antidepressants.

Conclusion

Nausea is a common clinical presentation. If the patient's clinical history and examination are normal and the patient appears well, then usually the diagnosis will be functional or idiopathic nausea. This is a diagnosis of exclusion and a few basic tests will often rule out serious pathology. Treatment can involve reassurance and short- or long-term medications, but in some patients nausea becomes chronic/refractory and medications are ineffective. The possibility of organic pathology, such as cancer, inflammatory diseases, drug side effects and central nervous system causes of nausea, should always be considered. Nausea can be the main manifestation of anxiety and this diagnosis should be considered in all patients where no other cause is obvious. It is important not to over-investigate unnecessarily when initial basic investigation results are normal because this may lead to unnecessary worry, waste time and money, and suggest to the patient that there is a rare or missed diagnosis. Often a period of observation will result in improvement in symptoms and confirm the nonserious nature of the nausea.

I would give the patient who does not have worrisome symptoms or signs a month or two of observation and then reassess them. Then investigate with some basic tests if they are no better. I would investigate anyone over the age of 40 years early and/or refer them to a specialist. MT

Further reading

Lee M, Feldman M. Nausea and vomiting. In: Sleisenger M, Fordtran J, eds. Gastrointestinal disease. 5th ed. Philadelphia: WB Saunders; 1993. pp. 509-518.

Longstreth GF. Approach to the adult with nausea and vomiting. In: Talley NJ, Grover S, eds. UptoDate. Wolters Kluwer; 2014. Available online at: http://www.uptodate.com/contents/approach-to-the-adult-with-nausea-and-vomiting (accessed July 2015).

Longstreth GF, Hesketh PJ. Characteristics of antiemetic drugs. In: Talley NJ, Grover S, eds. UptoDate. Wolters Kluwer; 2014. Available online at: http://www.uptodate.com/contents/characteristics-of-antiemetic-drugs (accessed July 2015).

Longstreth GF, Lacy BE. Functional dyspepsia in adults. In: Talley NJ, Grover S, eds. UptoDate. Wolters Kluwer; 2014. Available online at: http://www.uptodate.com/contents/functional-dyspepsia-in-adults (accessed July 2015).

COMPETING INTERESTS: None.

Ask an expert

Puzzled by a presentation? Is the diagnosis a dilemma? What would a specialist in the relevant field do? Send us your baffling or hard-to-treat general practice cases for consideration in our 'Clinical case review' series. The case synopsis should be no longer than 150 words and include one or two specific questions that you want answered. Write to:
Medicine Today, PO Box 1473,
Neutral Bay NSW 2089 or
editorial@medicinetoday.com.au