Antiemetics: types, actions and uses

Abstract

Nausea and vomiting are common symptoms in the hospital setting, with numerous causes. Common precipitants leading to or complicating inpatient hospital admissions include nausea and vomiting secondary to drugs, gastrointestinal disturbances, metabolic aberrancies, and vestibular pathologies. Appropriate selection and prescribing of antiemetic drugs is therefore important for healthcare professionals. There are numerous antiemetics available to physicians, ranging from muscarinic, dopaminergic and serotoninergic drugs, each acting on a different part of the nausea–vomiting cascade. This review describes the main pathophysiological processes involved in the development of symptomatic nausea and vomiting, and gives an overview of how common antiemetic drugs function to alleviate symptoms, alongside cautions and contraindications in their usage.

Key words: Antiemetic; Cyclizine; Metoclopramide; Nausea; Ondansetron; Vomiting

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Introduction

Nausea and vomiting are common symptoms in the secondary care setting, both as frequent causes of emergency department admissions (Meek et al, 2015), and in patients admitted as a result of other conditions. Both symptoms are associated with significant socioeconomic costs (Quigley et al, 2001). In an inpatient and outpatient setting, medication can provide symptomatic relief, rendering use of antiemetic drugs an important consideration for clinicians. Notably, the most recent *World Health Organization List of Essential Medicines* (World Health Organization, 2019) had a specific antiemetic subheading, listing the commonly prescribed pharmacotherapies metoclopramide, ondansetron and aprepitant.

With a variety of causative factors, including postoperative nausea and vomiting, chemotherapy-associated nausea and vomiting, pregnancy, drugs and vestibular disturbances (Table 1), different antiemetics have a range of therapeutic indications. However, with varying degrees of unfavourable side effects, establishing risk–benefit profiles can prove difficult with these drugs.

This review describes the pathophysiological processes involved when patients develop symptomatic nausea and vomiting, and highlights factors that clinicians may wish to consider when using antiemetic agents for their patients.

From nausea to vomiting: brief pathophysiological mechanisms

The symptoms of nausea and vomiting arise from complex interactions between the CNS and gastrointestinal–neuroendocrine systems (Figure 1).

It is hypothesised that certain stimuli trigger neuroendocrine signalling in the nucleus tractus solitarius of the medulla oblongata (Hornby, 2001; Singh et al, 2016). This region of the CNS has been described as the 'vomiting centre' (Becker, 2010), although the complexity and anatomical diversity of the structures involved in the nausea–vomiting cascade have questioned the validity of this term (Diemunsch et al, 2009). Specific triggers can activate the nucleus tractus solitarius directly, for example, with vestibular causes, or gastrointestinal signalling secondary to vagal stimulation or serotonergic signalling (Sanger and Andrews, 2018). Alternatively, the nearby area postrema can undergo stimulation (usually secondary to recognition of circulating vomit-inducing drugs or compounds), in turn activating the nucleus tractus solitarius (Sanger and Andrews, 2018).

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Table 1. Common causes of symptomatic nausea and vomiting

Cause	Common examples
Drugs	Chemotherapeutic agents, antibiotics, opiates, anticonvulsants, alcohol, recreational drugs, anaesthetic agents
Abdominal pathologies	Bowel obstruction, gastroenteritis, appendicitis, cholecystitis, pancreatitis, inflammatory bowel disease, gastroparesis, gastro-oesophageal reflux disease, peptic or duodenal ulcer disease, constipation
Metabolic	Diabetic ketoacidosis, hyperuraemia, Addisonian crisis, hypercalcaemia
Vestibular	Ménière's disease, benign paroxysmal positional vertigo, viral labyrinthitis, vestibular neuronitis
Cardiac	Myocardial infarction, arrhythmia
Central nervous	Raised intracranial pressure, migraine, space-occupying lesion, meningoencephalitis, seizures
Psychiatric	Eating disorders, anxiety, cyclical vomiting disorders
Pregnancy	Hyperemesis gravidarum
Postoperative	-
Idiopathic	-

Adapted from Quigley et al (2001)

The overall result of nucleus tractus solitarius stimulation is output to motor neurones in the gastrointestinal tract, resulting in diaphragmatic and abdominal musculature contractility, retch and subsequent vomiting (Becker, 2010; Sanger and Andrews, 2018).

It is worth noting that symptomatic nausea is likely driven by vasopressin, higher cerebral function and subsequent imbalances in gastric function, but the exact mechanisms are yet to be fully understood (Singh et al, 2016; Sanger and Andrews, 2018).

Antiemetics: which, and when?

Numerous pharmacological agents are used as antiemetics by targeting different molecular pathways within the nausea–vomiting cascade (Figure 1). Table 2 summarises common antiemetic drugs discussed in this article, alongside indications for their use.

In practical terms, initiating management of nausea and vomiting should always be preceded by thorough history taking, examination and appropriate investigations to establish a cause. This will often allow successful identification of suitable antiemetic agents and thus provision of symptomatic relief (Quigley et al, 2001; Singh et al, 2016). Notably, management of the underlying cause is crucial in attempting to resolve symptoms (Quigley et al, 2001).

In cases of symptomatic nausea without vomiting, oral agents can be trialled first line in most cases, before using injectable forms with established vomiting in which absorption would be a concern (Table 2).

With each commonly prescribed class of drugs mentioned, there are a varying number of side effects to consider, outlined within each class of antiemetic.

Antihistamines and anticholinergics

Antihistamine agents antagonise both histamine and muscarinic receptors, and are effective agents for alleviating vestibular, motion-induced and more generalised symptoms of nausea and vomiting (Figure 1; Flake et al, 2015). In the UK, cyclizine is a commonly prescribed antiemetic within this class of drugs and can be bought over the counter in the USA (Arnestad et al, 2014). While the manufacturer advises caution regarding its use in the management of nausea and vomiting associated with pregnancy, it is commonly used (Jarvis and Nelson-Piercy, 2011; ADVANZ Pharma, 2018), and no

increased malformation rates have been observed with use in the first trimester (Briggs et al, 2017). Cyclizine should be used with caution in patients with hepatic impairment (ADVANZ Pharma, 2018).

Although cyclizine is usually well tolerated, its anti-muscarinic component can cause undesirable side effects – notably tachycardia, dry mouth, constipation and hypertension (Singh et al, 2016). There is also some evidence that hallucinogenic side effects, along with a user-perceived 'high', may be associated with addiction and misuse of this drug in its intravenous formulation, especially in younger people (Bassett et al, 1996; Bailey and Davies, 2008; Arnestad et al, 2014).

Anticholinergic antiemetics are also useful for motion-induced nausea and vomiting (Sanger and Andrews, 2018). They antagonise muscarinic receptors within the vestibular pathway (Figure 1). Hyoscine hydrobromide is a readily available example, purchasable as an over-counter preparation for travel sickness in the UK. Common side effects include

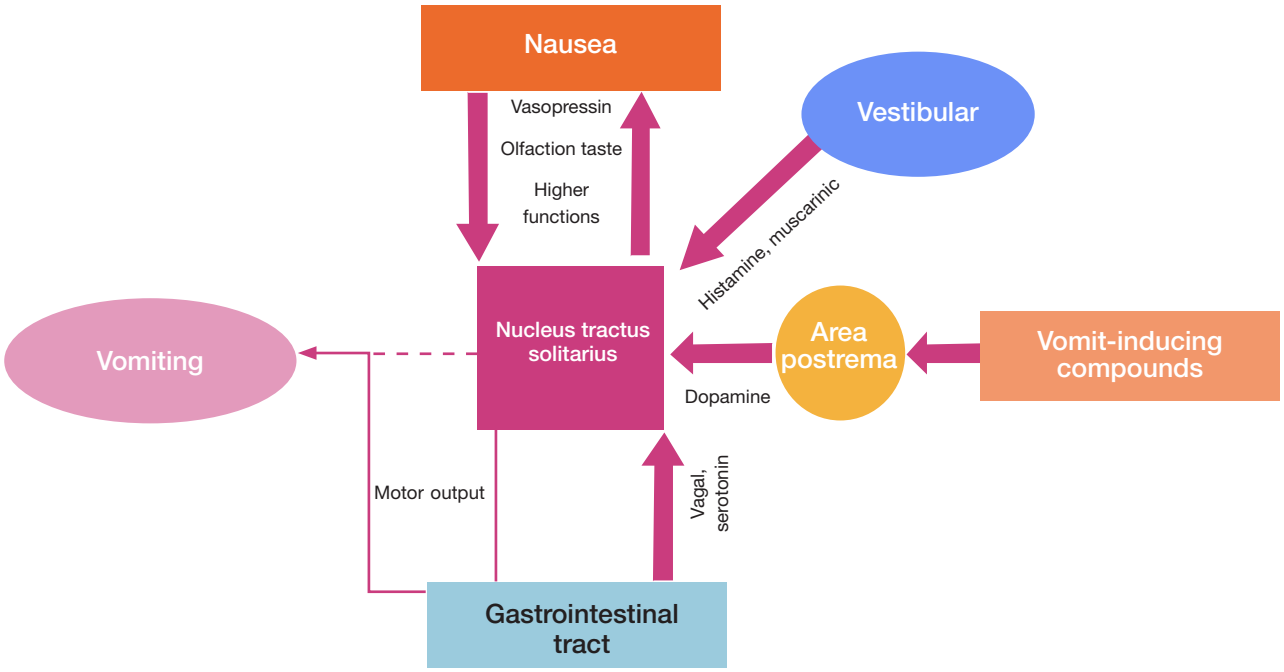

Figure 1. Summary of the nausea–vomiting cascade. Adapted from Singh et al (2016) and Sanger and Andrews (2018).

Table 2. Common antiemetic agents with predominant mechanisms of action and potential reasons for use

Drug	Receptor(s)	Potential indications
Cyclizine	Histamine, muscarinic	Motion-induced, vestibular
Hyoscine hydrobromide	Muscarinic	Motion-induced, vestibular
Domperidone	Dopamine	Gastroparesis, postoperative, chemotherapy-induced, acute generalised causes
Metoclopramide	Dopamine, serotonin	Gastroparesis, postoperative, chemotherapy-induced, acute generalised causes
Prochlorperazine	Dopamine, histamine, serotonin	Vestibular, migraine associated, acute generalised causes
Levomepromazine	Dopamine, histamine, muscarinic	Palliative
Ondansetron	Serotonin	Postoperative, chemotherapy-induced
Aprepitant	Neurokinin	Chemotherapy-induced
Xonvea	Histamine	Pregnancy induced

For drug dosages and formulations, refer to local trust guidelines

drowsiness, tachycardia, visual blurring, dry mouth, constipation and urinary retention. The drug should be used with caution in patients with hepatic or renal impairment (Bayer plc, 2019).

Anti-dopaminergic agents

Dopamine is a centrally acting neurotransmitter, responsible for potentiating signalling from the area postrema to the nucleus tractus solitarius (Figure 1; Sanger and Andrews, 2018).

Prochlorperazine is a commonly used phenothiazine antiemetic, recognisable as a first-generation antipsychotic drug. It acts predominantly by antagonising D_2 dopamine receptors in conjunction with histamine (H_1 and H_2) and serotonin receptors (Sanger and Andrews, 2018). Notable side effects include extrapyramidal-driven dyskinesias and, crucially, QTc interval prolongation (Becker, 2010; Flake et al, 2015). The drug should be avoided in patients with hepatic impairment, and starting doses reduced in those with severe renal impairment (Sanofi, 2020). Prochlorperazine is used in the management of pregnancy-induced nausea and vomiting (Jarvis and Nelson-Piercy, 2011), but if used in the third trimester, the neonate should be monitored for potential extrapyramidal side effects, irritability, tremors and agitation (Sanofi, 2020).

Levomepromazine is another phenothiazine agent, antagonising muscarinic M_1/M_2, dopaminergic $D_{1–4}$ and histamine H_1 receptors (Sanger and Andrews, 2018). Its neuroleptic and antiemetic properties give it an important role in the management of nausea and vomiting in the palliative setting, especially given its sedating and concomitant anti-anxiolytic properties (Leach, 2019). As with prochlorperazine, the manufacturer advises caution in patients with hepatic impairment, and lower starting doses with those with severe renal impairment (Sanofi, 2019).

Benzamides

Benzamides are another group of dopaminergic antagonists in the management of nausea and vomiting – two pertinent examples being metoclopramide and domperidone.

Metoclopramide antagonises D_2 dopamine receptors, with later literature establishing its ability to also agonise serotonergic 5-HT_4 receptor in the gut – it is therefore a useful prokinetic and antiemetic drug (Becker, 2010; Sanger and Andrews, 2018).

Domperidone acts as a selective D_2/D_3 dopamine receptor antagonist and is an effective, generally well-tolerated antiemetic agent (Sanger and Andrews, 2018). It also has activity as a prokinetic agent in the proximal gut (Lewis et al, 2016).

While both drugs cause QTc prolongation, domperidone has negligible penetration across the blood–brain barrier and thus patients are at a far lower risk of extrapyramidal side effects unlike with metoclopramide (Quigley et al, 2001; Sanger and Andrews, 2018). Domperidone has the advantage that it can be used in patients taking dopaminergic agonists, namely antipsychotics or drugs to treat Parkinson's disease (Quigley et al, 2001).

The Medicines and Healthcare products Regulatory Agency (2019) issued a safety update regarding use of domperidone. Important contraindications to its use remain in patients with moderate to severe hepatic impairment, underlying cardiac disease or known prolonged QTc interval, or significant electrolyte disturbances. Domperidone is not indicated for use in children aged 12 years and under because of a lack of supportive evidence.

Metoclopramide is useful in pregnancy-induced nausea and vomiting, with no known adverse side effects to the developing neonate (Jarvis and Nelson-Piercy, 2011; Briggs et al, 2017). Domperidone, however, should only be used if the potential benefit would outweigh risk given a lack of supportive evidence (Aurobindo Pharma - Milpharm Ltd, 2019). There is some evidence to support its safe use as an antiemetic in pregnancy – one prospective cohort study of approximately 200 pregnant south Korean women did not show any statistically significant increase in teratogenicity with domperidone administration (Choi et al, 2013).

Long-term use of metoclopramide has been linked to tardive dyskinesias that may persist even after cessation; the risk of this may be less prevalent than clinicians envisage (Rao and Camilleri, 2010). Metoclopramide should also be used with caution in younger

cohorts given the risk of provoking oculogyric crisis (Koban et al, 2014). An alert from the Medicines and Healthcare products Regulatory Agency (2013) advises that such potential neurological side effects should preclude long-term or high dose prescribing of metoclopramide.

In patients with severe hepatic impairment, metoclopramide doses should be halved; in those with severe renal impairment, it is advised the drug should either be avoided or used in small doses (Accord-UK Ltd, 2019). Domperidone should be avoided in those with moderate to severe hepatic impairment, whereas for those with renal impairment the frequency of administration should be reduced rather than the dose adjusted (Aurobindo Pharma - Milpharm Ltd, 2019).

As both drugs aid gut motility, they are useful in patients prone to suffering from gastroparesis (Quigley et al, 2001). Metoclopramide and domperidone are therefore contraindicated in cases of acute bowel obstruction or perforation (Accord-UK Ltd, 2019; Aurobindo Pharma - Milpharm Ltd, 2019).

Finally, mention must be given to haloperidol, an antipsychotic agent with antagonistic action upon D_2 receptors. While haloperidol has become established in the palliative care setting for control of symptoms of agitation as well as nausea (Leach, 2019), a meta-analysis demonstrated a powerful antiemetic property of the drug in both treatment and prevention of postoperative nausea and vomiting (Büttner et al, 2004).

Serotonin antagonists

Serotonin-mediated signalling occurs in the gut via 5-HT_3 receptors and has been implicated in the nausea and vomiting cascade (**Figure 1**; Sanger and Andrews, 2018). The likely mechanism is serotonin release from gastrointestinal enterochromaffin cells in response to stimuli, and subsequent 5-HT_3 mediated activation of vagal afferent nerves giving rise to symptomatic nausea and vomiting (Diemunsch et al, 2009; Smith et al, 2012). Important stimuli involved in the initial secretion of serotonin include gastrointestinal toxins and cytotoxic chemicals – 5-HT_3 antagonists were therefore heavily implicated in the treatment and prevention of chemotherapy-induced nausea and vomiting (Sanger and Andrews, 2018).

Ondansetron is well established as a powerful antiemetic within this group of drugs; it is commonly used in the management of postoperative, chemotherapy-induced as well as generalised nausea and vomiting with other causes (Wilde and Markham, 1996). The most commonly reported side effects include headache, constipation and dizziness (Wilde and Markham, 1996). Ondansetron causes QTc prolongation, but studies in adult and paediatric emergency department settings have shown no significant QTc prolongation with intravenous ondansetron when used acutely only (Moffett et al, 2016; Krammes et al, 2018).

Ondansetron has no established safety profile for use in pregnancy (Briggs et al, 2017). An American retrospective cohort study of nearly 89 000 women exposed to ondansetron during the first trimester of pregnancy showed a small but statistically significant increase in cleft palate formation, but no reported increase in the incidence of congenital cardiac defects (Huybrechts et al, 2018).

Finally, ondansetron should be used with caution in patients with moderate to severe hepatic impairment, with dose adjustments advisable (Wockhardt UK Ltd, 2019).

Neurokinin inhibitors

The role of antagonising neurokinin receptors to achieve antiemesis was first demonstrated in animal models and is linked to preventing the vomit-inducing effects of tachykinin 'substance P' in the CNS (Diemunsch et al, 2009; Sanger and Andrews, 2018).

Aprepitant, with its intravenous form fosaprepitant, is a relatively new antiemetic which is clinically effective in the treatment of postoperative and chemotherapy-induced nausea and vomiting (Diemunsch et al, 2009; Nishimura et al, 2015; Morais et al, 2018). The drug is not known to prolong the QTc interval (Marbury et al, 2009). Notable side effects include loss of appetite, gastrointestinal discomfort, lethargy, hiccups and headache (Zentiva, 2019).

Key points

- Nausea and vomiting are common symptoms leading to or complicating inpatient admissions.
- There are numerous causes to consider – different antiemetics are more effective than others depending upon the cause.
- It is crucial to ensure side-effect profiles are taken into consideration before administration of antiemetic drugs.
- Numerous antiemetics prolong the QTc interval and this must always be a consideration in each patient being treated.
- Future directions will likely focus upon the use of known pharmacological agents with favourable antiemetic profiles.

Future directions and conclusions

The future of antiemetic therapies remains vast.

In 2018, Xonvea – a preparation of the antihistaminergic agent doxylamine in combination with pyridoxine (vitamin B6) – became available for use in the UK following evidence demonstrating its effectiveness in treating pregnancy-induced nausea and vomiting (Koren et al, 2010).

Agonism of cannabinoid receptors has value in achieving antiemesis, particularly in the context of chemotherapy-induced nausea and vomiting (Parker et al, 2011). Likely mechanisms of action centre around both peripheral and central agonism of CB_1 receptors (Darmani, 2010; Parker et al, 2011). The development of therapeutic agents has been somewhat hindered by concerns about side-effect profiles subsequently, development of agents in the context of antiemesis is an ongoing challenge (Parker et al, 2011; Sanger and Andrews, 2018). Current National Institute of Health and Care Excellence (2019) guidelines only recommend usage of nabilone (a synthetic cannabinoid) in the context of chemotherapy-induced nausea and vomiting when symptoms persist despite usage of pre-existing agents.

While focus is often directed toward discovery of new drugs, does the future of antiemetic therapies in fact lie with pharmacotherapies we already know about?

Increasingly, existing drugs with traditionally different purposes have found a role to play as antiemetic agents. Antipsychotics, such as olanzapine and mirtazapine, and neuropathic agents, such as gabapentin, have been shown to have antiemetic properties (Sanger and Andrews, 2018).

Conclusions

Regardless of future therapies, clinicians have an array of effective antiemetic agents at their disposal – identification of the precipitating cause, in conjunction with appropriate patient selection, can allow successful treatment of nausea and vomiting in the majority of cases. Knowledge of contraindications and side-effect profiles can help clinicians make informed prescribing decisions for their patients.

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Conflicts of interest

The authors declare no conflicts of interest.

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