

Gastrointestinal Pharmacology: Antiemetics

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Antiemetics are used to prevent or stop vomiting; they act on the esophagus, stomach, intestines and even on the central nervous system where the vomiting center is located. In this article, we will cover in detail the various antiemetics, their mechanism of action, adverse effects/toxicity, contraindications, drug interactions and drugs of choice. Other important pharmacological and therapeutic aspects of individual drugs will also be noted.



Definition

Antiemetics are a group of drugs that suppress or prevent vomiting. The **chemoreceptor trigger zone (CTZ)**, vestibular system, vagal and spinal afferents, and other areas in the central nervous system relay to the **nucleus tractus solitarius (NTS, the vomiting center)**. As the CTZ (in area postrema) is unprotected by the blood-brain barrier, it is exposed to drugs in the bloodstream, hormones, toxins, and other substances that may stimulate emesis.

Pathophysiology

Radiation, cytotoxic drugs, and other gastrointestinal irritants cause the release of **5-HT** from **enterochromaffin cells**, which in turn acts on **5-HT₃ receptors** present on the extrinsic primary **afferent neurons** of the enteric nervous system. These afferent neurons have connections with **vagal and spinal visceral afferents**, which send

impulses to the NTS and CTZ. As 5-HT is released in large quantities, it may spill over into the circulation and reach the CTZ. It may also be released from platelets due to the effect of inflammatory mediators. However, 5-HT is not the only mediator involved in such signals; many peptides and other messengers are also involved.

When the body is rotated or equilibrium is disturbed—or as a result of ototoxic drugs—the **vestibular apparatus** generates impulses. These impulses reach the vomiting center in the **medulla oblongata** (mainly via the **cerebellum**) and utilize muscarinic as well as H1 receptors. Unpleasant sensory stimuli such as a startling vision, foul odor, severe pain or fear, the recalling of an unpleasant event, or the anticipation of an emetic stimulus (such as a repeat dose of cisplatin) cause nausea and vomiting through the higher centers.

Nausea is usually accompanied by reduced gastric tone and peristalsis. In the vomiting response, the fundus and body of the stomach, the **esophageal sphincter**, and the **esophagus** relax, while the duodenum and pylorus contract in a retrograde manner. **Rhythmic contractions** of the **diaphragm** and **abdominal muscles** then cause compression of the **stomach**, evacuating its contents via the **mouth**. Conditions that inhibit gastric emptying predispose individuals to vomiting.

Classification

Antiemetics are classified on the basis of their target receptors (see table). The **CTZ** and **NTS** express many receptors including histamine (H1), serotonin (5-HT3), cholinergic (muscarinic), dopamine (D2), opioid, and, probably, NK1.

	Category	Drugs
1	Serotonin (5-HT3) antagonists	Ondansetron , granisetron, dolasetron, palonosetron, tropisetron
2	Corticosteroids	Dexamethasone , methylprednisolone
3	Neurokinin receptor antagonists	Aprepitant , fosaprepitant
4	Phenothiazines and butyrophenones	Prochlorperazine, promethazine , thiethylperazine, droperidol, doxylamine
5	Substituted benzamides/prokinetics	Metoclopramide , trimethobenzamide, domperidone
6	H1 antihistamines	Diphenhydramine, dimenhydrinate, meclizine, hyoscine (scopolamine)
7	Benzodiazepines	Diazepam, lorazepam
8	Cannabinoids	Dronabinol, nabilone

- Setrons are 5-HT3 antagonists.
- Azepams are benzodiazepines.

Individual Drugs

Ondansetron is a **selective 5-HT3 antagonist** that acts mainly by affecting the **peripheral 5-HT3 receptors** on the spinal and vagal afferents. Thus, vomiting related to **vagal stimulation** (such as **postoperative vomiting**) and chemotherapy-associated emesis is effectively controlled with this drug. **Motion sickness-related** vomiting is poorly controlled.

Ondansetron, granisetron, and dolasetron have a serum half-life of 4–9 hours. They are administered once daily orally or intravenously, usually 30 minutes prior to **chemotherapy**. **Granisetron** is 10–15 times more potent than ondansetron.

Palonosetron has a greater affinity to **5-HT₃ receptors**. Its serum half-life is 40 hours.

All of these drugs undergo **hepatic metabolism** (dose reduction is not needed in renal disease). They are generally well-tolerated and safe. They can **prolong the QT interval** (most prolongation is accomplished with dolasetron).

Dexamethasone: This corticosteroid **potentiates the effect of 5-HT₃ antagonists**, especially in chemotherapy. Adverse effects include **weight gain, osteoporosis**, and increased hair growth. Dexamethasone should be used only in highly **emetogenic chemotherapy**.

Aprepitant: This **neurokinin receptor (NK1) antagonist** acts on the area postrema (central blockade). It is taken **orally** and has a half-life of 12 hours.

Fosaprepitant is administered **intravenously** and is converted to aprepitant within 30 minutes of infusion. Aprepitant undergoes hepatic metabolism (**cytochrome P3A4**).

These drugs are used in combination with a **5-HT₃ antagonist** and a corticosteroid to prevent delayed emesis in chemotherapy patients. Adverse effects include fatigue, **diarrhea**, and dizziness. Drugs that **inhibit CYP3A4** (eg, ketoconazole, ciprofloxacin, and clarithromycin) may lead to increased plasma levels of aprepitant. They can also **decrease the international normalized ratio** in individuals on warfarin.

Promethazine and other phenothiazines have antiemetic and sedative actions in addition to being **antipsychotics**. Promethazine has a duration of action of 4–6 hours. Adverse effects include mouth dryness and sedation. Intravenous administration can cause severe **tissue injury**, burning, or **thrombophlebitis**, leading, in some cases, to **gangrene** and the need for amputation. The preferred mode of administration is deep intramuscular. It is avoided in children < 2 years of age due to the risk of **respiratory depression**. It is metabolized in the liver (CYP2D6) and has a half-life of 10 hours intramuscularly, 9–16 hours intravenously, and 16–19 hours orally.

Droperidol, an antipsychotic butyrophenone, exhibits antiemetic properties secondary to central dopaminergic blockade. The onset of action is within 3–10 minutes of intake. Usually, its action lasts for 2–4 hours, although sometimes it reaches up to 12 hours. Adverse effects include extrapyramidal symptoms and hypotension. It may cause QT prolongation leading to **torsades de pointes**.

Doxylamine is an H₁ antihistaminic that has a pronounced anticholinergic activity. It is specifically promoted in India in combination with pyridoxine (vitamin B) for **pregnancy-related emesis**. However, it is not recommended for this use in the United States or the United Kingdom.

Metoclopramide is thought to prevent emesis by **dopamine receptor blockade**. It enhances **gastric peristalsis** and causes relaxation of the pylorus and the proximal duodenum. Consequently, gastric emptying is sped up. As well, it increases lower esophageal sphincter tone, preventing **gastroesophageal reflux**. Its antiemetic action is brought about by **antidopaminergic (D₂)** action on the CTZ. Adverse effects include sedation, dizziness, **galactorrhea, gynecomastia**, and **extrapyramidal features** such as dystonia, **parkinsonism**, and restlessness. It can block the therapeutic action of levodopa due to dopamine receptor blockade in the basal ganglia.

Domperidone is a **D₂ antagonist**, related chemically to haloperidol but pharmacologically to metoclopramide. It has a lower antiemetic and **prokinetic effect** compared with metoclopramide. Domperidone crosses the blood–brain barrier

poorly and therefore extrapyramidal side effects are rare, although **hyperprolactinaemia** may occur. It acts on the CTZ, which is not protected by the blood-brain barrier. It has been administered with levodopa and bromocriptine as it counteracts their dose-limiting emetic action in parkinsonism, while the therapeutic effect remains unchanged. Domperidone is absorbed orally but due to considerable first-pass metabolism, bioavailability is only 15%. Metabolites are released via urine. Its plasma half-life is around 7.5 hours. Adverse effects are fewer compared with metoclopramide. However, **cardiac arrhythmias** have been reported with rapid intravenous administration.

Diphenhydramine is a first-generation H₁ antihistaminic agent with a good sedative effect. It is indicated for **motion sickness**. Its onset of action is within 15–30 minutes and its duration reaches 10–12 hours. It undergoes first-pass metabolism in the liver and metabolites are excreted mainly via urine. Adverse effects include **anticholinergic effects** such as dry mouth, cycloplegia, urinary retention, and confusion.

Meclizine is also an H₁ antihistaminic, with fewer anticholinergic effects. Other than for motion sickness, it may also be used for the treatment of **vertigo** due to **labyrinthitis**. Onset of action is within 30–60 minutes and it lasts for 12–24 hours. It is metabolized in the liver (**CYP2D6**).

Hyoscine (scopolamine) is a muscarinic receptor antagonist and a **preferred agent for motion sickness**. As its anticholinergic manifestations are high when administered orally or parenterally, it is usually used as a **transdermal patch**. The patch contains 1.5 mg of hyoscine, which can be placed behind the pinna, and delivers the drug over a span of 3 days. The patch should be applied 4 hours before planned travel. Hyoscine is metabolized by the liver and excreted in the urine. It has a half-life of 9.5 hours.

Lorazepam and diazepam are used prior to chemotherapy to decrease anticipatory or anxiety-related vomiting. They increase the **frequency of opening** of GABA_AR-Cl⁻ channels. Onset of action is within 1–3 minutes and lasts for up to 8 hours. They undergo **glucuronic acid conjugation** in the liver and inactive metabolites are excreted via urine.

Dronabinol is a synthetic form of Δ^9 -**tetrahydrocannabinol (THC)**, the main psychoactive constituent in marijuana. It undergoes significant first-pass metabolism in the liver and its metabolites are excreted gradually over days to weeks. Its major use is to prevent chemotherapy-related emesis. Adverse effects include **tachycardia**, **conjunctival congestion**, and **orthostatic hypotension**.

Nabilone is a related **THC analog** approved for clinical use in the United States. It acts on cannabinoid receptors in the central nervous system and therefore its use should be avoided in emotionally disturbed patients and those with **concomitant alcohol or substance use disorder** (ie, psychotropic drugs). It can affect the ability to drive a vehicle and perform hazardous tasks. The elimination half-life for the parent compound is 2 hours; for the metabolites, it is 35 hours. Most nabilone is excreted via bile after undergoing metabolism by direct enzymatic oxidation.

References

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