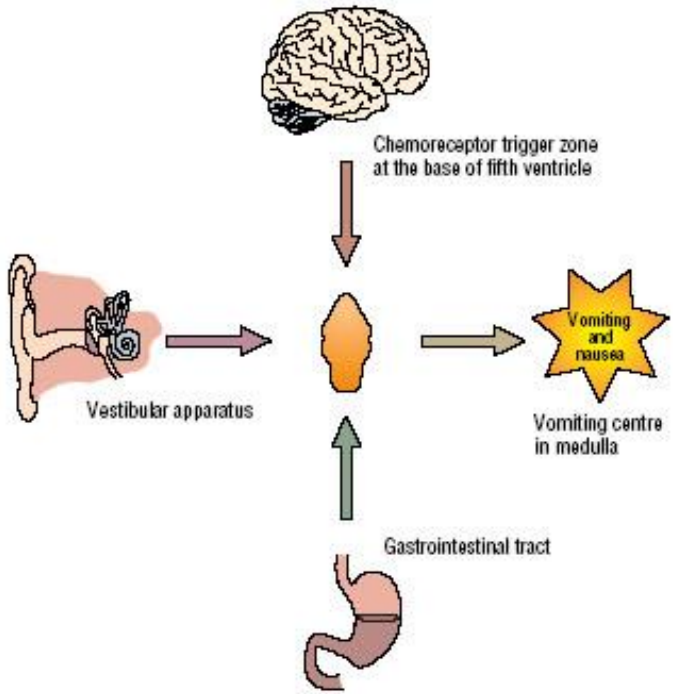
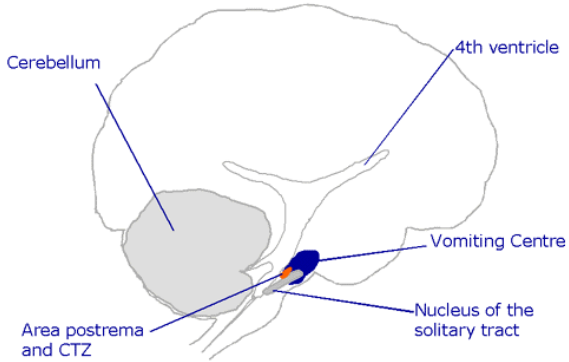
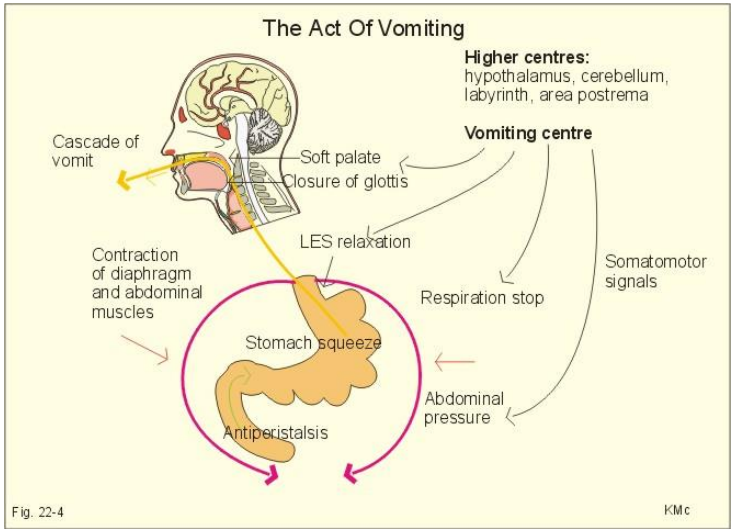
# Drugs used in the treatment of gastric tract disease

## 41. Anti-emetic drugs




| Pathway | Potentially beneficial drugs |
|---|---|
| Chemoreceptor trigger zone | Dopamine and 5-HT3 serotonin receptors |
| Vestibular | Cholinergic muscarinic receptors |
| Vomiting centre pathways | Histamine and cholinergic muscarinic receptors |
| Gastric stasis | Dopamine and 5-HT4 serotonin receptors |



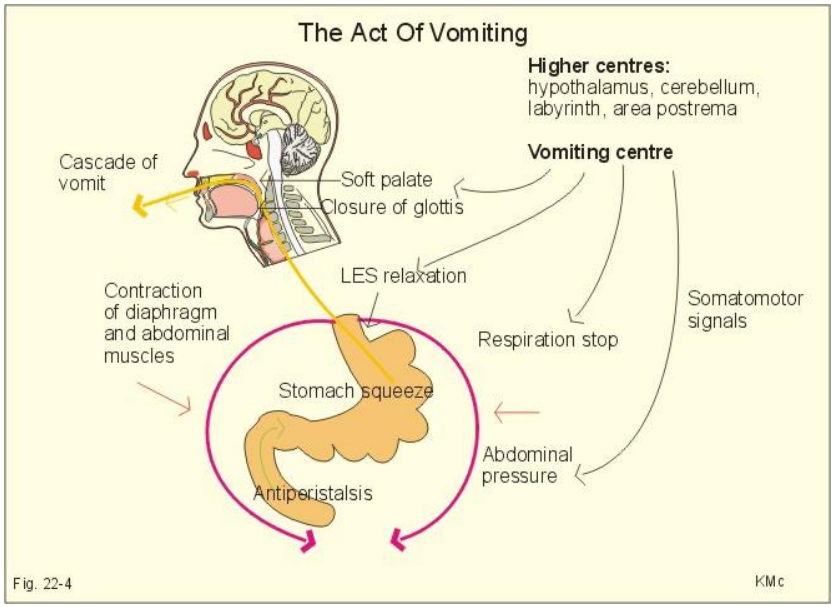



The term *anti-emetic* was derived from *emesis*, the Greek word for *to vomit*. Hence, vomiting is also referred to as emesis.

The vomiting centre in the brain consists of two areas located symmetrically in the medulla which coordinate the sequence of muscular contractions involved in vomiting.

Additionally, the chemoreceptor trigger zone (CTZ), which consists of twin areas in the floor of the fourth ventricle, detects noxious ingested chemical stimuli and may be stimulated directly by parenteral drugs.

Central and afferent signalling involves serotonin at 5-$HT_3$ receptors, dopamine at $D_2$ receptors, acetylcholine at muscarinic receptors and histamine at $H_1$ receptors.



The following causes of nausea and vomiting are known:

- Dietary indiscretion, food ‘poisoning’, alcohol excess
- Fever
- Pregnancy
- Organic disease: e.g. renal failure (uremia), diabetic ketoacidosis, hypercalcemia, myocardial infarction, chronic bronchitis
- Gastrointestinal diseases and procedures: e.g. peptic ulcer, appendicitis, peritonitis, constipation, gastric carcinoma, gastric surgery
- Central nervous system disease: e.g. migraine, meningitis, vestibular Méniere’s disease, abscesses and tumours, motion sickness
- Psychogenic symptoms
- Drugs: e.g. opioids, cytotoxic chemotherapy, digoxin overdose.

## The cytostatics cause:

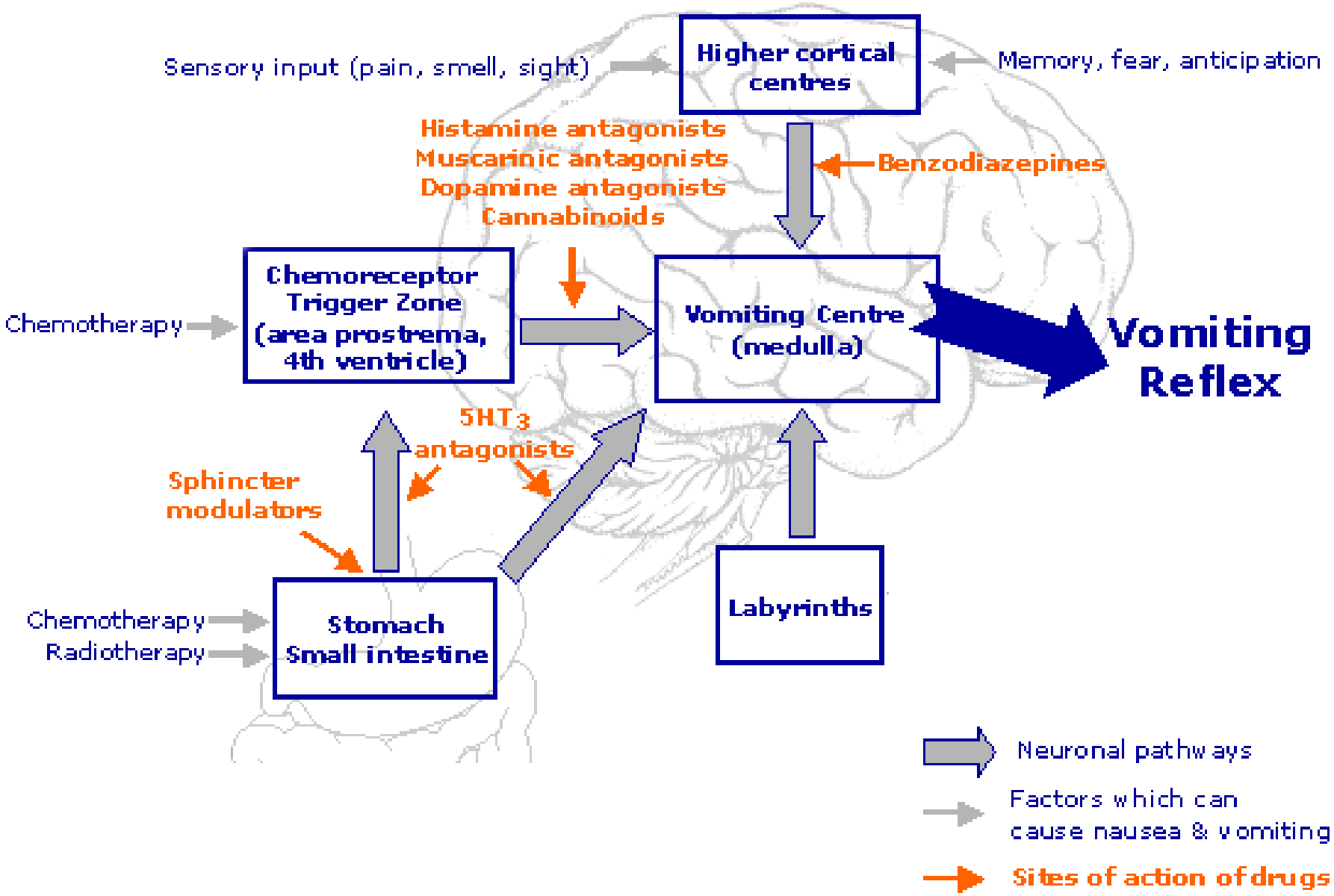
- Psychogenic vomiting, which appears before or at the beginning of therapy
- Intense vomiting, appearing up to 24 h after the administration of a cytostatic, which is caused by its toxic action on the digestive tract
- Less intense, delayed vomiting, occurring more than 24 h after administering a cytostatic.

*The British National Formulary* (BNF) lists three classes of potentially emetogenic antineoplastic drugs and procedures but this depends on dosage:

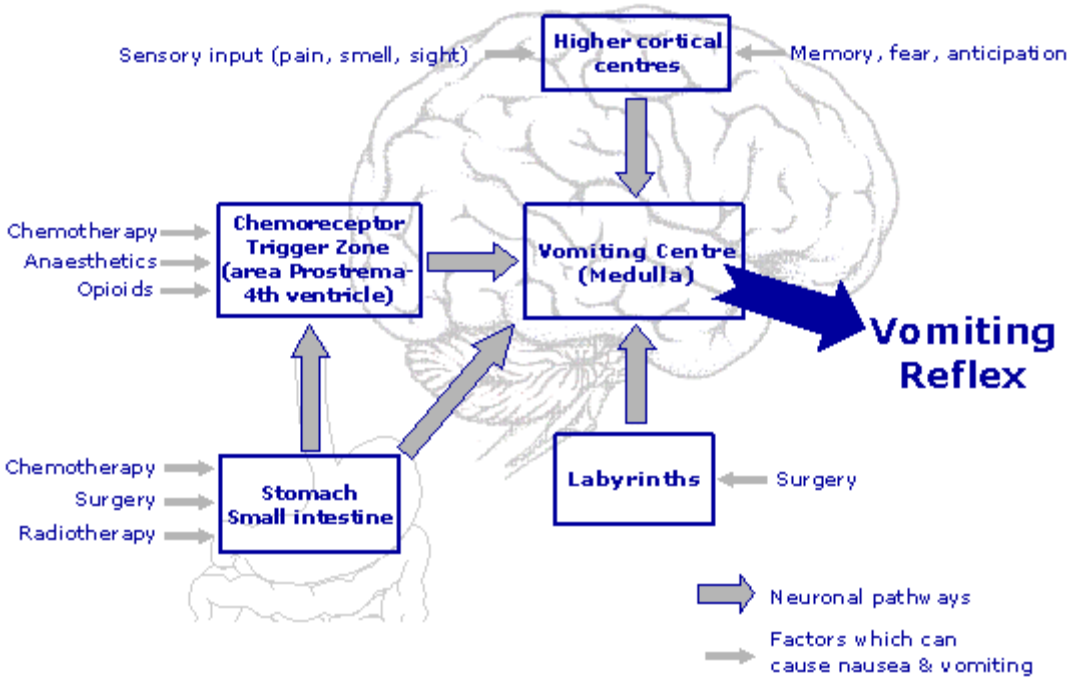
- Highly emetogenic: cisplatin, dacarbazine, high-dose cyclophosphamide
- Moderately emetogenic: doxorubicin, low to moderate doses of cyclophosphamide, high-dose methotrexate, mitoxantrone (mitozantrone)
- Mildly emetogenic: etoposide, fluorouracil, methotrexate (<0.1 $g/m^2$), vinca alkaloids, abdominal radiotherapy.

The following drugs are used to remedy or prevent vomiting:

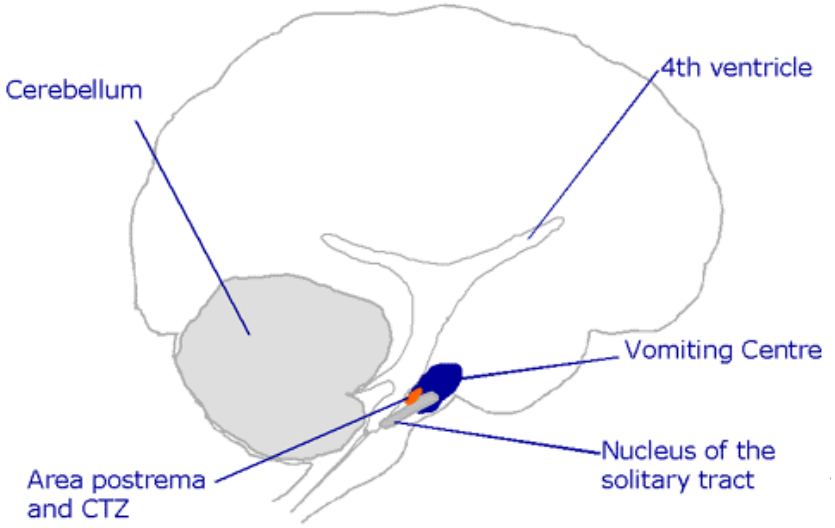
- $H_1$ antagonists: e.g. dimenhydrinate, cyclizine, meclozine, promethazine
- $D_2$-antagonists: phenothiazines (e.g. chlorpromazine, prochlorperazine, thiethylperazine), butyrophenones (e.g. droperidol, haloperidol), benzimidazoles (domperidone), substituted benzamides (metoclopramide, trimethobenzamide)
- Specific 5-$HT_3$ antagonists: granisetron, ondansetron, tropisetron, dolasetron, palonosetron
- Other anti-emetic drugs
  - Cannabinoids (dronabinol, nabilone),
  - Antimuscarinics (hyoscine = scopolamine)
  - $NK_1$ receptor antagonists (aprepitant).


Sensory input (pain, smell, sight)
Higher cortical centres
Memory, fear, anticipation
Histamine antagonists
Muscarinic antagonists
Dopamine antagonists
Cannabinoids
Benzodiazepines
Chemoreceptor Trigger Zone (area prostrema, 4th ventricle)
Chemotherapy
Vomiting Centre (medulla)
Vomiting Reflex
5HT3 antagonists
Sphincter modulators
Chemotherapy
Radiotherapy
Stomach Small intestine
Labyrinths
Neuronal pathways
Factors which can cause nausea & vomiting
Sites of action of drugs

The anti-emetics are used prophylactically or therapeutically in the prevention of nausea and vomiting caused by the disturbance of the labyrinth, postoperative problems and during therapy with cytostatics and radiotherapy.



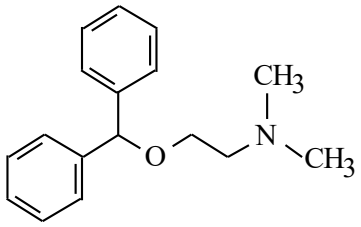

Long-lasting vomiting may lead to the disturbance of the water-electrolyte balance, oliguria, dehydration, increased body temperature or even a coma.



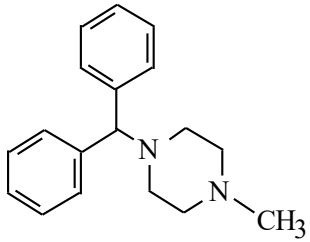
# 41.1. $H_1$-Histaminergic receptor antagonists

Some antihistaminics show slight secondary anti-emetic action.

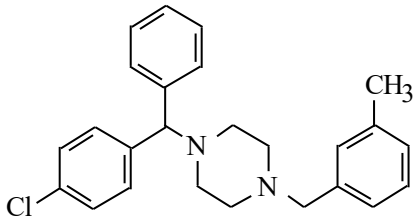
As a result of their chemical modification new drugs have been synthesized which demonstrate better anti-emetic action and weak antihistaminic activity, such as benzhydryl ethanolamine derivatives (diphenhydramine) and piperazine derivatives (cyclizine, meclozine). Diphenhydramine is mostly used with 8-chlorotheophylline (dimenhydrinate).




*Diphenhydramine*




*Cyclizine*, MAREZINE




*Meclozine*, BONAMINE

*Dimenhydrinate* (aviomarin) = diphenhydramine + 8-chlorotheophiline (1:1)

These drugs act peripherally.

They are recommended in the prevention and therapy of motion sickness (kinetosis), Méniere's disease and in postoperative vomiting.

Dimenhydrinate is a drug of choice in motion sickness.

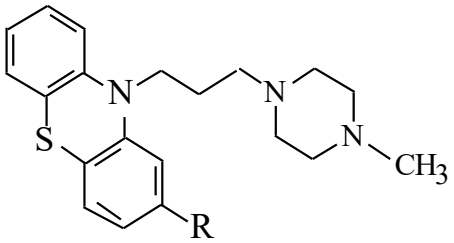
Those anti-emetics that act selectively on the CTZ are ineffective in kinetosis.

# 41.2. $D_2$-Dopaminergic receptor antagonists

The tricyclic phenothiazine neuroleptics (e.g. chlorpromazine) also demonstrate weak anti-emetic activity.

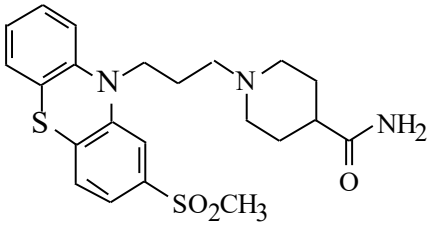
This action has been enhanced by the introduction of an ethylthiol substituent into position 2 of the phenothiazine ring or by introducing a carbamoyl substituent into the piperazine or piperidine ring.

Thioproperazine, tiethylperazine and metopimazine are used as anti-emetics.




*Thioproperazine*, R = $SO_2(CH)_2$; MAJEPTIL

*Thiethylperazine*, R = -S-$C_2H_5$; TORECAN




*Metopimazine*, VOGALEN

In terms of anti-emetic action, VOGALEN acts 150 times more strongly and MAJEPTIL 50 times than chlorpromazine (the parent phenothiazine neuroleptic).

The phenothiazine anti-emetics decrease the sensitivity of the vomiting center (central action) and cholinergic nerves (peripheral action).

The phenothiazine derivatives are recommended in the patient's intolerance to cytostatics, tuberculostatics, antibiotics and salicylates.

They may also be used in the cases of severe vomiting in pregnancy but only for a short time (24–48 h) and under specialist obstetric supervision.

Generally, nausea and vomiting in the first trimester can be tolerated and no drug treatment is indicated because of the risk of teratogenicity.

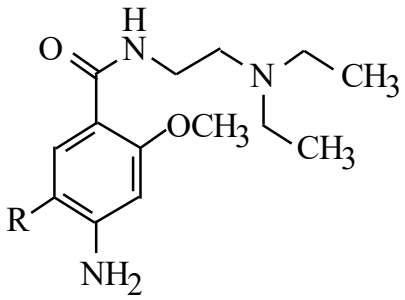
In common with other drugs, anti-emetics should be avoided in pregnancy, especially in the 3rd to 11th weeks.

**The benzamide derivatives** (bromopride and metoclopramide) and benzimidazolone derivatives (domperidone) also show anti-emetic activity.

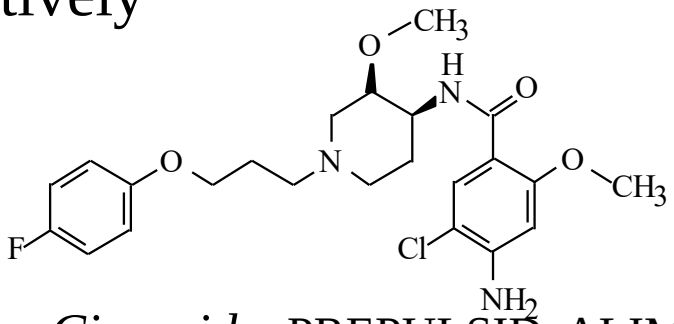
They are recommended in post-operative vomiting and vomiting caused by cytostatics.

Benzamide and benzimidazolone derivatives do not prevent vomiting caused by the disturbance of the labyrinth.

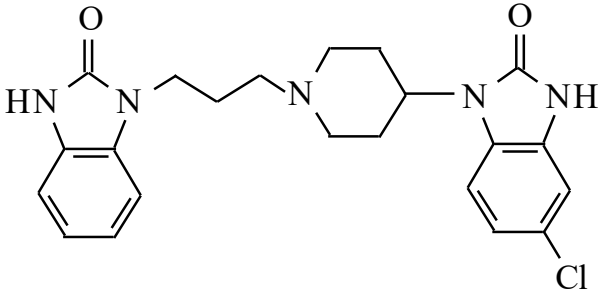
They also act laxatively




*Metoclopramide*, R = Cl; METOCLOPRAMIDUM
*Bromopride*, R = Br; CASCAPRIDE




*Cisapride*, PREPULSID, ALIMIX

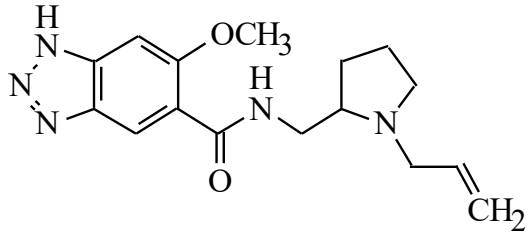



*Domperidone*, MOTILIUM

Domperidone shows a similar chemical structure to benperidole (butyrophenone-derivative neuroleptic) but it does not demonstrate central action because its octanol/water partition coefficient is approximately 16 times less than that of benperidole and so it does not permeate the blood-brain barrier.

Some drugs of that group, e.g. cisapride, do not only block peripheral $D_2$-dopaminergic receptors but also stimulate the release of acetylcholine, mainly in the myenteric plexus (a group of small ganglions, composed of parasympathetic nervous cells).

Alizapride (benzotriazole derivative) is used to prevent vomiting during antineoplastic therapy.




*Alizapride*, PLITICAN

# 41.3. 5-$HT_3$-Serotoninergic receptor antagonists

The cytostatics and radiotherapy cause the release of serotonin (5-HT) in the small intestine. The stimulation of the central and peripheral 5-$HT_3$ receptors by serotonin leads to nausea and vomiting.

Such receptors are present mostly on the ends of the afferent branches of the vagus nerve, which send signals directly to the brain's vomiting center in the medulla oblongata, and in the chemoreceptor trigger zone of the brain, which receives "input" from nausea-inducing agents in the bloodstream and communicates with the vomiting center.

By preventing activation of these receptors, 5-$HT_3$ antagonists interrupt one of the pathways that lead to vomiting.

**Derivatives of**

- carbazole (ondansetron),
- indole (tropisetron and dolasetron),
- indazole (granisetron) or
- isoquinoline (palonosetron)

**are used to achieve that.**

Their advantage is the selectivity of action at 5-$HT_3$ receptors.

The 5-$HT_3$ receptors antagonists are more effective for this purpose than metoclopramide and other anti-emetics.

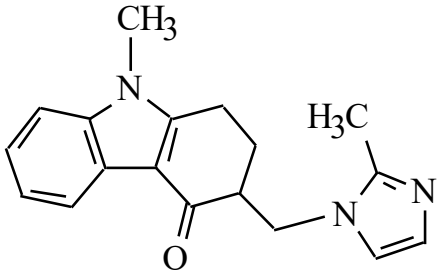
Palonosetron is the most effective of the 5-$HT_3$ antagonists in controlling delayed chemotherapy-induced nausea and vomiting (CINV) and is the only drug of its class approved for this use by the US FDA in 2007.

The adverse effects of the 5-$HT_3$, receptor antagonists have not been sufficiently documented yet.

The most frequent ones include sedation, headache, vertigo, gastrointestinal disturbances, temporary asymptomatic increased liver aminotransferase levels and, rarely, type 1 hypersensitivity (immediate).

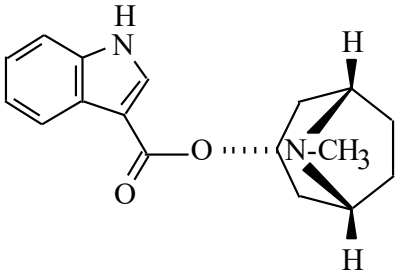
Heart action disturbances, blood pressure changes, influenza-like symptoms (fever, cough, shivers), blurred vision and others can also appear.

All of these 5-$HT_3$ receptor blockers are considerably more expensive than other agents and are used as first-line drugs only in oncology and intractable vomiting.



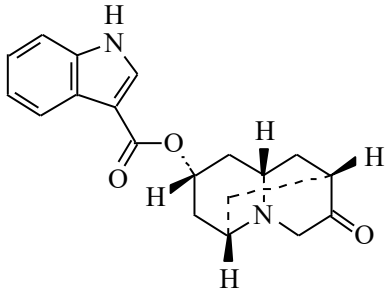

*Ondansetron*, ATOSSA, EMETRON, ZOFRAN

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1*H*-imidazol-1-yl)-methyl]4*H*-carbazol-4-one



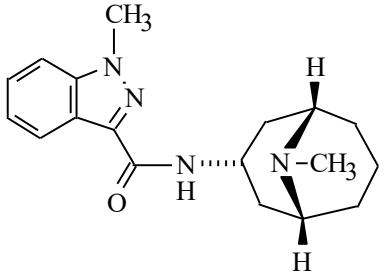

*Tropisetron*, NAVOBAN

*endo*-8-Methyl-8-azabicyclo[3.2.1]-oct-3-yl 1*H*-indole-3-carboxylate



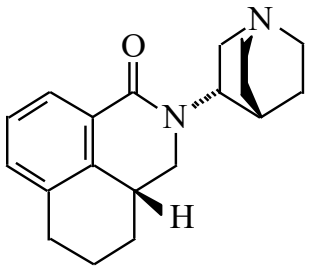

*Dolasetron*, ANZEMET

2α,6α,8α,9aβ-Octahydro-3-oxo-2,6-methane-2*H*-quinolizine-8-yl 1*H*-indole-3-carboxylate




*Granisetron*, KYTRIL

*endo*-1-Methyl-*N*-(9-methyl-9-azabicyclo-[3.3.1]non-3-yl)-1*H*-indazole-3-carboxamide




*Palonosetron*, ALOXI

(3*aR*)-2-[(3*S*)-1-azabicyclo[2.2.2]oct-3-yl]-2,3,3*a*,4,5,6-hexahydro-1*H*-benz[*de*]isoquinoline-1-one

It is believed that ondansetron may have other interesting properties, e.g. the improvement of memory in the elderly.

Dolasetron also demonstrates antimigraine action.

Alosetron and cilansetron - are not antiemetics; instead, they are indicated in the treatment of a subset of irritable bowel syndrome where diarrhea is the dominant symptom.

# 41.4. Other anti-emetic drugs

*Antimuscarinics*

Motion sickness is best controlled with drugs which act at the vomiting center, especially hyoscine (scopolamine).

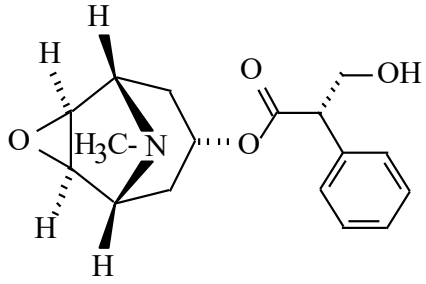
Hyoscine is available as tablets, slow-release tablets and a transdermal formulation.

The latter two formulations may help to minimize the anticholinergic side effects of hyoscine: drowsiness, blurred vision, cardiovascular disease, dry mouth, urinary retention, and confusion in the elderly.

Hyoscine is contraindicated in patients with closed-angle glaucoma.

*Hyoscine*

BUSCOLYSIN, BUSCOPAN, SCOPOLAN

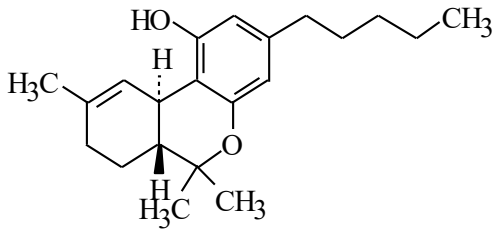


*Cannabinoids*

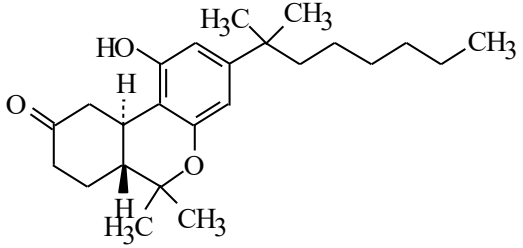
Dronabinol stimulates $CB_1$–cannabinoid receptors on the neurons of the vomiting center. Its use is limited to the prevention of vomiting in patients during antineoplastic chemotherapy, unresponsive to other anti-emetics.

Dronabinol is effective but it has a low therapeutic coefficient and demonstrates many adverse effects such as tachycardia, personality disorders characteristic of the dependence drugs (mood change, paranoidal reactions, thinking disturbance).

After this drug is discontinued withdrawal syndrome can appear.




*Dronabinol*, MARINOL



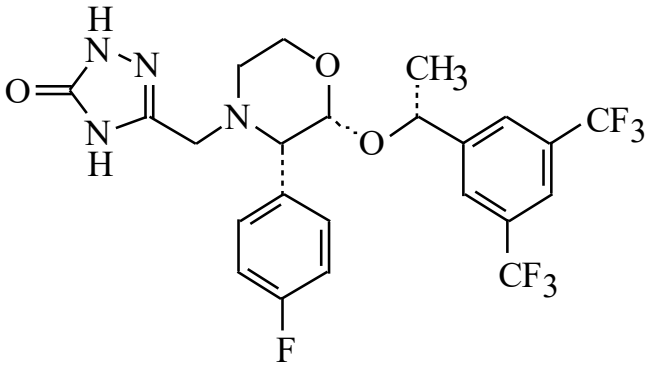

*Nabilone*, CESAMET

Nabilone demonstrates anxiolytic, myorelaxative and anti-emetic action. Long-term use of nabilone is contraindicated because it may be neurotoxic.

## *$NK_1$ receptor antagonists*

Recently, aprepitant has been approved as an anti-emetic drug during antineoplastic chemotherapy.

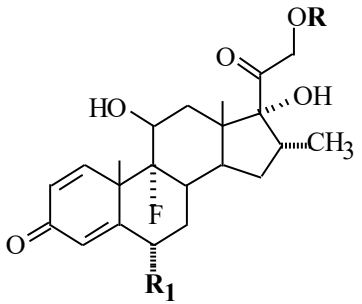
In combination with ondansetron and dexamethasone it is also effective during cisplatin therapy.




*Aprepitant*

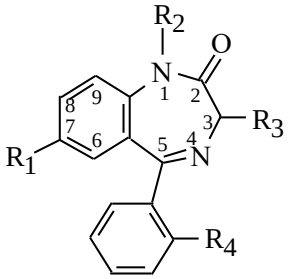
(3-[[(2*R*,3*S*)-3-(*p*-Fluorophenyl)-2-[[(α*R*)- α-methyl-3,5-bis-(trifluoromethyl)benzyl]oxy]morpholine]methyl-$\Delta_2$-1,2,4-triazolin-5-one

*Dexamethasone*, R = H, $R_1$ = H
DEXAMETHASON, DEXAPOLCORT




*Corticosteroids*

Dexamethasone has also been reported to be as effective as ondansetron in controlling the acute vomiting caused by moderately emetogenic cytotoxic chemotherapy, and is the drug of choice for preventing delayed vomiting. It is thought that it may act at both $D_2$ and 5-$HT_3$ receptors.




$R_1 = R_4 = Cl$; $R_2 = H$; $R_3 = OH$

*Anti-emetic adjuncts*

The benzodiazepines, e.g. lorazepam, are useful for the management of cytotoxic drug-induced emesis, because they have sedative and amnesic effects. If a benzodiazepine is administered before chemotherapy the patient has little recall of the procedure and its effects.

*Betahistine*

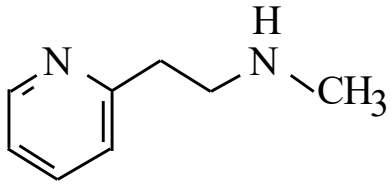
Betahistine is used in Méniere's disease.

This is associated with idiopathic dilatation of the endolymph system in the inner ear. It causes recurrent attacks of vertigo, deafness and tinnitus (a subjective sensation of noise generated within the auditory system), associated with nausea and vomiting.

Over a period of years the disease progresses to permanent deafness, and the vertigo remits.

Betahistine reduces endolymph pressure in the inner ear and so is used in treatment, with variable benefit. In an acute attack cyclizine and prochlorperazine may be useful.

Cinnarizine, dimenhydramine and hyoscine may also be beneficial.




*Betahistine*, BETASERC, FIDIUM