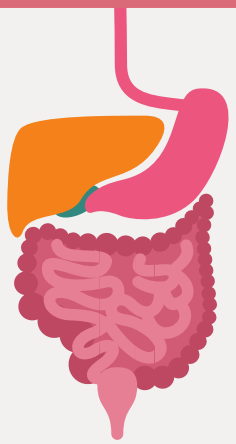
Anti-emetic drugs



Objectives:

- Classify the main different classes of antiemetic drugs according to their mechanism of action.
- Know the characteristic pharmacokinetics & dynamics of different classes of antiemetic drugs.
- Identify the selective drugs that can be used according to the cause of vomiting.
- Learn the adjuvant antiemetics.
- Describe the major side effects for the different classes of antiemetics.

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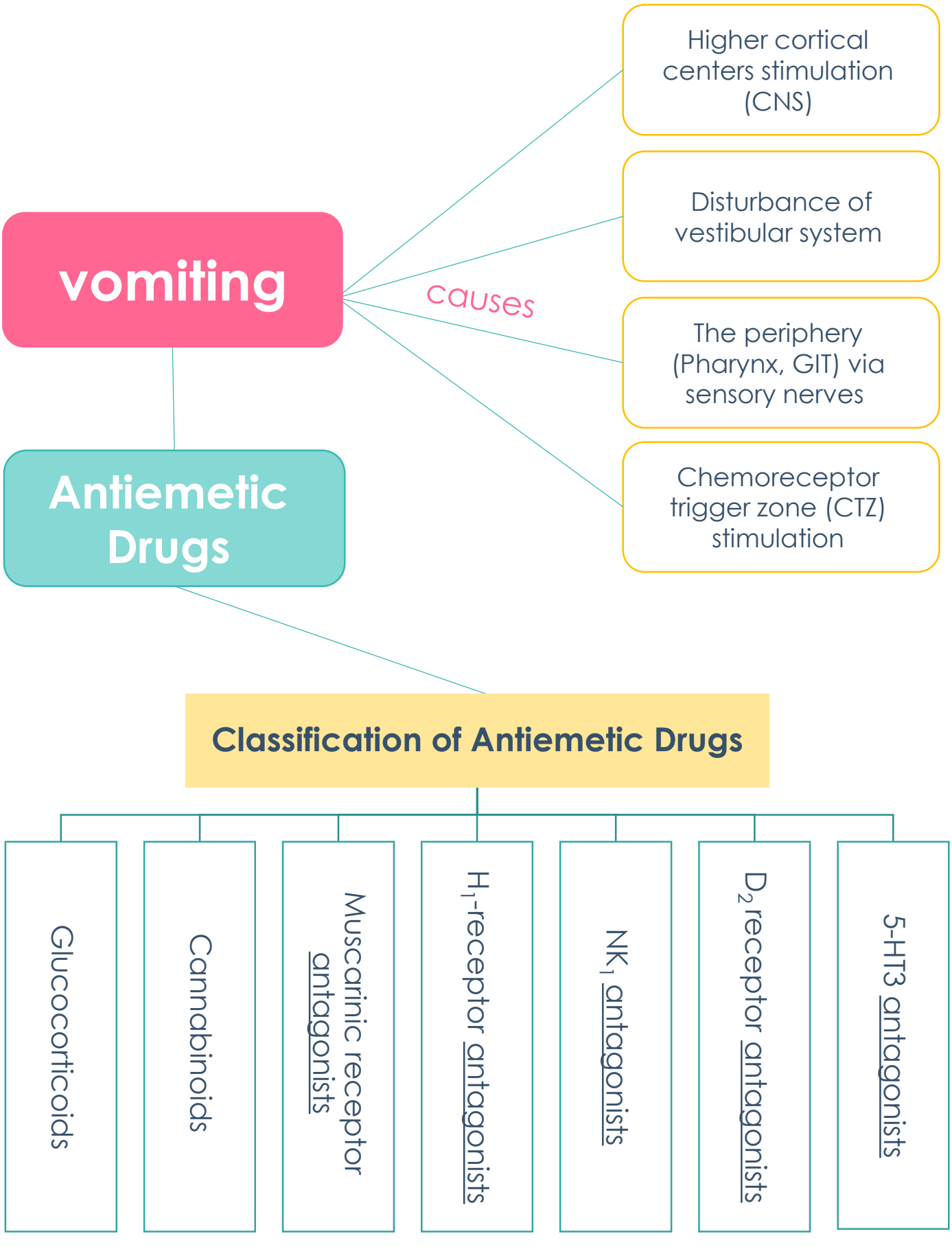
Drugs names | Doctors notes | Important | Extra

« **باذلًا وسعي** في استنقاذها من الهلاك والمرض، والألم والقلق »

Mind Map


vomiting
causes
Higher cortical centers stimulation (CNS)
Disturbance of vestibular system
The periphery (Pharynx, GIT) via sensory nerves
Chemoreceptor trigger zone (CTZ) stimulation
Antiemetic Drugs
Classification of Antiemetic Drugs
Glucocorticoids
Cannabinoids
Muscarinic receptor antagonists
H_1-receptor antagonists
NK_1 antagonists
D_2 receptor antagonists
5-HT3 antagonists

To understand better

Vomiting

Is a complex series of integrated events culminating in the forceful expulsion of gastric contents through the mouth.
It is a manifestation of many conditions and diseases.

Vomiting can be a valuable, life-saving physiological response. WHY?

Because it's an adaptive behavior that can work to eliminate toxic substances that have been ingested.

Severe vomiting may result in

- **Dehydration**
- **Acid-base imbalance**
- **Electrolyte depletion**
- **Aspiration, pneumonia** (if it reached the larynx)

Causes of vomiting

(Vomiting center respond to inputs from)

- Higher cortical centers stimulation (CNS)
- Disturbance of vestibular system
- The periphery (Pharynx, GIT) via sensory nerves
- Chemoreceptor trigger zone (CTZ) stimulation

To Understand Better

Causes of vomiting:

1- Chemoreceptor trigger zone (CTZ)

- CTZ is an area of medulla that communicate with vomiting center to initiate vomiting.
- CTZ is physiologically outside BBB.
- CTZ contains D_2 receptors, $5HT_3$ receptors & opioid receptors.

Stimulated by:

1. Emetogenic drugs (opioids, general anesthetics, digitalis, L-dopa).
2. chemicals and toxins in (blood, CSF).
3. Radiation.
4. Uremia

2- The periphery via sensory nerves

Stimulated by :

1. GIT irritation
2. Myocardial infarction
3. Renal or biliary stones

3- Disturbance of vestibular system

Stimulated by:
motion sickness (H_1 & M_1 receptors)

4- Higher cortical centers stimulation

Stimulated by :

- Emotional factors
- Nauseating smells or sights

Chemical transmitters & receptors involved in vomiting:

Transmitter	Receptor
Acetylcholine	Muscarinic receptors
Dopamine	D_2
Histamine	H_1
Serotonin	5 -HT_3
Substance P	Neurokinin receptors, NK1
Opioid	Opioid receptors

Pathophysiology of Emesis

Another very helpful diagram

7:57 min

Stimulated by:
Smell
Sight
Thought
(anticipatory emesis)

Cerebral cortex

Stimulated by:
Chemotherapy
Opioids
Anesthetics

Stimulated by:
Motion sickness

Chemoreceptor or Trigger Zone
(found outside BBB)

Vomiting Centre (medulla)
(receptors : Muscarinic , 5HT3)

Vestibular nuclei

Receptors :
5 HT_3
Dopamine (D2)
Opioid receptors
Substance P

Receptors :
Muscarinic (M1)
Histaminic (H_1)

Pharynx & GIT

Stimulated by:
Chemotherapy
Radiotherapy
Gastroenteritis

Receptors :
5 HT_3

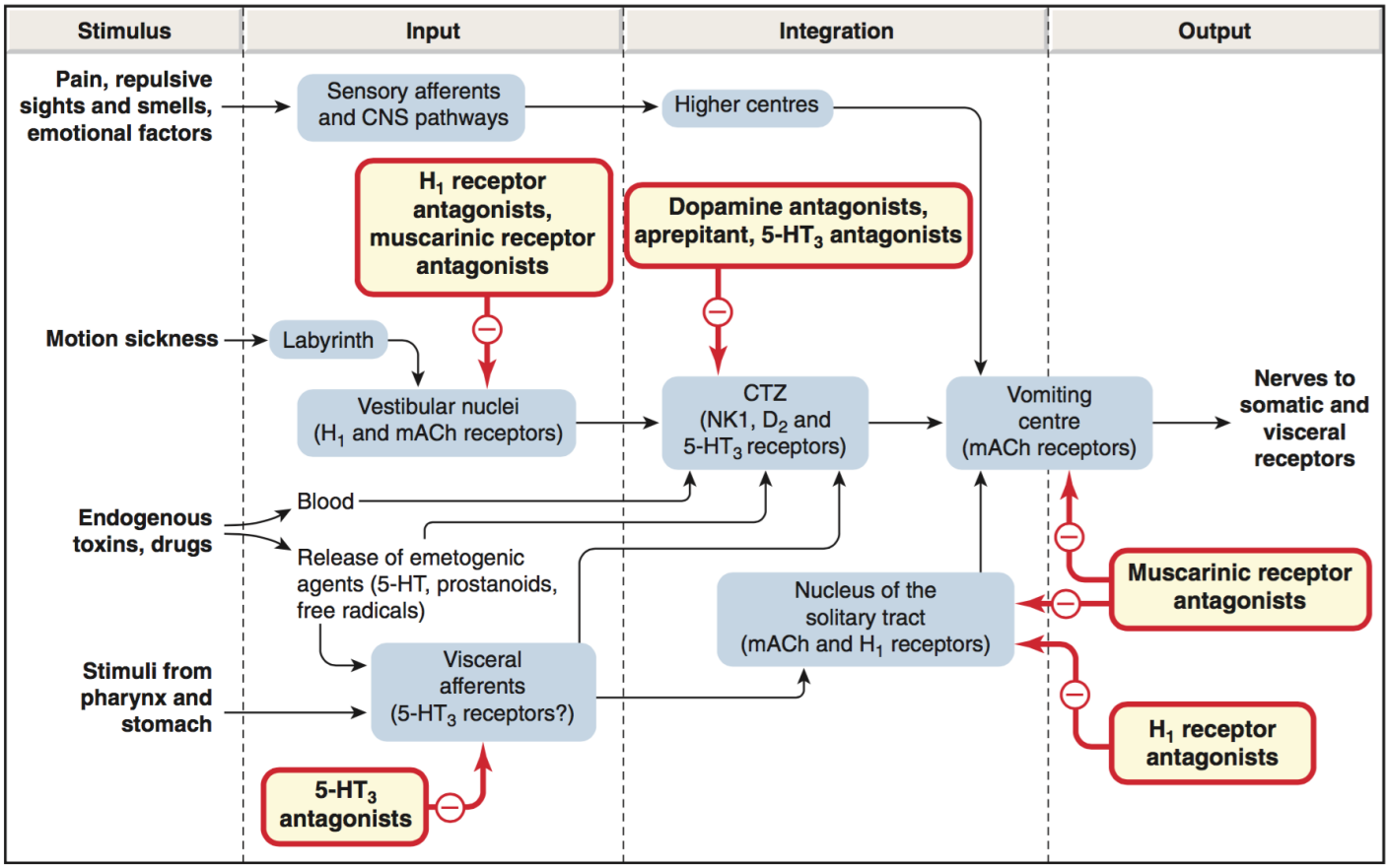


Fig. 29.5 Schematic diagram of the factors involved in the control of vomiting, with the probable sites of action of antiemetic drugs. The cerebellum may function as a second relay or gating mechanism in the link between the labyrinth and chemoreceptor trigger zone (CTZ; not shown). 5-HT_3, 5-hydroxytryptamine type 3; D_2, dopamine D_2; H_1, histamine H_1; mACh, muscarinic acetylcholine; NK_1, neurokinin 1. (Based partly on a diagram from Borison H L et al. 1981 J Clin Pharmacol 21: 235–295.)

الصورة هذي فيها زبدة المحاضرة، إذا تبعت من المسبب إلى الريسبتور بتطلع نقاط التداخل للأدوية وعلى إيش تشتغل ومتى تنوصف.

Classification of Antiemetic Drugs

7:55 min

- 5-HT_3 antagonists
- D_2 receptor antagonists
- NK_1 antagonists
- H_1-receptor antagonists
- Muscarinic receptor antagonists
- Cannabinoids → has an adductive effect
- Glucocorticoids

Used as an adjuvant therapy, not an essential drug.

Serotonin ($5\text{-}HT_3$) antagonists

Drug	Ondansetron and Granisetron
MOA	○ Act by blocking $5\text{-}HT_3$ receptor: • **Centrally** (in **vomiting center**, **CTZ**) • **Peripherally** ($5HT_3$ receptors on GI vagal afferents) → Chemotherapeutic drugs can act peripherally by causing cell damage in the GI tract and releasing serotonin from the enterochromaffin cells of the small intestinal mucosa. The released serotonin activates 5-HT3 receptors on **vagal and splanchnic afferent** fibers, which then carry sensory signals to the medulla, leading to the emetic response. See diagram in slide 6.
P.K	○ Orally or parenterally ○ Have long duration of action, **first pass effect**. ○ The **most potent** antiemetic drugs.
Indications	○ **First choice** for prevention of moderate to severe emesis: • Chemotherapy-induced nausea and vomiting (CINV) especially **Cisplatin** → it severely induces vomiting, the patient have to take these medication. • **Post-radiation** NV (nausea & vomiting) & **Post-operative** NV Chemotherapeutic agents can directly **activate** the medullary CTZ, or vomiting center by several neuroreceptors, including dopamine receptor Type 2 and serotonin Type 3 (5-HT3) play critical roles. ○ Their effects is **augmented** (make it stronger) by combination with corticosteroids and NK1 antagonists. ○ The anti-emetic action of these agents is restricted to emesis attributable to vagal stimulation (e.g, postoperative) and chemotherapy; other emetic stimuli such as motion sickness are poorly controlled.
ADRs	○ Low ADRs because the are well tolerated. ○ Headache, dizziness and **constipation.** ○ **Minor** ECG abnormalities (QT prolongation) → it produced by the action of 5-HT**4** not **3**)

D_2 receptor antagonists

block D_2 dopamine receptors in the CTZ.

Two types exist:

Remember, CTZ stimulated by chemical substances

Prokinetic drug

- Like: **domperidone** and **metolclopramide**.
- Are prokinetic agents (increased GI motility & gastric emptying).

Neuroleptic (antipsychotics)

- Like **Chlorpromazine** (CPZ) and **droperidol**
- used for **postoperative vomiting** and **chemotherapy-induced emesis**.

Neuroleptics (antipsychotics)

D_2 receptor antagonists

Drug	Chlorpromazine (CPZ)	Droperidol
MOA	○ block D_2 dopamine receptors in the CTZ.	
P.K	○ Mainly Oral administration. ○ Absorption increased with food. ○ Large volume of distribution. ○ Metabolized by cytochrome p450 system in the liver.	
Indications	○ Used for **postoperative** vomiting and chemotherapy-induced emesis.	
ADRs	○ Extra pyramidal symptoms → because they block D_2 **centrally**. ○ Sedation ○ Postural hypotension. (alpha1 blockers)	

Prokinetic drug

D2 receptor antagonist

Drug	Domperidone Dom = دوم = دوم سليم	Metoclopramide Meto = موتوا= ↑ ADRs
MOA	**Act peripherally** → do not block D_2 in the basal ganglia (centrally) → can be given to parkinson's pts.	**Act peripherally & centrally.** It has more potency.
	○ **increased upper GI motility & gastric emptying** If it acts on the lower part it will result in diarrhea.	
P.K	○ Orally.	○ Oral or IV ○ Metoclopramide **crosses BBB** but domperidone **cannot** (both have antiemetic effects as **CTZ has incomplete blood brain barrier**). CTZ located mainly outside BBB.
Indications	1. Antiemetics (**blocking D_2** receptors in **CTZ**) ○ Effective against vomiting due to cytotoxic drugs, gastroenteritis, surgery, toxins, uremia, radiation. 2. Prokinetic (5-HT_4 agonist activity) → they increase the motility by **5-HT_4** not D_2 Rs. ○ **Gastroesophageal reflux disease** (**GERD**) ○ Gastroparesis (شلل العضلات) (impaired gastric emptying after surgery).	
ADRs	○ It can cause galactorrhea but at lesser amounts than metoclopramide.	○ **Dyskinesia** (extra-pyramidal side effects) → not given to parkinson's pts. ○ **Galactorrhea, menstrual disorders, impotence**. ○ Postural hypotension (α-blocking action). ○ Sedation, drowsiness

NK1 antagonist & H_1 R antagonist

Drug	Neurokinin1 (NK_1) receptor antagonists	H_1-receptor antagonists
	Aprepitant	**Diphenhydramine, Promethazine Meclizine, Cyclizine**
Mech. of action	○ Acts centrally as **substance P antagonist** by blocking **neurokinin1** receptors in vagal afferent fibers in STN (spinal trigeminal nucleus) and area postrema. The area postrema is a medullary structure in the brain that controls vomiting, located at the caudal end of the fourth ventricle& contains CTZ. ○ NK1 R is found in CTZ.	○ Inhibit competitively H_1 receptors. ○ H1 Rs are found in the vestibular nucleus. ○ First generation H_1-RAs used as anti-emetics.
P.K	○ Orally	———
Indications	○ Usually **combined** with 5-HT3 antagonists and corticosteroids in prevention of **chemotherapy-induced nausea and vomiting** and **post-operative nausea & vomiting**. → produce synergism action.	○ **Motion sickness** ○ **Morning sickness in pregnancy.** ○ Promethazine: **severe morning sickness of pregnancy** (if only essential). ○ Ineffective against substances that act directly on the chemoreceptor trigger zone. → Not used with chemotherapy-induced vomiting. ○ Promethazine has been used by **NASA** to treat space motion sickness. ☺
ADRs	○ Constipation. ○ Fatigue.	○ **Prominent sedation** → bc of the blocking effct of H1R. ○ Hypotension. ○ Anticholinergic effects or atropine like actions (dry mouth, dilated pupils, urinary retention, constipation).

Muscarinic receptor antagonist & Glucocorticoids

Drug	Muscarinic receptor antagonists	Glucocorticoids
	Hyoscine (scopolamine)	**Dexamethasone, methylprednisolone**
Mech. of action	○ Reduce impulses from **vestibular apparatus**. ○ Muscarinic Rs are found in the vestibular nucleus.	○ Antiemetic mechanism is not known, but it may involve blockade of prostaglandins.
P.K	○ Orally, injection, **patches***. 1:18 min * Preferred, better to take it before the induction of vomiting. Has a **long duration of action**.	
Indications	○ Used as **transdermal patches** in **motion sickness** (applied to the postauricular area -behind the external ear-). ○ Not effective w\ **chemotherapy-induced** vomiting.	○ chemotherapy-induced vomiting (**adjuvant therapy**), combined with 5-HT_3 antagonists or NK1 receptor antagonists.
ADRs	○ Sedation. ○ Tachycardia, blurred vision, dry mouth, constipation, urinary retention → (atropine-like actions).	Hypers: غالبًا الأعراض الجانبية كلها في الزيادة ○ **Hyperglycemia** → use with caution with DM pts. ○ Hypertension ○ Cataract ○ Osteoporosis ○ Increased intraocular pressure. ○ Increased susceptibility to infection. ○ **Increased appetite & obesity** ○ Insomnia.

Summary according to etiology

Motion sickness

- Muscarinic antagonists.
- Anti-histaminics (H_1R antgonist)

Vomiting with pregnancy (morning sickness)

- **Avoid all drugs in the first trimester** (first 3 months).
- **Pyridoxine** (B6) + Doxylamine = very nice action on pregnancy vomiting without prominent ADRs on pregnant.
- **Promethazine** (late pregnancy).

Drug-induced vomiting (CTZ), uremia, gastritis

- **Dopamine antagonists**. → 1st choice, 5-HT3 antagonist are expensive.

Post operative nausea & vomiting

- Dopamine antagonists.

Vomiting due to cytotoxic drugs :

- **5-HT_3 antagonists** → 1st choice, if not responded, it combined with:
  - NK1 antagonists.
  - Glucocorticoids.
- D_2- antagonists.

Combination therapy effectiveness

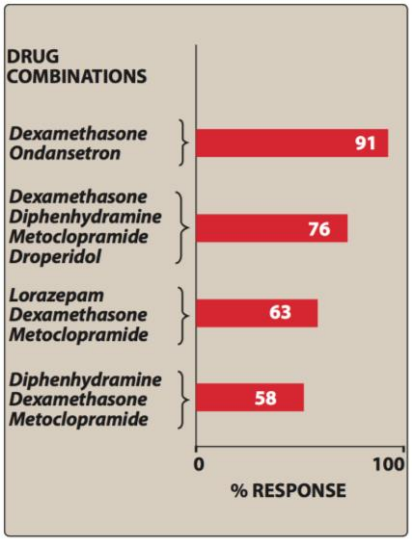


Figure 28.12
Effectiveness of antiemetic activity of some drug combinations against emetic episodes in the first 24 hours after *cisplatin* chemotherapy.

Clinical use of antiemetic drugs

- Histamine H_1 receptor antagonists (see also clinical box in Ch. 26):
  - **cyclizine**: motion sickness
  - **cinnarizine**: motion sickness, vestibular disorders (e.g. Ménière's disease)
  - **promethazine**: severe morning sickness of pregnancy.
- Muscarinic receptor antagonists:
  - **hyoscine**: motion sickness.
- Dopamine D_2 receptor antagonists:
  - phenothiazines (e.g. **prochlorperazine**): vomiting caused by uraemia, radiation, viral gastroenteritis, severe morning sickness of pregnancy
  - **metoclopramide**: vomiting caused by uraemia, radiation, gastrointestinal disorders, cytotoxic drugs.
  - **Domperidone** is less liable to cause CNS side effects as it penetrates the blood-brain barrier poorly.
- 5-Hydroxytryptamine 5-HT_3 receptor antagonists (e.g. **ondansetron**): cytotoxic drugs or radiation, postoperative vomiting.
- Cannabinoids (e.g. **nabilone**): cytotoxic drugs (see Ch. 18).

A helpful diagram summarize all MOA

Summary-1

	Serotonin (5-HT3) antagonists	D2 receptor antagonists	
		Prokinetics drugs	Neuroleptics (antipsychotics)
Drug	**Granisetron** **Ondansetron** Orally or parenterally	**Metoclopramide** oral, I.V. **Domperidone** oral	**Chlorpromazine (CPZ), droperidol**
MOA	**Act by:** **1- blocking 5-HT3 receptor centrally** (in vomiting center, CTZ). **2- peripherally (**5HT3 receptors on GI vagal afferents).	**block D2 dopamine receptors in the CTZ**	
Uses	**The most potent antiemetic drugs.** First choice for prevention of moderate to severe emesis **:** **1-** Chemotherapy-induced nausea and vomiting (CINV) especially cisplatin. 2- Post-radiation NV& Post-operative NV. Their effects is augmented by combination with corticosteroids and NK1 antagonists**.**	**Increased upper GI motility & gastric emptying.** 1- Antiemetics (blocking D2 receptors in CTZ): Effective against vomiting due to cytotoxic drugs, gastroenteritis, surgery, toxins, uremia, radiation 2- Prokinetic (5 HT4 :agonist activity) Gastroesophageal reflux disease (GERD). Gastroparesis (impaired gastric emptying after surgery).	used for postoperative vomiting and chemotherapy-induced emesis.
ADRs	Less side effects (well tolerated), Headache, dizziness and constipation, minor ECG abnormalities (QT prolongation).	Dyskinesia (extra-pyramidal side effects), Galactorrhea, menstrual disorders, impotence. Postural hypotension (α-blocking action). Sedation, drowsiness.	Extra pyramidal symptoms, Sedation, Postural hypotension.

Summary-2

	Neurokinin1 (NK1) receptor antagonists	H1-receptor antagonists
Drug	Aprepitant	Diphenhydramine , Promethazine, Meclizine , Cyclizine
MOA	**Acts centrally as substance P antagonist (block neurokinin 1)**	**Block H1 receptors**
uses	Usually combined with 5-HT3 antagonists and corticosteroids in prevention of chemotherapy-induced nausea and vomiting and post- operative NV.	**Motion sickness, Morning sickness in pregnancy. (**Promethazine: severe morning sickness of pregnancy -if only essential-).
ADRs	–	Prominent sedation, Hypotension, atropine like actions (dry mouth, dilated pupils, urinary retention, constipatin).

	Muscarinic receptor antagonists	Glucocorticoids
Drug	Hyoscine (scopolamine)	Dexamethasone – methylprednisolone
P.K	Orally, injection, patches. Used as transdermal patches in motion sickness (applied behind the external ear).	–
uses	**Reduce impulses from vestibular apparatus**	**Used in chemotherapy-induced vomiting,** combined with 5-HT3 antagonists or NK1 receptor antagonists.
ADRs	**atropine-like Action**: (Sedation, Tachycardia, blurred vision, dry mouth, constipation, urinary retention).	Hyperglycemia, Hypertension, Cataract, Osteoporosis , ↑ IOP , Increased susceptibility to infection, Increased appetite & obesity.

MCQs

1- Emotional factors stimulate which of the following:
A- Chemoreceptor trigger zone (CTZ)
B- The periphery(Pharynx, GIT)
C- vestibular system
D- Higher cortical centers (CNS)

2- The Disturbance of vestibular system is stimulated by:
A- GIT irritation
B- Uremia
C- Motion sickness
D- Emotional factors

3- Which type of drugs is mainly used for Post operative nausea & vomiting?
A- Dopamine antagonists
B- Glucocorticoids
C- H1-receptor antagonists
D- 5-HT3 antagonists

4- Which of the following drugs is <u>not</u> effective in case of chemotherapy induced vomiting?
A- Hyoscine
B- Domperidone.
C- Dexamethasone
D- Aprepitant

5- Which one of the following antiemetic drug has extrapyramidal symptoms?
A- Meclizine
B- Hyoscine
C- Chlorpromazine
D- Ondansetron

6- A 68-year-old patient with cardiac failure is diagnosed with ovarian cancer. She begins using cisplatin but becomes nauseous and suffers from severe vomiting. Which of the following medications would be most effective to counteract the emesis in this patient without exacerbating her cardiac problem?
A- Droperidol
B- Ondansetron
C- Hyoscine
D- Dolasetron

Answers: 1-D 2-C 3-A 4-A 5-C 6-B

Thank you for checking our team!

Pharmacology 435

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Sources:

1. 435's slides.
2. Pharmacology (Lippincotts Illustrated Reviews Series), chapter 28, 5th edition.
3. Basic & Clinical Pharmacology by Katzung, chapter 62,12th edition.
4. Rang & Dale's pharmacology, chapter 29, 7th edition.
5. Wikipedia.