



Antiemetics

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.

Color Guide

Slides = Black
Females slides = Green
Males slides = Blue
Explanation = Orange

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Vomiting

Is a complex series of integrated events culminating in the forceful expulsion of gastric content through the mouth.

Causes of nausea and vomiting

a useful abbreviation for remembering causes of nausea and vomiting is **VOMIT**.

Vestibular

Obstruction or drugs like **o**piates

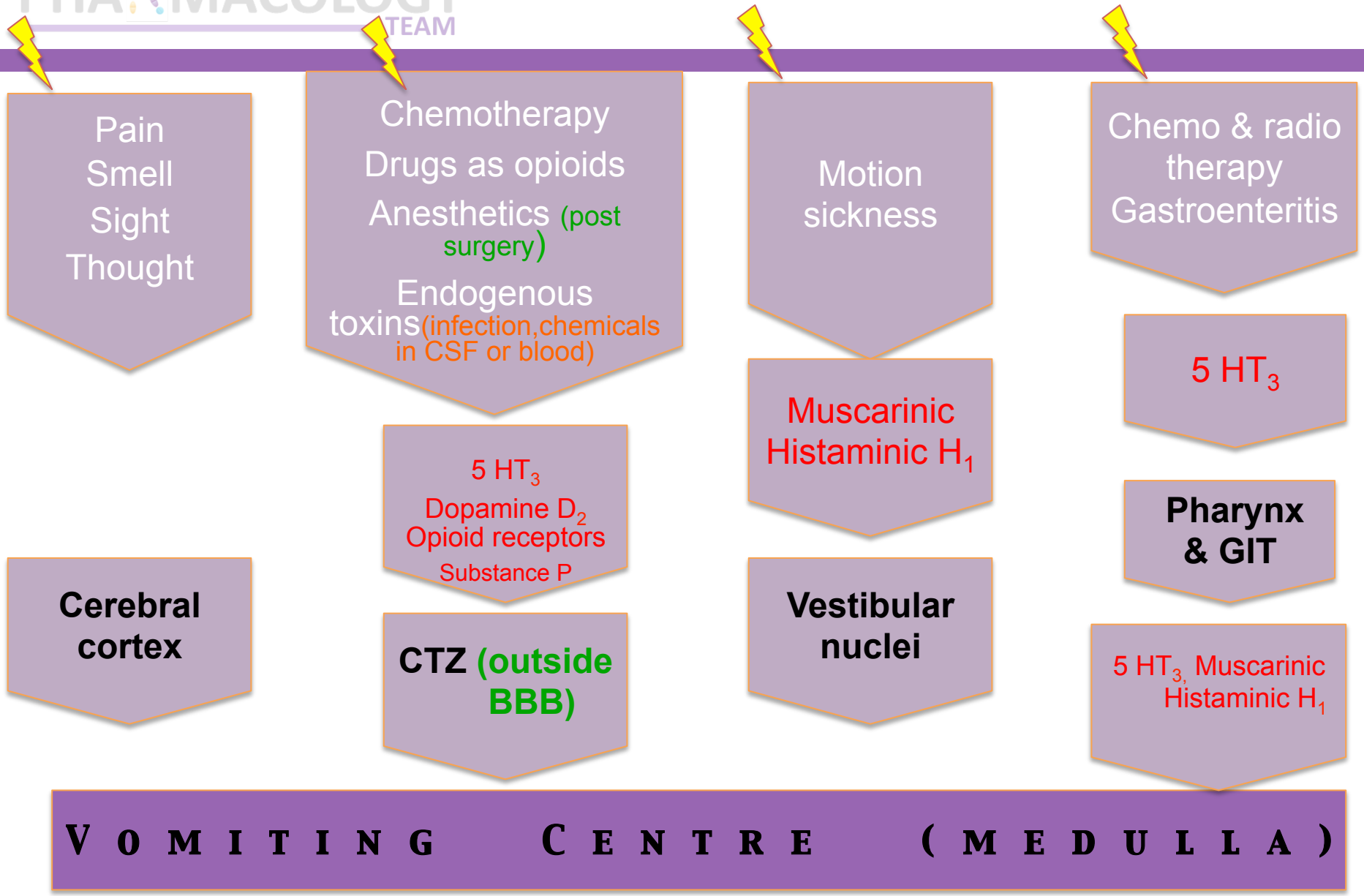
Mind (dysmotility)

Infection (irritation of gut)

Toxins (taste and other senses) **ex: food toxicity**

Maybe a manifestation of many conditions occur due to stimulation of vomiting center that respond to inputs from:

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



 stimulus

Nerves to somatic and visceral receptors
(respiratory + abdominal muscles)

Antiemetic Drugs

5-HT ₃ Antagonist (in CRTZ)	D ₂ Antagonist (in CRTZ)	NK ₁ antagonist Substance P	H1 antagonist	Muscarinic antagonist
Ondansteron	metoclopramide	Aprepitant	Diphenhydramine	Hyoscine (scopolamine)
	domperidone		Cyclizine	
Granisteron	Chlorpromazine		Meclizine	
	droperidol		Promethazine	

Cannabinoids	Glucocorticoids
Nabilone	Dexamethasone
dronabinol	methylprednisolone



**5-HT₃ antagonist
Ondanisteron & Granisteron**

<p>Mechanism</p>	<p>mediated through central (vomiting center, chemoreceptor trigger zone) and peripheral (5HT₃ receptors on GI vagal afferents) (intestinal and spinal) act by 5-HT₃ receptor blockade The most potent antiemetic</p>
<p>Rout</p>	<p>Orally or i.v. have long duration of action</p>
<p>Indication</p>	<p>First choice for prevention and treatment of moderate to severe emesis: Chemotherapy-induced nausea and vomiting (CINV) especially cisplatin (highly emetogenic anticancer). cuz it's stimulated by chemicals. Cytotoxic drugs (cisplatin) Post-radiation and Post-operative (second line). Their effects is augmented by combination with corticosteroids or NK1 antagonists (in case of delay emesis), otherwise its effective if taken alone)</p>
<p>Side effects</p>	<p>Well tolerated Headache, dizziness and constipation (decrease GI motility) minor ECG abnormalities (QT prolongation) (not to cardiac patient)</p>

D₂ antagonist (potent but less than 5HT₃ antagonist)
block D₂ dopamine receptors in the CTZ

	prokinetic	Antipsychotics (neuroleptics)
	metoclopramide & domperidone	Chlorpromazine & droperidol
Mechanism	prokinetic agents due to their 5 HT ₄ agonist activity (increased GI motility +Gastric emptying)	potent antiemetic property due to D ₂ antagonism. acts centrally to block D ₂ at CTZ
Rout	Domperidone- oral; Metoclopramide- oral, i.v. (crosses BBB) both have antiemetic as CRTZ outside BBB)	orally, parentally, suppository
Indication	<p>Antiemetic: Effective against vomiting due to drugs, gastroenteritis, surgery, toxins, uremia, radiation. (used in unknown vomit etiology)</p> <p>Prokinetic: Can be used in reflux esophagitis and Gastroparesis (impaired gastric emptying after surgery) >> GI hypomotility in diabetic patient + post surgery)</p>	<p>chemotherapy- induced emesis</p> <p>postoperative vomiting</p>
Side Effects	<p>extrapyramidal symptoms dyskinesia , galactorrhea, menstruation disorders, sedation, impotence, postural hypotension (a blocking), drowsiness</p>	<p>extrapyramidal symptoms hypotension, sedation, restlessness</p>

ADS arranged according to the prominent
 For metoclopramide only.
 Because it crosses BBB but domperidone does not.

Other indication for metoclopramide

- ★ Facilitate duodenal intubation & endoscopy
- ★ Regurgitation & reflux oesophagitis
- ★ Diagnostic radiology of gut → ↓ time required for barium to reach caecum
→ ↓ No. of films required
- ★ Clears gastric contents in emergency anaesthesia

Neurokinin1 (NK1) receptor antagonists

Aprepitant

Mechanism

Is a **substance P** (found peripherally but the receptor centrally) **antagonists** that acts by **blocking neurokinin 1 receptors** in **vagal afferent fibers** in **STN(solitary tract nucleus) and area postrema**.

Indication

Usually combined with **5-HT3 antagonists and corticosteroids** in chemo-therby induced nausea and vomiting (CINV) and post operative NV prevention of acute and delayed prevention of postoperative nausea and vomiting (Third line).

route

orally

H1-receptor antagonists (H₁ crosses BBB)

Diphenhydramine **best for motion sickness**, Cyclizine, Meclizine, Promethazine

Indication

for **motion sickness**, morning sickness in pregnancy, Vestibular Disturbances and to combat opioid nausea

Promethazine: severe morning sickness of pregnancy (if only essential

Side effects

Prominent sedation, hypotension **a blocking especially with promethazine**, Anticholinergic effects (dry mouth, dilated pupils, urinary retention, constipation).

Muscarinic receptor antagonists

Hyoscine (scopolamine)

route

Used as **trans-dermal patches in motion sickness** (applied behind the external ear).
Orally **common**, injection, patches

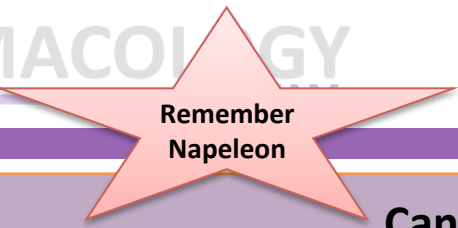
mechanism

Acts centrally by reduce impulses from vestibular nuclei

Not in chemotherapy-induced vomiting **No effect in CRTZ**

Side effects

Sedation, Tachycardia, blurred vision, dry mouth, constipation, urinary retention (atropine like action)



Remember
Napeleon

Cannabinoids (rarely used)



Nabilone, dronabinol

mechanism

Mechanism is not understood. act at central cannabinoid receptors.

Indication

adjuvant in chemotherapy induced vomiting.

It has a limited use due its side effects. It's only used if the patient is resistance to other drugs

Side Effects

Sedation, hallucination, euphoria and dysphoria.

Glucocorticoids

Dexamethasone and methylprednisolone

Indication

acute emesis alone or combined with ondansetron (5-HT3 antagonist) or NK1 receptor antagonist

vomiting by cytotoxic drugs. (chemotherapy-induced vomiting)

Side Effects

(Hyperglycemia, Hypertension)metabolic disorder, Cataract, Osteoporosis risk old female , Increased intraocular pressure, Increased susceptibility to infection, Increased appetite & obesity

Summary

- ★ **Motion sickness**
 - ★ Hyoscine: For short Journey.
 - ★ Diphenhydramine: For Long Journey.

- ★ **Vomiting with pregnancy (morning sickness)**
 - ★ avoid all drugs in the first trimester.
 - ★ Pyridoxine (B6).
 - ★ Promethazine (late pregnancy).

- ★ **Drug- induced vomiting (CTZ)**
 - ★ domperidone & metoclopramide.

- ★ **Vomiting due to cytotoxic drugs.**
 - ★ Ondansetron.
 - ★ D2- antagonists.
 - ★ Dexamethazone.
 - ★ Nabilone .

- ★ **Post operative vomiting**
 - ★ Dopamine antagonists (Metoclopramide or Domperidone).

Antiemetic drugs

Drug	MOA	Pharmacokinetics and Uses	ADRs
1-5-HT3 antagonists : e.g. Ondansetron, Granisetron	Blocks 5HT-3 receptors in central (vomiting center, chemoreceptor trigger zone) and peripheral (intestinal and spinal)	<ul style="list-style-type: none"> • Taken Orally or i.v., long duration of action • Has high first pass metabolism • Very effective in nausea & vomiting due to: Cytotoxic drugs (cisplatin) Post-radiation and Post-operative 	
2- Dopamine (D2) receptor antagonists -metoclopramide, domperidone -Antipsychotics with potent antiemetic property due to D2 antagonism e.g.: Chlorpromazine, droperidol <ul style="list-style-type: none"> • Taken orally, parentally, suppository • used for vomiting due to chemotherapy-induced emesis -Side effects: extrapyramidal symptoms, hypotension, sedation, restlessness	Antagonize D2 receptors in CTZ Both drugs have 5 HT4 agonist activity (prokinetic) Metoclopramide has a 5HT3 blocking activity	- Domperidone - oral; Metoclopramide -oral, i.v . Metoclopramide crosses BBB ,but domperidone cannot . Effective against vomiting due to drugs, gastroenteritis, surgery, toxins, uremia, radiation -Can be used in reflux esophagitis .	Uses and ADRs of Metoclopramide : -Facilitate duodenal intubation & endoscopy -↓ Regurgitation & reflux esophagitis -Diagnostic radiology of gut → ↓ time required for barium to reach caecum → ↓ No. of films required -Clears gastric contents in emergency anesthesia Side effects (extrapyramidal): dyskinesia, galactorrhea, menstruation disorders, sedation (only for metoclopramide).
3-Neurokinin1 (NK1) receptor antagonists e.g.: Aprepitant	Is a substance P antagonist that acts by blocking neurokinin 1 receptors .	In prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV) and for prevention of postoperative nausea and vomiting.	
4-H1-receptor antagonists (Antihistamines): - Diphenhydramine, Cyclizine, Meclizine -Promethazine: severe morning sickness of pregnancy (if only essential)		-Effective for motion sickness, morning sickness in pregnancy, and to combat opioid nausea . - Not in chemotherapy-induced vomiting .	
5-Muscarinic receptor antagonists:	<ul style="list-style-type: none"> ✓ Used as trans-dermal patches in motion sickness (applied behind the external ear) ✓ Not in chemotherapy-induced vomiting. 		
6-Cannabinoids -Nabilone, dronabinol (psychoactive drugs)		<ul style="list-style-type: none"> ✓ Used as adjuvant in chemotherapy induced vomiting . 	Sedation, hallucination and dysphoria
7-Glucocorticoids Dexamethasone and methylprednisolone		<ul style="list-style-type: none"> ✓ Highly effective in acute emesis alone or combined with ondansetron. ✓ Used for vomiting by cytotoxic drugs . 	<ul style="list-style-type: none"> × Hyperglycemia × Hypertension × Cataract × Osteoporosis × Increased intraocular pressure × Increased susceptibility to infection × Increased appetite & obesity
Summary for Therapeutic Choice of Antiemetics			
Motion sickness: <ul style="list-style-type: none"> • Hyoscine: For short Journey. • Diphenhydramine: For Long Journey. 	Vomiting with pregnancy (morning sickness): <ul style="list-style-type: none"> ⚡ avoid all drugs in the first trimester ⚡ Pyridoxine (B6) ⚡ Promethazine (late pregnancy) 	Drug- induced vomiting (CTZ) uremia -gasteritis: domperidone & metoclopramide Post-operative vomiting: <ul style="list-style-type: none"> ⚡ Dopamine antagonists (Metoclopramide or Domperidone) 	Vomiting due to cytotoxic drugs: <ul style="list-style-type: none"> ⚡ Ondansetron ⚡ D2- antagonists. ⚡ Dexamethasone ⚡ Nabilone.

1. Metoclopramide (Reglan) is useful to treat postoperative nausea and vomiting because it
 - A) decreases mobility in the gastrointestinal tract.
 - B) decreases chemoreceptor stimulation.
 - C) improves the body's response to analgesia.
 - D) promotes motility in the small intestine.

2. Which drug works by blocking serotonin in the gastrointestinal tract, vomiting center, and chemoreceptor trigger zone (CTZ)?
 - A) metoclopramide (Reglan)
 - B) meclizine (Antivert)
 - C) droperidol (Inapsine)
 - D) ondansetron (Zofran)

PHARMACOLOGY



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