

Gastrointestinal Block

Pharmacology Team 439



Helpful video

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

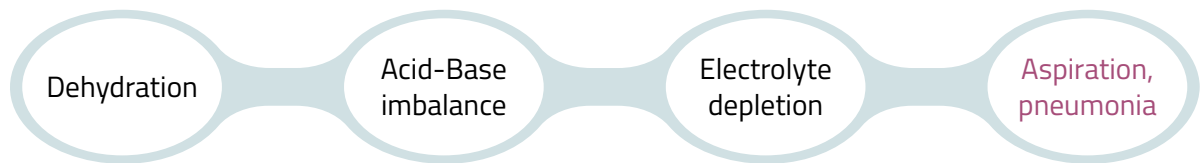
Antiemetic Drugs

Objectives:

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

Vomiting: is forceful expulsion of gastric contents through the mouth. Can vomiting be considered as a disease? It is a **manifestation** (symptom) of many conditions and diseases.

Consequences



How is it induced?¹

Causes of Vomiting: Nausea and vomiting occurs due to stimulation of **vomiting center** that respond to inputs from:

1) Stimulation of chemoreceptors trigger zone (CTZ): *(it is sensitive to chemicals)*

General info:

- CTZ is an area of medulla that communicate with vomiting center to initiate vomiting
- **CTZ is physiologically outside BBB** (can be stimulated by drugs in the circulation whether they can cross the BBB or not).
- **CTZ contains D₂ receptors, 5-HT₃ receptors & opioid receptors** so in order to treat vomiting caused by the stimulation of CTZ the options are: drugs can block D₂, 5-HT, and opioid receptors

Stimulated by:

- Emetogenic drugs (Opioids, general anesthetics, Digitalis, L-Dopa)
- Chemicals & toxins (blood, CSF)
- Radiation
- Uremia, estrogen (vomiting of pregnancy)

2) Disturbance of vestibular system:

- Motion sickness (H₁ & M₁ receptors)

3) The periphery (pharynx, GIT) via sensory nerves:

- GIT irritation
- Myocardial infarction
- Renal or biliary stones

4) Higher cortical centers stimulation (CNS):

- Emotional factors
- Nauseating smells or sights

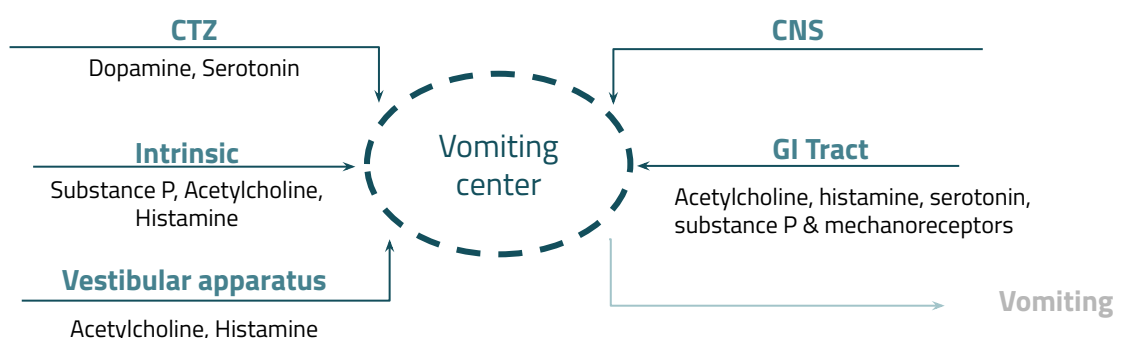
Chemical, transmitters & receptors involved in vomiting and drug targets²:

- Ach (Muscarinic receptors)
- Dopamine (D₂)
- Histamine (Histaminergic receptors H₁)
- Serotonin (5-HT₃)
- Substance P (Neurokinin receptors, NK1)
- Opioid (Opioid receptors)

1- it's **important** to know which receptors are in which site because a question in the exam might be "what is the best drug to be prescribed in a certain case." for example in a case of motion sickness the answer would be antimuscarinic or antihistaminic.

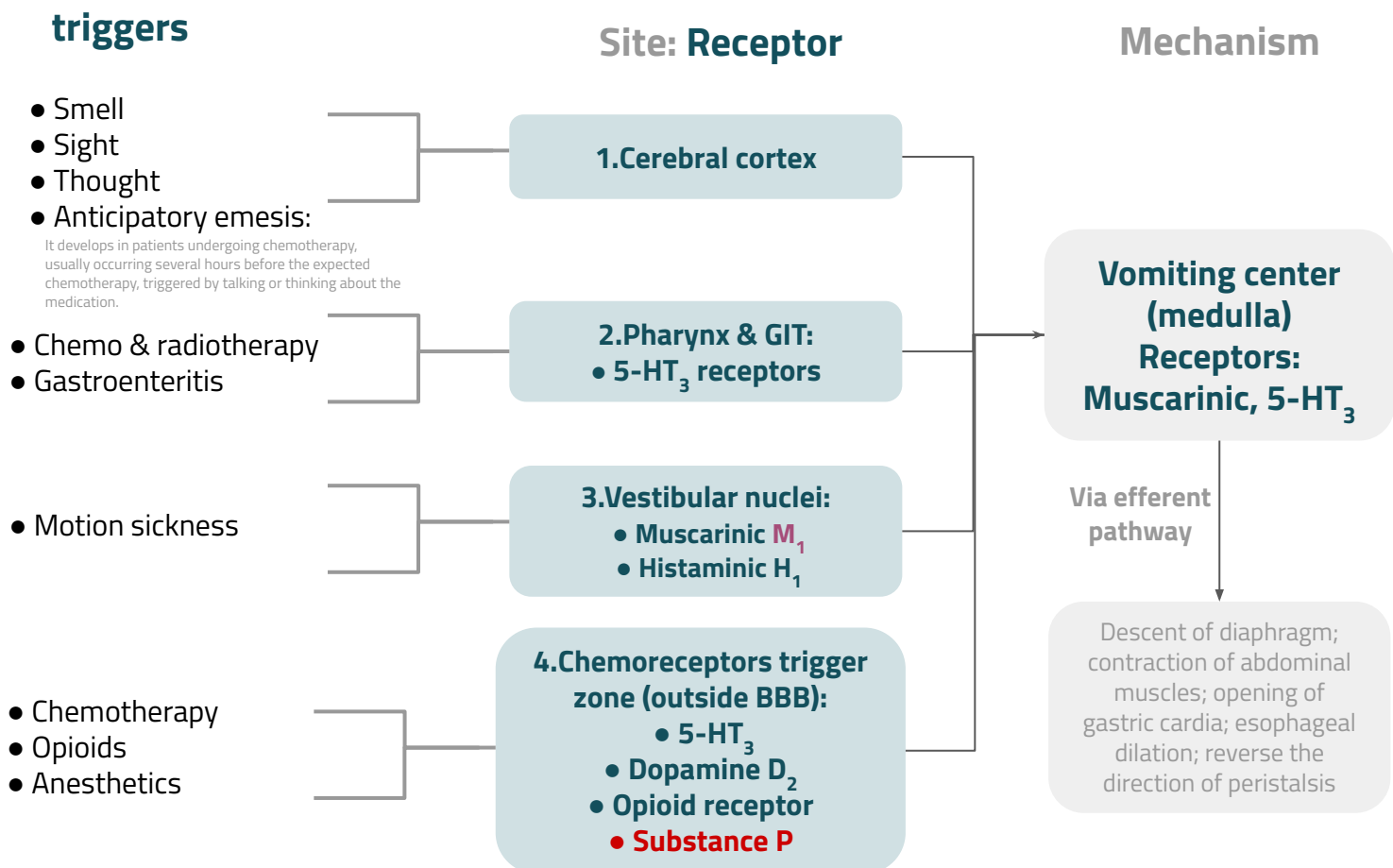
2- it's **important** to know which subclass of receptor e.g. 5-HT₃

Receptors Associated with Nausea and Vomiting:

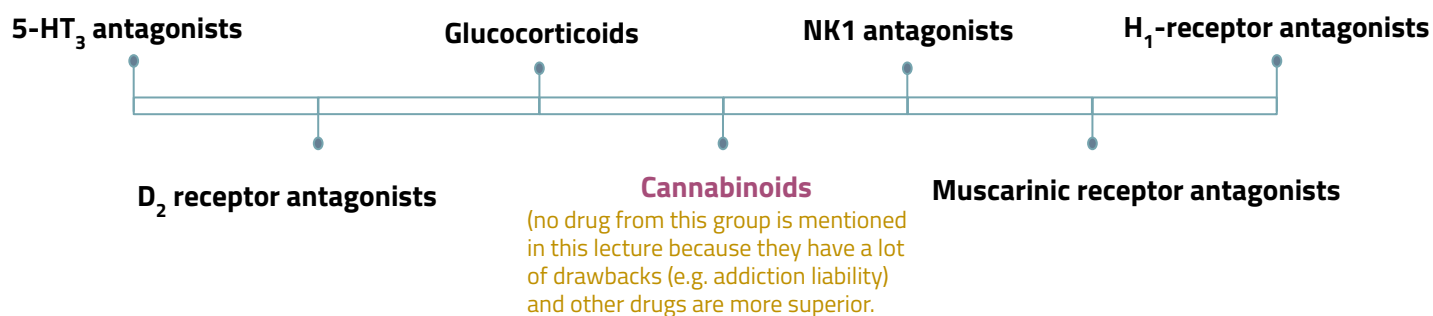


The illustration from slide 7 is "very very important", especially to identify drug targets. [Click here](#)

Pathophysiology of Emesis: [click here](#)



Antiemetics classes



Serotonin (5-HT₃) antagonists

Drug	Ondansetron	Granisetron
M.O.A	Act by blocking 5-HT ₃ receptor centrally (in vomiting center, CTZ) and peripherally (5-HT ₃ receptors on GI vagal afferents)	
P.k	Orally or parenterally <ul style="list-style-type: none"> • Have long duration of action, and is subject to first pass effect • The most potent antiemetic drugs due to its dual effect centrally and peripherally 	
Uses	First choice for prevention of moderate to severe emesis: - Chemotherapy-induced nausea and vomiting (CINV) especially cisplatin (induce severe emesis); Different chemotherapeutic agents have variable degrees of vomiting (range from mild, moderate, severe) - Post-radiation NV & Post-operative NV (radiation and general anesthetics (chemicals) stimulate CTZ) Their effects are augmented by combination with corticosteroids and NK ₁ antagonists. They are very effective alone but there is a variability in response within patients so we combine it with other drugs depending on patient's response.	
ADRs	They are well tolerated in general <ul style="list-style-type: none"> • Headache, dizziness and constipation. • Minor ECG abnormalities (QT prolongation) (be careful with cardiovascular patients) 	

D₂ receptor antagonists (Block D₂ dopamine receptors in the CTZ)

Prokinetics
drugs¹

Neuroleptics
(antipsychotics)

A) Prokinetic D₂ receptor antagonists

Drug	Domperidone	Metoclopramide
M.O.A	<ul style="list-style-type: none"> Blocks D₂ Dopamine receptors in the CTZ (both drugs have antiemetic effects as CTZ is outside the blood brain barrier). They are prokinetic agents (5-HT₄ agonist activity): Increases upper GI motility and gastric emptying 	
P.k	<ul style="list-style-type: none"> Given orally. Does not cross BBB <small>mnemonic: Domperidone Doesn't cross BBB</small> It's has an antiemetic action even though it doesn't cross the BBB because it blocks the D2 receptor in the CTZ which is located physiologically outside the CNS 	<ul style="list-style-type: none"> Given orally Or IV. Cross BBB
Uses	<p>Antiemetic action (due to blocking D₂ receptor in CTZ):</p> <ul style="list-style-type: none"> Effective against vomiting due to cytotoxic (anticancer) drugs, gastroenteritis (cause secretion of chemicals that stimulate the CTZ), post surgery (general anesthetics), toxins, uremia, radiation. <p>Prokinetic action (due to 5-HT₄ agonist activity):</p> <ul style="list-style-type: none"> Used in Gastroesophageal reflux disease (GERD) Used in gastroparesis² (impaired gastric emptying after surgery, it can also be associated with diabetes) 	
ADRs	<p>Only for Metoclopramide:</p> <ul style="list-style-type: none"> Dyskinesia (extrapyramidal side effects) Galactorrhea, menstrual disorders, infertility in females, impotence (with prolonged use) Prolactin is inversely related to dopamine when dopamine is reduced prolactin increases and causes those side-effects Postural hypotension (α- blocking action) Sedation, drowsiness <p>Can domperidone produce these side effects? Metoclopramide crosses BBB but domperidone can not cross in a significant amount. (both have antiemetic effects as CTZ has incomplete blood brain barrier).</p>	

B) D₂ receptor antagonists Neuroleptics (Antipsychotics)

Drug	Chlorpromazine (CPZ)	Droperidol
Uses	<ul style="list-style-type: none"> Postoperative vomiting Chemotherapy-induced emesis 	
ADRs	<ul style="list-style-type: none"> Extrapyramidal symptoms Sedation Postural hypotension (alpha blocking effect) 	

Doctors Notes and Extra:

1) A prokinetic agent is a type of drug which enhances gastrointestinal motility by increasing the frequency or strength of contractions, but without disrupting their rhythm.

2) Gastroparesis (stomach paralysis) is defined as delayed gastric emptying of a solid meal in the absence of mechanical obstruction and it can be due to vagus nerve injury by trauma or during surgery. Characteristic symptoms is nausea and vomiting.

Neurokinin-1 (NK1) receptor antagonists

Drug	Aprepitant ¹
M.O.A	<ul style="list-style-type: none"> Acts centrally as substance P antagonist by blocking neurokinin 1 receptors in vagal afferent fibers in STN and area postrema.
P.k	<ul style="list-style-type: none"> Given orally.
Uses	<ul style="list-style-type: none"> can be used alone but clinically Usually combined with 5-HT₃ antagonists and corticosteroids in prevention of chemotherapy-induced nausea and vomiting and post-operative NV.

H₁-receptor antagonists ²

Drug	Diphenhydramine	Promethazine	Meclizine	Cyclizine
Uses	<ul style="list-style-type: none"> Motion sickness³ Morning sickness in pregnancy Dr. Ishfaq: Remember the uses are double Ms (Morning sickness and Motion sickness) Promethazine: Severe morning sickness of pregnancy (only if essential because it has worse ADRs) 			
ADRs	<ul style="list-style-type: none"> Prominent sedation (because they are First generation Antihistamines so can cross BBB) Hypotension. (alpha blocking effect) Anticholinergic effects or atropine like actions (dry mouth, dilated pupils, urinary retention, constipation) 			

Muscarinic receptor antagonists

Drug	Hyoscine (Scopolamine)
M.O.A	<ul style="list-style-type: none"> Reduces impulses from vestibular apparatus
P.k	Orally, injection, patches (preferably)
Uses	<ul style="list-style-type: none"> Used as transdermal patches in motion sickness (given before trip as prophylaxis therapy) (applied to the postauricular area "behind the external ear") almost no ADRs Not in chemotherapy-induced vomiting
ADRs	<ul style="list-style-type: none"> Sedation (Very minor, especially with patches although it can pass the BBB) Atropine like actions: <ul style="list-style-type: none"> Blurred vision Tachycardia Dry mouth Constipation Urinary retention

Doctors Notes and Extra:

1) Too weak to be used alone

2) We prefer using 1st gen antihistamines because we want the sedative effect

3) effective due to H₁ receptors that are present in the vestibular system

Glucocorticoids

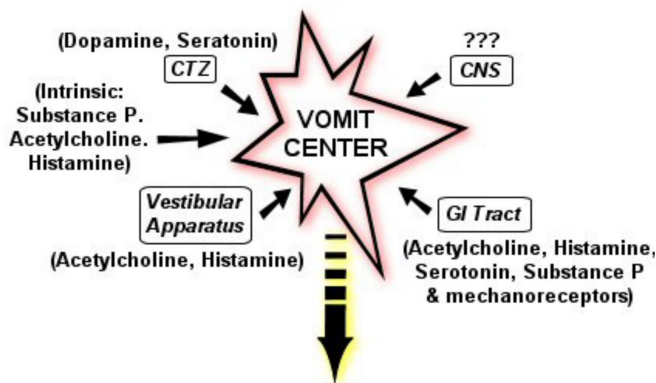
Drug	Dexamethasone	Methylprednisolone
Uses	<ul style="list-style-type: none"> Used in chemotherapy-induced vomiting (it's unknown how Glucocorticoids produce an antiemetic effect) Combined with 5-HT₃ antagonists or NK1 receptor antagonist or both (all three) Glucocorticoids are very effective but have too many ADRs 	
ADRs For long term use	<ul style="list-style-type: none"> Hypertension Cataract Increased susceptibility to infection Increased appetite & obesity. 	<ul style="list-style-type: none"> Hyperglycemia Increased intraocular pressure Osteoporosis Mineralocorticoids action causing water retention

Summary

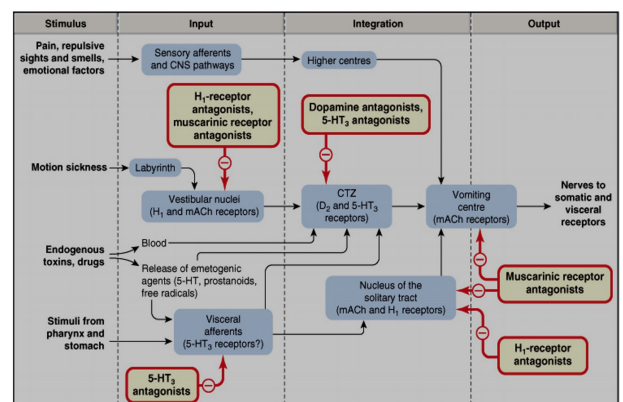
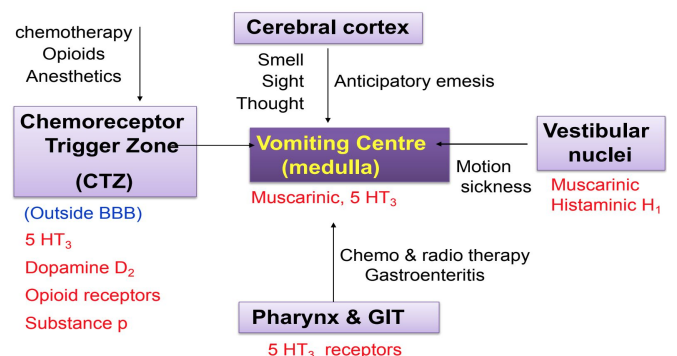
The choice of antiemetic depends on the etiology:

- Motion sickness:**
 - Muscarinic antagonists
 - Antihistamines
- Vomiting with pregnancy (morning sickness):**
 - Avoid all drugs in the first trimester
 - Pyridoxine (B6)
 - Promethazine (late pregnancy).
- Vomiting due to cytotoxic drugs:**
 - 5-HT₃ antagonists (best choice)
 - D₂- antagonists
 - NK1 antagonists
 - Glucocorticoids
 - Cannabinoids: they are especially used in brain ischemia
- Post operative nausea & vomiting:**
 - Dopamine antagonists
- Drug- induced vomiting (CTZ), uremia, gastritis:**
 - Dopamine antagonists

Receptors Associated with Nausea and Vomiting (important):



Pathophysiology of Emesis:



Summary

focus on MoAs, Specific indication and Specific side effects

Class	Drug	M.O.A	Uses	ADRs D.I
Serotonin (5-HT ₃) antagonists	Ondansetron	5-HT ₃ receptor centrally and peripherally	<ul style="list-style-type: none"> -First choice -Chemotherapy induced nausea and vomiting (CINV) especially cisplatin -Post-radiation NV& Post-operative NV 	Headache, dizziness, constipation and QT prolongation
	Granisetron			
Prokinetic D ₂ receptor antagonists	Domperidone	<ul style="list-style-type: none"> -D₂ Dopamine receptors in the CTZ -prokinetic agents (5-HT₄ agonist activity) 	<ul style="list-style-type: none"> - vomiting due to cytotoxic drugs, gastroenteritis, surgery, toxins, uremia, radiation. - Gastroesophageal reflux disease (GERD) - Gastroparesis 	Only for Metoclopramide: <ul style="list-style-type: none"> -Dyskinesia -Galactorrhea, menstrual disorders, impotence -Postural hypotension -Sedation, drowsiness
	Metoclopramide			
D ₂ receptor antagonists Neuroleptics (Antipsychotics)	Chlorpromazine (CPZ)	—	<ul style="list-style-type: none"> -Postoperative vomiting Chemotherapy-induced emesis 	<ul style="list-style-type: none"> -Extrapyramidal symptoms -Sedation -Postural hypotension
	Droperidol			
Neurokinin-1 (NK1) receptor antagonists	Aprepitant	Acts centrally as substance P antagonist by afferent fibers.	<ul style="list-style-type: none"> -combined with 5-HT₃ antagonists and corticosteroids in prevention of chemotherapy-induced nausea and vomiting and post-operative NV 	—
H1-receptor antagonists	Diphenhydramine	—	<ul style="list-style-type: none"> -Motion sickness -Morning sickness in pregnancy -Promethazine: Severe morning sickness of pregnancy (only if essential) 	<ul style="list-style-type: none"> -Prominent sedation. -Hypotension. -Anticholinergic effects or atropine like actions
	Promethazine			
	Meclizine			
	Cyclizine			
Muscarinic receptor antagonists	Hyoscine (Scopolamine)	Reduces impulses from vestibular apparatus	<ul style="list-style-type: none"> transdermal patches in motion sickness 	<ul style="list-style-type: none"> -Sedation -Atropine like actions
Glucocorticoids	Dexamethasone	—	<ul style="list-style-type: none"> -chemotherapy induced vomiting -Combined with 5-HT₃ antagonists or NK1 receptor antagonist 	<ul style="list-style-type: none"> -Hypertension -Hyperglycemia -Cataract -Osteoporosis -Increased intraocular pressure -Increased susceptibility to infection -Increased appetite & obesity.
	Methylprednisolone			

MCQs

Q1: which of the following would be useful for promoting gastric emptying in a patient with a gastrostomy tube?			
A- Diphenhydramine	B- Metoclopramide	C- Ondansetron	D- Aprepitant
Q2: which is not one of the 5 main neurotransmitters involved in nausea and vomiting?			
A- Histamine	B- Norepinephrine	C- Substance P	D- Dopamine
Q3: A 24-year-old woman is undergoing chemotherapy for acute leukaemia. She is admitted to the Acute Medical Unit due to severe vomiting and you decide to administer intravenous hydration and antiemetic treatment. Which of the following would be the most appropriate antiemetic choice?			
A- Metoclopramide IM	B- Ondansetron IV	C- Oral domperidone	D- Prochlorperazine IM
Q4: A 50-year-old woman complained to her physician of regurgitation of foul-tasting fluid into her mouth and occasional nausea and vomiting. The physician prescribed a drug that can both prevent nausea and vomiting and promote upper gastrointestinal motility. Blockade of which of the following receptors most likely contributed to the therapeutic effect of the drug in the patient's disease?			
A- M3 cholinergic	B- D ₂ dopaminergic	C- Beta-2 adrenergic	D- H ₂ histaminergic
Q5: A 35-year-old woman presented to her physician complaining of recent onset of nausea and vomiting in the mornings. A pregnancy test confirmed she was pregnant. Which of the following drugs is most likely included in the treatment?			
A- Promethazine	B- Ondansetron	C- Scopolamine	D- Metoclopramide
Q6: Applied to the skin in a transdermal patch (transdermal therapeutic delivery system), this drug is used to prevent or reduce the occurrence of nausea and vomiting that are associated with motion sickness.			
A- Scopolamine	B- Ondansetron	C- Diphenhydramine	D- Chlorpromazine
Q7: At a follow-up visit one month after a 22-year-old male was newly diagnosed with schizophrenia and started on chlorpromazine, he has several complaints, listed below. Which of the following cannot be attributed to chlorpromazine?			
A- Restless feeling	B- Sexual dysfunction	C- Urinary hesitancy	D- Vomiting
Q8: Glucocorticoids have proved useful in the treatment of which of the following medical conditions?			
A-Chemotherapy-induced vomiting	B-Essential hypertension	C-Hyperprolactinemia	D-Parkinson's disease
Q9: A 20-year-old woman is taking diphenhydramine for severe hay fever. Which of the following adverse effects is she most likely to report?			
A- Vertigo	B- Nausea	C- Muscarinic increase in bladder tone	D- Sedation

1	2	3	4	5	6	7	8	9
B	B	B	B	A	A	D	A	D

SAQ

Q1) A patient is receiving highly emetogenic chemotherapy for metastatic carcinoma. To prevent chemotherapy-induced nausea and vomiting, she is likely to be treated with which of the following?

- A. What is your drug of choice?
- B. Mention two other drugs from different classes can be used for his condition with and their MOA
- C. The patient's vomiting was induced by chemotherapy, list three other conditions that induce vomiting

Q2) A 44-year-old man asks for advice. He is due to go on a long bus journey but suffers from debilitating motion sickness.

- A. Mention two medications from different classes can be used for his condition?
- B. For each drug list 1) the MOA, 2) 2ADRs

Match

Match the following antiemetic drugs with their respective categories:

Drug	Uses	Receptor
Ondansetron	1) combined with 5-HT ₃ antagonists and corticosteroids in post-operative NV	A) muscarinic
Aprepitant	2) Gastroparesis	B) D ₂ Dopamine Serotonin 5-HT ₄
Metoclopramide	3) Motion sickness	C) Serotonin 5-HT ₃
Scopolamine	4) Vomiting due to cytotoxic drug	D) neurokinin 1

Answers

SAQs:

A1) A) Ondansetron

B) Aprepitant: antagonist at NK1 receptors, Metoclopramide: D₂ receptor antagonist

C) Motion sickness, Gastroenteritis, anticipatory emesis

A2) A) Meclizine and Hyoscine

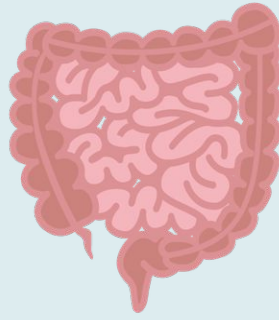
B) Meclizine: H₁ receptor antagonist. causes: Prominent sedation, Hypotension, Anticholinergic effects

Hyoscine: Muscarinic receptor antagonists. Causes: Sedation, Atropine like actions

Match: Ondansetron (4C), Aprepitant (1D), Metoclopramide (2B), Scopolamine (3A)



Feedback Form



Gastrointestinal Block

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