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Pharmacology
Team 437

MED437
KING SAUD UNIVERSITY

Antiemetic drugs

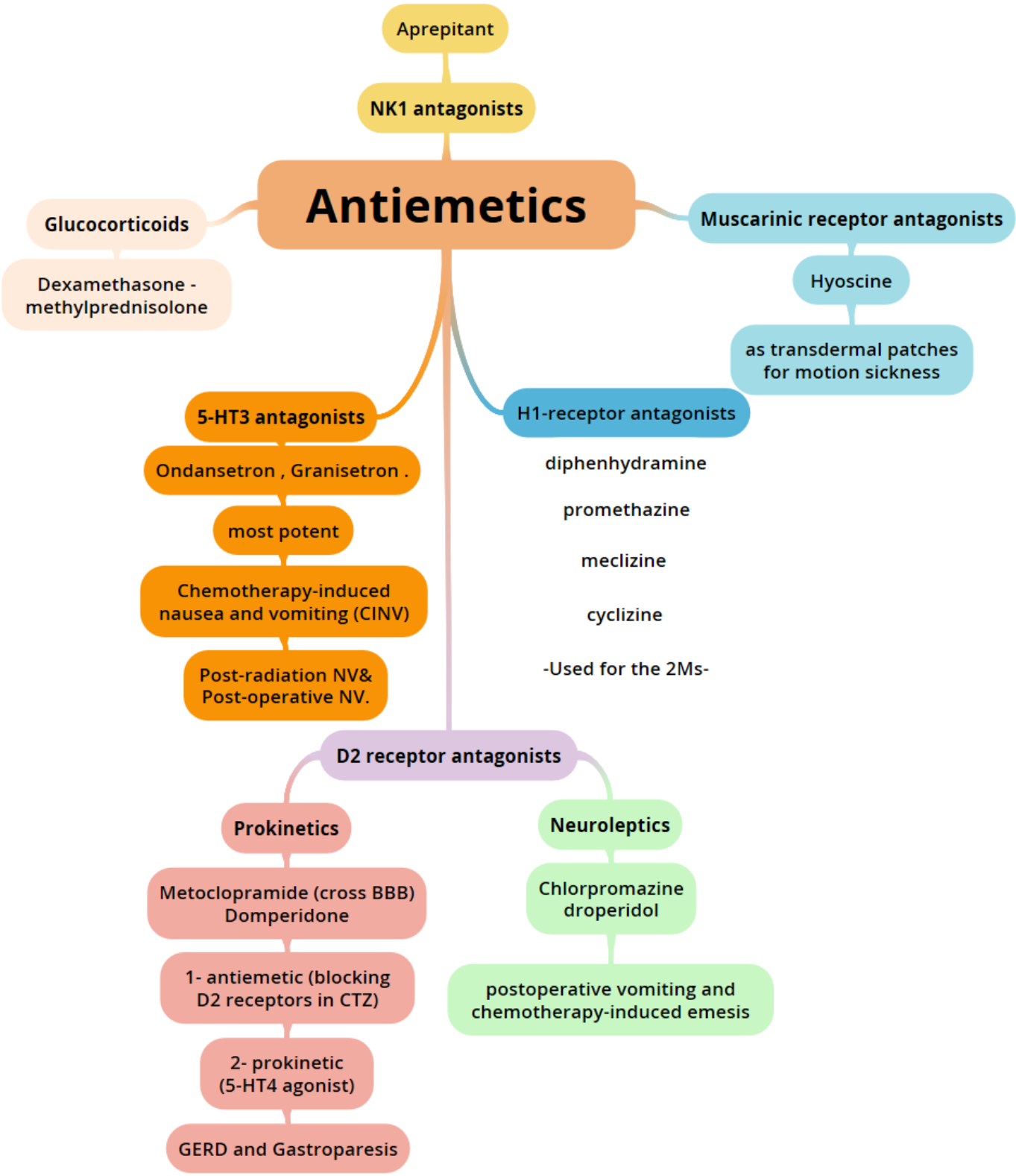
Objectives:

- 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.

Editing File

Color index: Important Note Extra

Mind Map


Aprepitant
NK1 antagonists
Antiemetics
Glucocorticoids
Dexamethasone - methylprednisolone
Muscarinic receptor antagonists
Hyoscine
as transdermal patches for motion sickness
5-HT3 antagonists
Ondansetron , Granisetron .
most potent
Chemotherapy-induced nausea and vomiting (CINV)
Post-radiation NV& Post-operative NV.
H1-receptor antagonists
diphenhydramine
promethazine
meclizine
cyclizine
-Used for the 2Ms-
D2 receptor antagonists
Prokinetics
Metoclopramide (cross BBB) Domperidone
1- antiemetic (blocking D2 receptors in CTZ)
2- prokinetic (5-HT4 agonist)
GERD and Gastroparesis
Neuroleptics
Chlorpromazine droperidol
postoperative vomiting and chemotherapy-induced emesis

Vomiting

It is a forceful expulsion of gastric contents through the mouth.

Can vomiting be considered a disease?

It is a manifestation of many conditions and diseases.

Consequences of vomiting

Severe vomiting may result in :

- **Dehydration**
- Acid-base imbalance
- Electrolyte depletion Loss of water >> Dehydration >> Electrolytes depletion
- Aspiration (usually in old age), pneumonia

How is vomiting induced?

1. Higher cortical centers stimulation(CNS):

- Emotional factors
- Nauseating smells or sights

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. Stimulation of 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 D2 receptors, 5-HT3 receptors & opioid receptors

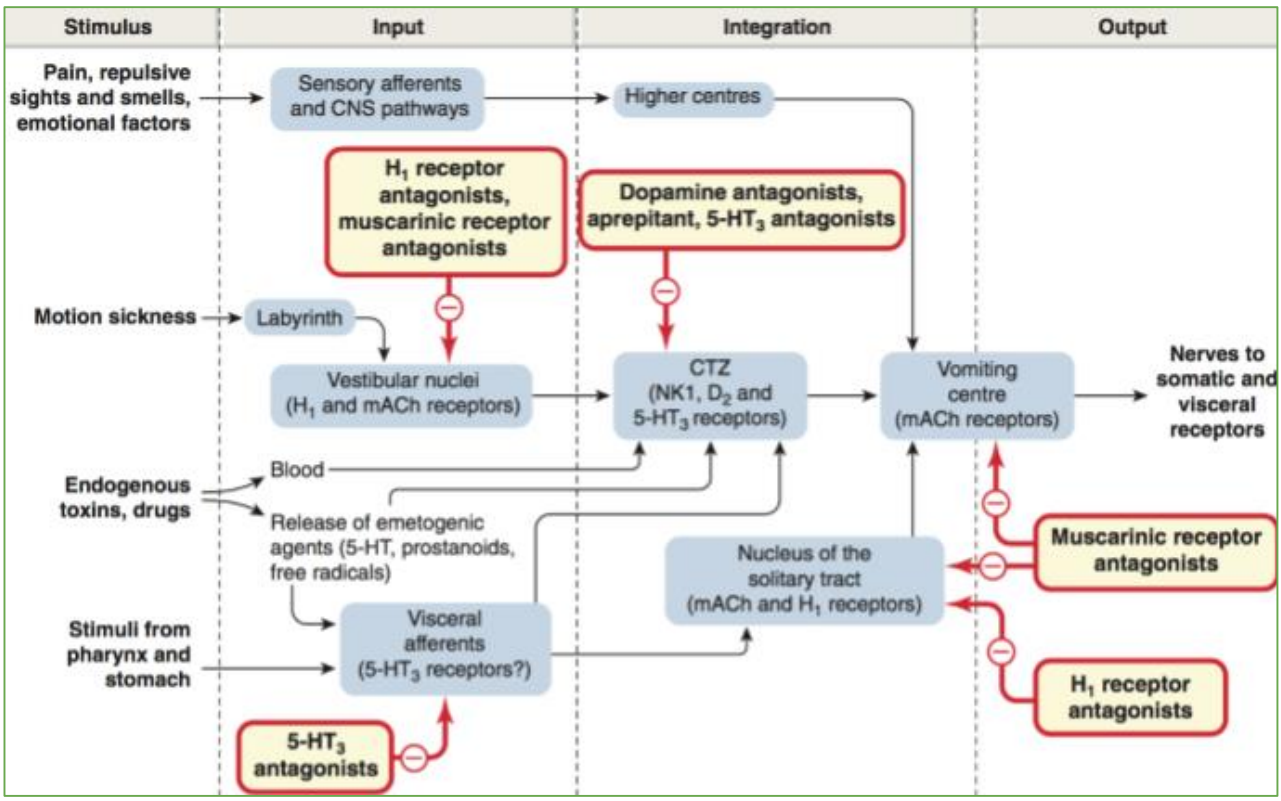
stimulated by:

- Emetogenic drugs (opioids, general anesthetics, digitalis, L-dopa)
- chemicals and toxins (blood, CSF)
- Radiation
- Uremia

Chemical transmitters & receptors involved in vomiting and drug targets:

- Ach **(Muscarinic receptors)**
- Dopamine **(D2)**
- Histamine **(Histaminergic receptors H1)**
- Serotonin **(5 -HT3)**
- Substance P **(Neurokinin receptors, NK1)**
- Opioid **(Opioid receptors)** (They are not used clinically as antiemetic)

****Extra information for reading only**



Pathophysiology of Emesis

All antiemetics are antagonists

Some CNS suppressant drugs can help decrease vomiting such as benzodiazepines, but they're dangerous and have many side effects

Triggered by:
- Sight
- Smell
- Thought
(anticipatory emesis)

1- Cerebral cortex

Triggered by:
- Chemotherapy
- Opioids
- Anesthetics
- Post surgery
+ Radiotherapy

2- Chemoreceptor trigger zone (outside BBB)
from blood or CSF

5-HT3
Dopamine D2
Opioid Receptor
Substance P

CTZ doesn't have complete BBB, so it can sense the chemicals circulating in the blood.

One of the possible ways:
Pain >> Vagal afferent >> vomiting • center

Motion sickness

3- Vestibular nuclei

Muscarinic M1
Histaminic H1

Vomiting centre (medulla)
(receptors : Muscarinic, **5-HT3**)

4- Pharynx & GIT

5-HT3 receptors

Triggered by:
- Chemo & radiotherapy
- Gastroenteritis

Classification of Antiemetic Drugs

- 5-HT3 antagonists
- D_2 receptor antagonists
- NK_1 antagonists (substance P)
- H_1-receptor antagonists
- Muscarinic receptor antagonists
- Cannabinoids (not used clinically anymore due to addiction)
- Glucocorticoids

Serotonin (5-HT3) antagonists

Drug	Ondansetron	Granisetron
M.O.A	• Act by blocking 5-HT3 receptor centrally (in vomiting center, CTZ) and peripherally (5HT3 receptors on GI vagal afferents). • (5-HT3 antagonist drugs are potent because they have dual action on both stomach and brain.)	
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 (*Cisplatin* is a chemotherapy medicine which causes severe vomiting because it acts on the vomiting center or CTZ)
	  ○ Post-radiation NV & Post-operative NV
	• Their effects are augmented by combination with corticosteroids and NK_1 antagonists. (We will not combine it with H1 blockers here, why? If there is a case which is not controlled with 5-HT3, H1 blockers surely will not control it because it's weaker. So the best choice is corticosteroids.)	

ADRs	They are well tolerated in general 1. Headache, dizziness and constipation 2. Minor ECG abnormalities (QT prolongation) most important ADR (very few side effects and it's well tolerated so it's a good class)	

D2 Receptor antagonists imp

Are prokinetic agents (increased GI motility & gastric emptying).

block D_2 dopamine receptors in the CTZ

Prokinetics drugs (increase motility)

Neuroleptics (antipsychotics)

used for postoperative vomiting and chemotherapy-induced emesis.

Prokinetic D2 Receptor antagonists

M.O.A	• Blocks D2 Dopamine receptors in the CTZ (both drugs have antiemetic effects as CTZ is outside the blood brain barrier) • they are prokinetic agents (5HT4 agonist activity): Increases upper GI motility (So we can't give it in case of constipation) and gastric emptying	
Drug	**Domperidone** (safer)	**Metoclopramide**
P.K and P.D	Given orally. Does not cross blood brain barrier (So no extrapyramidal side effects)	Given orally, or IV. Crosses blood brain barrier (so might be more toxic)
Indications	Antiemetic action (due to blocking D2 receptor in CTZ): • Effective against vomiting due to cytotoxic drugs, gastroenteritis, surgery (due to anesthesia), toxins, uremia, radiation. Prokinetic action (due to 5HT4 agonist activity): • Used in Gastroesophageal reflux disease (GERD): it increases the motility of the GI to increase the rate at which food is moving, which will decrease the acidity • Used in gastroparesis (impaired gastric emptying after surgery) (It happens in: 1- post surgery 2- diabetic patients [or in diabetic patients with peripheral neuropathy]) • Domperidone helps increase bioavailability of other drugs	
ADRs	Domperidone does not cross BBB therefore it doesn't have CNS side effects, so we can use it on patients with Parkinson's **Only for Metoclopramide:** 1. Dyskinesia (extrapyramidal side effects) parkinsonism 2. Galactorrhea, menstrual disorders, impotence, hyperprolactinemia which can cause infertility in female 3. Postural hypotension (α- blocking action), especially if combined with antihypertensives 4. Sedation, drowsiness	

Not commonly used. Usually used with psychotic patients.

D2 Receptor Antagonists
Neuroleptics (Antipsychotics)

Drug	Chlorpromazine (CPZ)	Droperidol
Uses	• Postoperative vomiting • Chemotherapy-induced emesis (We use them in severe and resistant cases, not a good choice due to its side effects.)	
Side effects similar to Metoclopramide	1. Extrapyramidal symptoms. (b/c they block D2 centrally) 2. Sedation 3. Postural hypotension	

Neurokinin-1 (NK1) receptor antagonists

Drug	Aprepitant
M.O.A	• Acts centrally as **substance P antagonist** by blocking neurokinin-1 receptors in vagal afferent fibers.
P.K	• Orally
Indications	• Usually combined with 5-HT3 antagonists OR corticosteroids in prevention of chemotherapy-induced nausea and vomiting and post-operative NV. We use this combination if the patient is not responding to 5HT3-antagonists.

As an antiemetic drug it would help if it is combined with other drugs because it has a different mechanism of action. But it is not strong enough to be given alone.

Chemotherapy-induced nausea:
We use 2 drugs only but in very severe cases we use 3, eg:

1. Corticosteroids + NK1 Receptor antagonist
2. Corticosteroids + 5-HT3 Antagonist
3. 5-HT3 Antagonist + NK1 Receptor antagonist

H1-receptor agonists.

Drug	Diphenhydramine	Promethazine	Meclizine	Cyclizine
			Longer Acting	
Uses	1. Motion sickness. 2. Morning sickness in pregnancy. 3. Promethazine: Severe morning sickness of pregnancy (only if essential) 4. 1st class to pass BBB			
ADRs	1. Prominent sedation. 2. Hypotension. (alpha blocking effect) 3. Anticholinergic effects or atropine like actions (dry mouth, dilated pupils blurred vision , urinary retention, constipation)			

	Muscarinic receptor antagonists	Glucocorticoids	
Drug	Hyoscine (scopolamine)	Dexamethasone	methylprednisolone
M.O.A	• Reduces impulses from vestibular apparatus	• The most potent anti-inflammatory drugs because They Inhibit phospholipase A2	
P.K	• Orally, injection, patches • Used as transdermal patches in motion sickness(applied behind the external ear).	-	
Indications	• Not in chemotherapy-induced vomiting	• Used in chemotherapy-induced vomiting • Combined with 5-HT3 antagonists or NK1 receptor antagonists	
ADRs	1. Sedation 2. Tachycardia 3. Atropine like actions: a. Blurred vision b. Dry mouth c. Constipation d. Urinary retention	1. Hyperglycemia 2. Hypertension 3. Cataract 4. Osteoporosis Because they interfered with the absorption of Ca 5. Increased intraocular pressure 6. Increased susceptibility to infection Because they suppress the immunity 7. Increased appetite & obesity water retention >> Obesity	

Summary - 1

The choice of antiemetic according to etiology

From the doctor's slides

Motion sickness	1. Muscarinic antagonists 2. Antihistamines
Vomiting with pregnancy (morning sickness)	• Avoid all drugs in the first trimester 1. Pyridoxine (B6) 2. Promethazine (late pregnancy).
Drug- induced vomiting (CTZ), uremia, gastritis	• Dopamine antagonists
Post operative nausea & vomiting	• Dopamine antagonists
Vomiting due to cytotoxic drugs.	1. 5-HT3 antagonists 2. NK1 antagonists 3. D2 antagonists 4. Glucocorticoids 5. Cannabinoids

Serotonin (5-HT3) antagonists

Drug	Ondansetron	Granisetron
M.O.A	• **Act by blocking 5-HT3 receptor centrally (in vomiting center, CTZ) and peripherally (5HT3 receptors on GI vagal afferents).**	
P.K	• **The most potent antiemetic drugs**	
Indications	**First choice for prevention of moderate to severe emesis:** 1. **Chemotherapy-induced nausea and vomiting (CINV) especially cisplatin** 2. **Their effects is augmented by combination with corticosteroids and NK_1 antagonists** 3. **Post-radiation NV & Post-operative NV**	
ADRs	1. **Headache, dizziness and constipation** 2. **Minor ECG abnormalities (QT prolongation)**	

Summary - 2

H1-receptor agonists.				
Drug	**Diphenhydramine**	**Promethazine**	**Meclizine**	**Cyclizine**
Uses	1- Motion sickness 2-Morning sickness in pregnancy 3- Promethazine: Severe morning sickness of pregnancy (only if essential)			
ADRs	1- Prominent sedation 2- Hypotension 3- Anticholinergic effects			

Prokinetic D2 Receptor antagonists		
M.O.A	• Blocks D2 Dopamine receptors in the CTZ • they are prokinetic agents (5HT4 agonist activity)	
Drug	**Domperidone** (safer)	**Metoclopramide**
P.K and P.D	Does not cross blood brain barrier (so no extrapyramidal side effects)	Crosses blood brain barrier (so might be more toxic)
Indications	Antiemetic action Effective against vomiting due to cytotoxic drugs, gastroenteritis, surgery, toxins, uremia, radiation.	Prokinetic action 1. Used in (GERD) 2. Used in gastroparesis (impaired gastric emptying after surgery)

Neuroleptic D2 Receptor Antagonists		
Drug	**Chlorpromazine (CPZ)**	**Droperidol**
Uses	• Postoperative vomiting • Chemotherapy-induced emesis (We use them in severe and resistant cases, not a good choice due to its side effects.)	
ADRs **like: Metoclopramide**	1- Extrapyramidal symptoms 2- Sedation 3- Postural hypotension	

Neurokinin-1 (NK1) receptor antagonists	
Drug	**Aprepitant**
M.O.A	• Acts centrally as **substance P antagonist** by blocking neurokinin 1 receptors in vagal afferent fibers.
Indications	• Usually combined with 5-HT3 antagonists OR corticosteroids in prevention of chemotherapy-induced nausea and vomiting and post- operative NV. We use this combination if the patient is not responding to 5HT3 antagonists.

MCQs

Q1- Which of the following is a Substance P antagonist?

A- Chlorpromazine B- Droperidol

C- Aprepitant D- Meclizine

Q2- A Pregnant mother is complaining of severe morning sickness, which drug should be prescribed for her case?

A- Aprepitant B- Promethazine

C- Diphenhydramine D- Chlorpromazine

Q3- What is the first choice for moderate to severe emesis?

A- D2 receptor antagonist B- H1 receptor antagonist

C- NK1 antagonist D- 5-HT3 antagonist

Q4- In case of chemotherapy induced nausea and vomiting if 5-HT3 does not control the problem we should combine it with?

A- D2 receptor antagonists B- Glucocorticoids

C- Muscarinic receptor antagonists D- H_1-receptor antagonist

Q5- Which one of these drugs can cross the BBB and be used for GERD?

A- Metoclopramide B- Droperidol

C- Aprepitant D- Chlorpromazine

Q6- Which one of the following does NOT cause extrapyramidal symptoms?

A- Droperidol B- Chlorpromazine

C- Metoclopramide D- Domperidone

Q7- Emotional factors stimulate which of the following:

A-Higher cortical centers (CNS) B-vestibular system

C-The periphery(Pharynx, GIT) D-Chemoreceptor trigger zone (CTZ)

Q8-The Disturbance of vestibular system is stimulated by:

A-GIT irritation B- Uremia

C-Motion sickness D-Emotional factors

Q9-Which one of the following antiemetic drug has extrapyramidal symptoms?

A- Meclizine B- Hyoscine

C-Chlorpromazine D- Ondansetron

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

SAQ:

Q1: Mention 3 Parts of body that are connected to chemoreceptor trigger zone which causes vomiting (medulla)

Gastrointestinal tract, Labyrinth (inner ear), cerebral cortex

Q2:A/ A female patient presented with vomiting so her doctor prescribed her an antiemetic drug that caused Dyskinesia and menstrual disorders what was the drug?

Metoclopramide

B/ What is the Mechanism of action of that drug

Blocks D2 Dopamine receptors in the CTZ

they are prokinetic agents (5HT4 agonist activity)

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References:

✓ Doctors' slides and notes

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