King Saud University
College of Medicine
2nd Year, 2nd Block

GIT BLOCK

PHARMACOLOGY 433

MED 433 Teams

L1- Antiemetic drugs

Learning 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.

-The First few slides was physiology so, we just mentioned the **important points HERE In three SLIDEs**
-The most important point from physiology part that we should understand is the receptors.
-Vomiting is a good thing some time because it remove the toxins and bad substances that may exceeds the gastric contents
--The cause of vomiting is stimulation of receptors so, in treatment we will block the receptors (most of antiemetic are blocking or antagonist the receptors)

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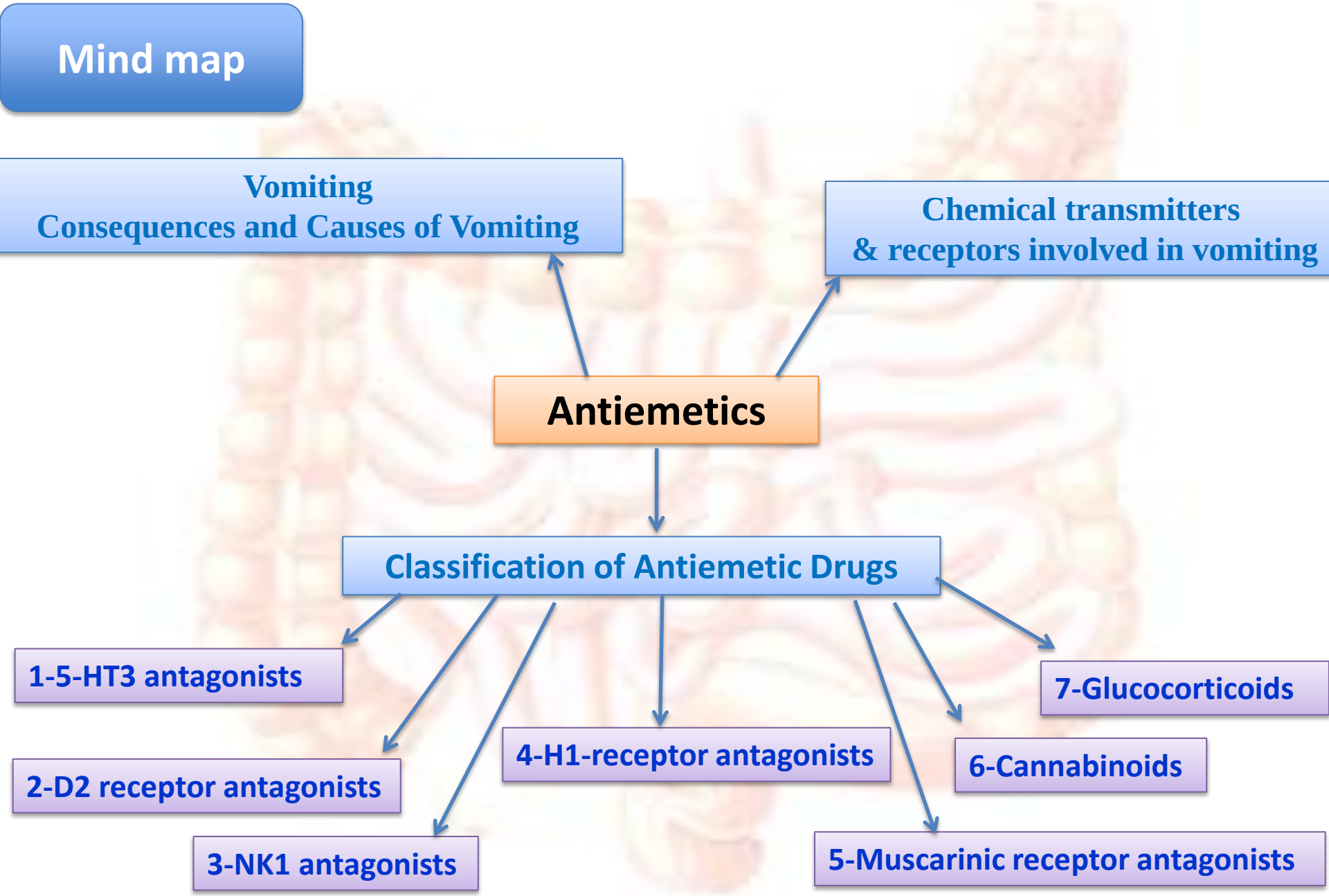
Mind map



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The chemoreceptor trigger zone (CTZ)

is an area of the medulla oblongata that receives inputs from blood-borne drugs or hormones, and communicates with other structures in the vomiting center to initiate vomiting. The CTZ is located within the area postrema , **which is on the floor of the fourth ventricle and is outside of the blood–brain barrier.**

It is also part of the vomiting center itself

·The neurotransmitters implicated in the control of nausea and vomiting include **acetylcholine**, **dopamine**, **histamine (H-1 receptor),substance P (NK-1 receptor),** and **serotonin (5-HT3 receptor)**. There are also **opioid receptors** present, which may be involved in the mechanism by which opiates cause nausea and vomiting. The blood brain barrier is not as developed here, **and drugs such as dopamine which can normally not enter the CNS may still stimulate the CTZ.**

Chemotherapy

Chemotherapy is a big cause of emesis, and often can cause severe and frequent emetic responses. This is because chemotherapy agents circulating in the blood activate the CTZ in such a way as to cause emesis.Patients receiving chemotherapy are often prescribed antiemetic medications = this is the meaning of **chemotherapy induced vomiting and nausea**

Introduction

Chemoreceptor trigger zone (CTZ)

-CTZ is an area of medulla that communicate with vomiting center to initiate vomiting.(the stimulus is chemical so, it is receptors for chemical substances that induce vomiting . E.g.: post surgery by anesthetics, side effect of some drugs, and uremia)
-CTZ is physiologically outside BBB.
-CTZ contains D_2 receptors, $5HT_3$ receptors & opioid receptors.

Stimulated by:

-Emetogenic* drugs *they are the drugs that induced emesis (opioids, general anesthetics, digitalis, L-dopa).
-chemicals and toxins (blood, CSF).
-Radiation.
-Uremia

Severe vomiting may result in :- Dehydration (due to loss of water contents)
- Acid-base imbalance (Abnormality in balance between hydrogen ions and bicarbonates)
- Electrolyte depletion
- Aspiration, pneumonia

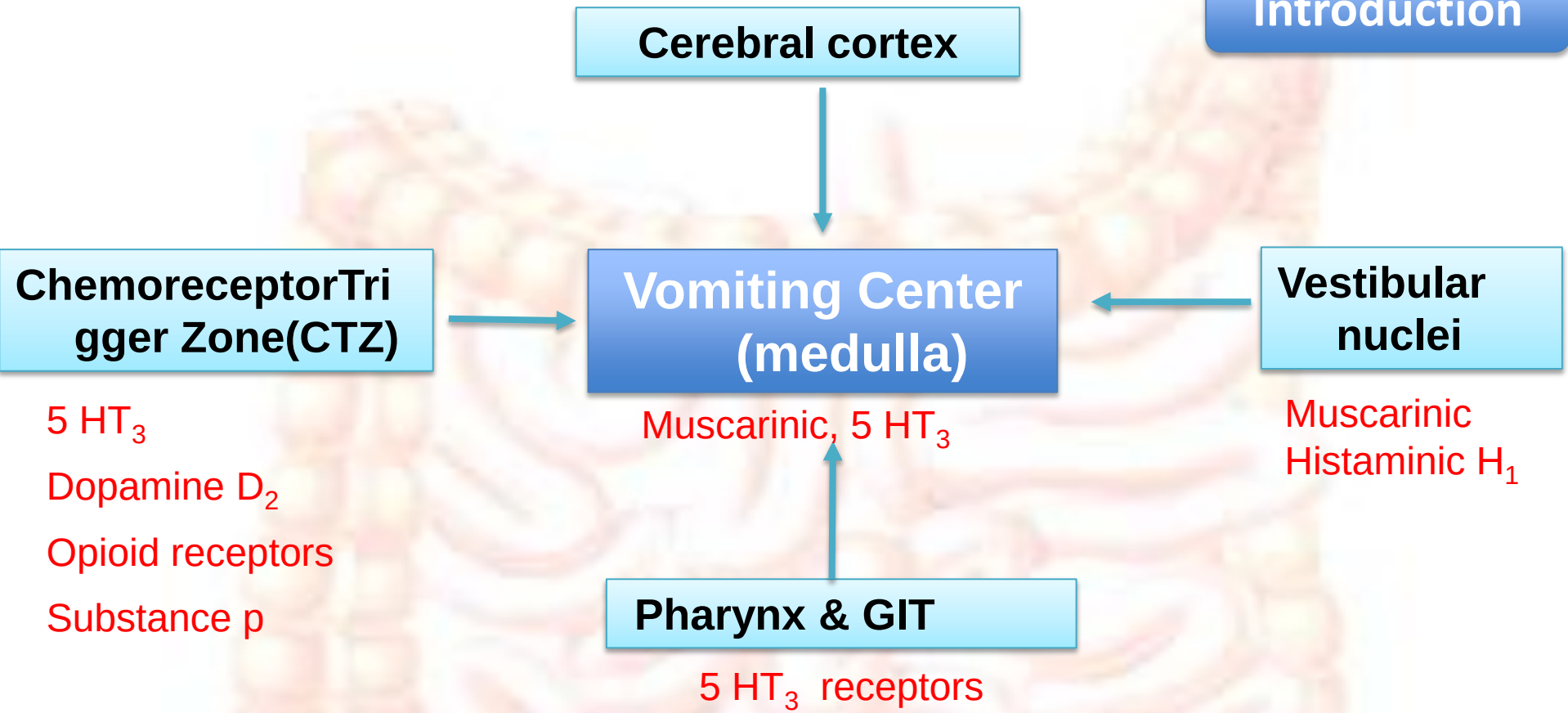
Vomiting "Emesis"

Is complex of series of integrated events culminating in the forceful expulsion of gastric contents through the mouth

Chemical transmitters & receptors involved in vomiting include:
-Ach (Muscarinic receptors)
-Dopamine (D2) (just in one case which is CTZ)
-Histamine (Histaminergic receptors H1 located in vestibular system)
-Serotonin (5 -HT3)
-Substance P (Neurokinin receptors, NK1)
-Opioid (Opioid receptors)

Causes of Vomiting: stimulation of vomiting center that respond to

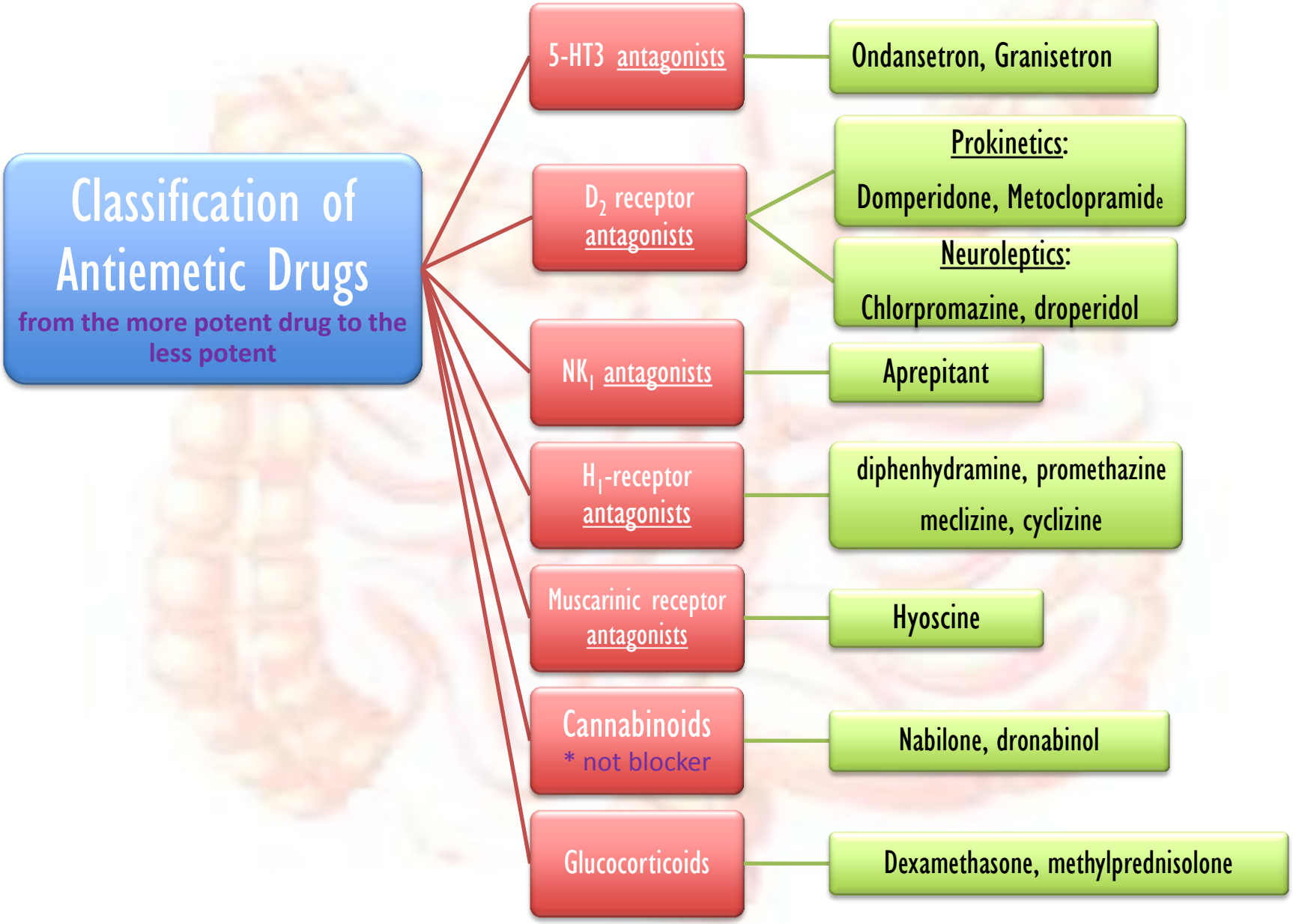
1.Stimulation of chemoreceptor trigger zone (CTZ).
2. The periphery via sensory nerves : GIT irritation, myocardial infarction, renal or biliay stones*, Chemo & radio therapy**
(*E.g.:pain in gastrointestinal tract ,radiating pain in failure or myocardial infarction , Inducing Vomiting with the Gag Reflex),(**most of anticancer drugs are sever emetogenic so, we have to start with them by antiemetic drug as precaution to prevent the emetic effects of cancer drugs then we give them their anticancer drugs then antiemetic drug so, we give them **antiemetic drug pre and post**)
3. Disturbance of vestibular system: motion sickness (H1 & M1 receptors). (in inner ear dysfunction or what ever the cause of motion sickness)
4. Higher cortical centers stimulation: Emotional factors*, Nauseating smells or sights. (*emotional factors such as sever sadness or sever happiness)



1) 5 HT_3 receptors found in center and periphery that is way 5 HT_3 is the most potent one

2) M1+H1 is responsible for motion sickness

3) Dopamine D2 is found only in CTZ so it is responsible for any chemical irritation



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Serotonin (5-HT3) antagonists

Drugs as	**Ondansetron** **Granisetron**
Pharmacokinetics	• Orally or parenterally, • have long duration of action, first pass effect • The most potent antiemetic drugs (because the affect centrally and peripherally)
MOA	Act by **blocking 5-HT3 receptor** centrally (in vomiting center, CTZ) and peripherally (5HT3 receptors on GI vagal afferents*) *afferents mean sensory nerve E.g.: pain for any reason
Uses	• First choice for prevention of moderate to severe emesis: (not in mild) -Chemotherapy-induced nausea and vomiting (CINV) especially cisplatin (with anticancer) -Post-radiation NV& Post-operative NV -Their effects is augmented (مسموح) by combination with corticosteroids and NK_1antagonists. .*Depend on the case, some patients respond very well so they doesn't need combination while others need combination
Side effects	• Well tolerated (*they don't cause sever S.E) • Headache, dizziness and constipation • minor ECG abnormalities (QT prolongation)

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D_2 receptor antagonist

	1- Prokinetics drugs (pro=بادئ, Kinetic= حركة so, they increased GI motility & gastric emptying)		2- Neuroleptics (antipsychotics)	
Drug	**Metoclopramide (I.V+oral)**	**Domperidone (oral)**	**Chlorpromazine**	**Droperidol**
M.O.A	Block D2 dopamine receptors in the CTZ (Chemoreceptor trigger zone, located in medulla)			
	Prokinetic (5 HT4 agonist activity) (We know that the parasympathetic increase the motility so, Ach is involved >> 5 HT4 serotonin receptor release Ach so, It increase the motility)			
Uses	▪ Nausea and vomiting ▪ GERD (cause peptic ulcer so, we use drug to treat peptic ulcer in addition to prokinetic) ▪ Gastroparesis*(as prokinitic* agent) (Gastroparesis=paralysis of the muscles of the stomach E.g. : diabetic patients* (*they have vitamin B12 deficiency or neuropathy) or after surgery we always ask the patient about the gases expulsion If it not happened we need to increase the motility so we give them prokinetic or parasympathomimetic)		▪ postoperative vomiting ▪ chemotherapy-induced emesis	
Side effect	- Extra pyramidal symptoms (because it cross BBB) - Galactorrhea & impotence (endocrine side effects) - Postural hypotension(α-blocking receptor responsible for vasoconstriction) - Sedation (because it cross BBB)	____	- Extra pyramidal symptoms - Postural hypotension - Sedation	
Notes	Metoclopramide cross BBB, while Domperidone don't cross, but both have antiemetic effects (because CTZ located before BBB)			

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Neurokinin1 (NK1) receptor antagonists

Drug	Aprepitant
M.O.A	Acts centrally as substance P antagonist by blocking neurokinin 1 receptors in vagal afferent fibers
Uses	Combined with 5-HT_3 antagonists and corticosteroids in prevention of chemotherapy induced nausea and vomiting and post-operative (also, It can used alone)

H_1-receptor antagonists

Drug	Diphenhydramine	Promethazine	Meclizine	Cyclizine
Uses	Motion sickness (because it cross BBB and cause sedation) and Morning sickness in pregnancy(**Promethazine is** the best in this case)			
Side effect	Sedation, Hypotension , and Anticholinergic effects			

Muscarinic receptor antagonists

Drug	**Hyoscine** (in British) or **scopolamine** (in USA)
Uses	Used as transdermal patches in motion sickness (it used as prophylaxes) Nausea and vomiting (**Not** in chemotherapy-induced vomiting)
Side effect	Sedation and anticholinergic effects

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Cannabinoids (adjuvant therapy)		
Drug	**Nabilone**	**Dronabinol**
MOA	Not understood ?	
Uses	vomiting due to cytotoxic drugs (Limited use due to side effects)	
Side effect	Euphoria, dysphoria, sedation, hallucination **(affect CNS so, its use is very rare)**	

Glucocorticoids		
Drug	**Dexamethasone**	**Methylprednisolone**
Uses	Chemotherapy-induced vomiting	
Side effect	(increase body weight due to urinary retention>> every thing ↑) Hyperglycemia, Hypertension, Cataract, Osteoporosis, weight gain	
Note	combined with 5-HT_3 antagonists or NK1 receptor antagonists. (also, It can used alone)	

summary

Drug	Uses	Side effects
5-HT antagonists Eg: ondansetron Granisetron	Very effective in nausea and vomiting due to: cytotoxic drugs and postoperative and postradiation (2ndline)	Well tolerated. Headache. Dizziness. Constipation. Qt interval prolongatoin
D2 receptor antagonists Eg: Metclopromide plasilR and domperidone (motiliumR)	Reflux Esophagitis. -Other uses of metclopromide 1-facilate intubation and endoscope. 2-decrease regurgitation and reflux esophagitis. 3-diagnostic radiology of gut. 4-clear gastric contents in emergency anasthesia. 5-in gastroenteritis(most common use)	Metoclopromide: 1-extrapyramidal side effects. 2-dyskinesia,galactorrhea,sedation Menstruation disorders. Domperidone: Cardiac arrest due to Qt prolongation.
D2 rceptor antagonist: Chlorpromazine Droperidol	For vomiting induced by chemotherapy.	Extra pyramidal symptoms , hypotension, Sedation, Restlessness
Neurokinin (nk1)receptor Antagonist: Aprepitant	1-prevention of acut and delayed chemotherapy induced nausea and vomiting . 2-prevent postoperative nausea and vomiting(3rd line)	

summary

Drug	Uses	Side effects
H1 receptor antagonist : Diphenhydramin,meclizine,cyclizine, promethazine	**Motion sickness, morning sickness(pregnancy), Vestibular disturbance and combat opioid nausea.**	
Muscarinic receptor antagonist : Hyoscin(scoplomine)	Trans dermal patches in motion sickness	
Cannabinoids: Nabilone , dronabilon(psychotic drugs)	Adjuvant in chemotherapy induced vomiting	Sedation ,hallucination, Dysphoria
Glucocorticoids: Dexamethasone mehtylprednisolone	Vomiting by cytotoxic drugs	Hyperglycimia,hypertension,cataract,Osteoporosis,increase intraocular pressure and obesity.

The choice of antiemetic depends on the etiology

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

Quiz yourself

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

1-svere vomiting may result in :
A-acid base balance
B-dehydration
C-elctrolytes increase
D- all

2-Vomiting may occur due to stimulation of vomiting center which receive inputs from
A-cerbral cortex
B-CTZ
C-periphery via sensory nerves
D-all

3-which one is the most potent antiemetic drug:
A- Domperidone
B- Metoclopromide
C-granisetron
D- Chlorpromazine

4-paitent comes with constipation.which drug we should avoid?
A-Ondansetron
B-Granisetron
C- Metoclopramide
D- A AND B

5-patient comes with gastroenteritis Which drug is best to give him ?
A- Metoclopramide
B-Granisetron
C- Chlorpromazine
D-non

6-which one of the following blocks nk1 receptor
A-aprepitant
B- Cyclizine
C-Diphenhydramine
D- Nabilone

7-cancer patient receives chemotherapy .which drug is used to treat his vomiting:
A- Cyclizine
B- Aprepitant
C- Diphenhydramine
D- Meclizine

8-which one of the following is used in motion sickness accompanied with long journey?
A- Hyoscine
B- Cyclizine
C-Diphenhydramine
D-non

9-which one of the following is not used in chemotherapy induced vomiting?
A- Cyclizine
B- Meclizine
C- Promethazine
D-all

Done by

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It always seems impossible until it is done

BEST OF LUCK

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