GI pharma HU

Lecture 1 antiemetics summary

Nearly **70% to 80%** of chemotherapy patients experience **nausea and/or vomiting(very common)**

• subdivided into:-

1. **Acute phase:** within 24 hours of chemotherapy

2. **Delayed phase:** after 24 hours

3. **Anticipatory phase**, brought about by the anticipation of chemotherapy administration

• **Treatment** usually necessitates **more than one class** **of antiemetic**

Influencing factors:

• Type of chemotherapy (mild e.g., methotrexate, moderate e.g., doxorubicin, severe emetic potential e.g., cisplatin)

• Patient variables (young patients and women > older patients and men

Other variables like dose,schedule etc…

CINV affects:-

1. quality of life
2. lead to rejection of potentially curative chemotherapy.
3. can produce dehydration, profound metabolic imbalances, and nutrient depletion.

•Pathways of CINV:-

Peripheral → **serotonin(5HT3) dependent** → acute phase

Central → **dopamine(D2) and serotonin(5HT3)** → delayed phase

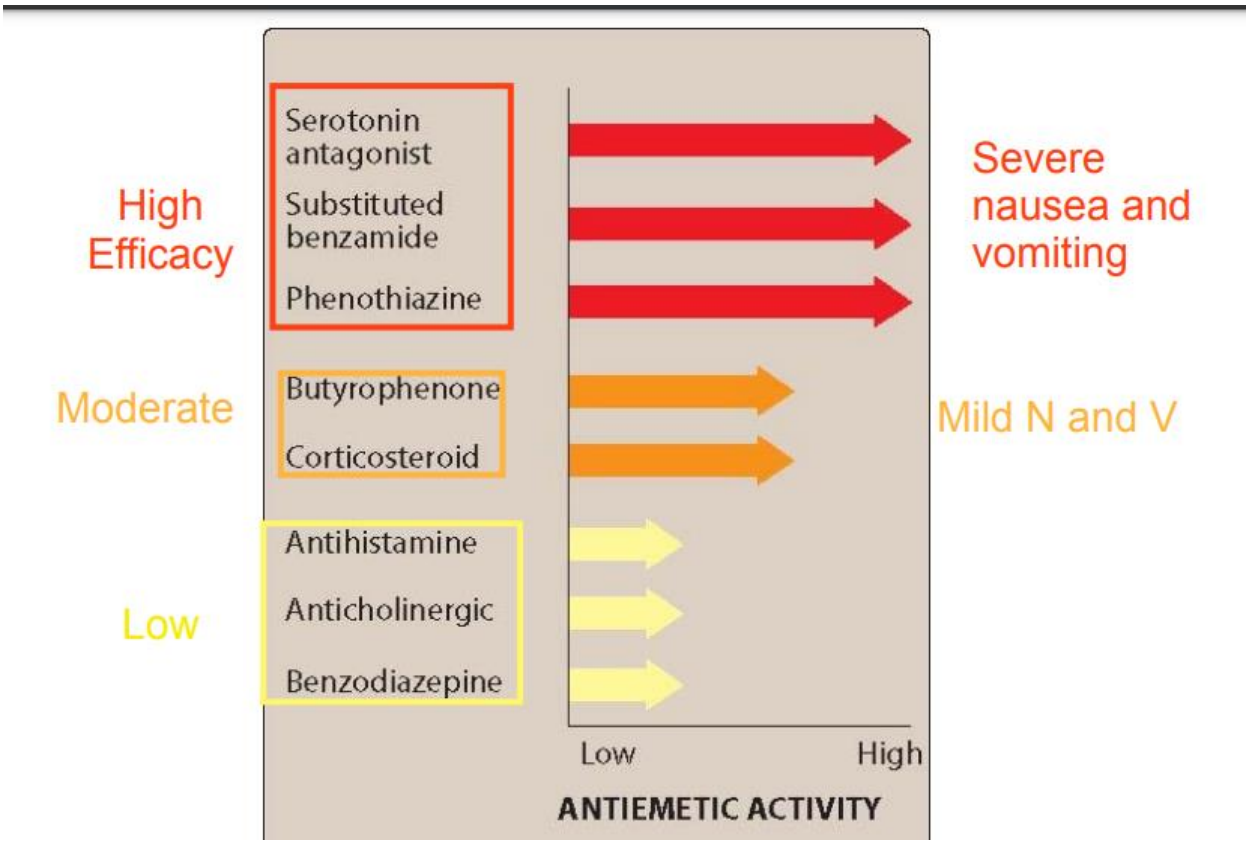
Drugs that antagonize **substance P and serotonin** are the **most potent**

Motion sickness antiemtics	
H1-receptor antagonist (antihistamine)	Muscarinic receptor antagonist(anticholinergic)
e.g. dimenhydrinate, meclizine, cyclizine	e.g Scopolamine
Used for motion sickness but not chemotherapy induced vomiting	

Main drugs for chemotherapy induced nausea and vomiting				
Phenothiazines	5-HT3 Receptor Blockers	Substituted Benzamides	Butyrophenones	Substance P/neurokinin-1 receptor blocker
prochlorperazine	• Examples: ondansetron, granisetron, palonosetron, dolasetron.	metoclopramide	• Examples: Droperidol and haloperidol Mnemonic: beautiful(butyrophenone) doll(drug ends with dol)	• Example: Aprepitant, netupitant and rolapitant
• **Mechanism of action:** **dopamine** receptor(D2) antagonism **(central)** **Uses:** Nausea and vomiting by **low to moderately** emetogenic chemotherapeutics So **can be used for methotrexate or doxorubicin** but not preferred for **cisplatin** • **Adverse effects:** **sedation, orthostasis(postural hypotension), and extrapyramidal effects**. • **side effects are dose limiting** • **Extrapyramidal effects(due to dopamine antagonism):** an inability to sit still, involuntary muscle contraction(dystonia), tremors, stiff muscles, slowed movement (bradykinesia)	**Mechanism of action:** Selective **serotonin type 3 (5-HT3)** receptor antagonism at **central (CTZ) and peripheral (visceral vagal afferent fibers)** • **Uses:-** **CINV** largely **because of their longer duration of action and superior efficacy**.(single dose prior chemotherapy iv or orally) **Postoperative and post-radiation nausea and vomiting** •**Pharmacokinetics(important):** - Metabolized in the liver **(only ondansetron requires dose adjustment in hepatic disease)** Excretion is via urine **Adverse effects:** **Prolongation of QT interval: •** occur with **dolasetron and high doses of ondansetron**. For this reason, **dolasetron is no longer approved for CINV prophylaxis.** • **Baseline ECG is recommended prior to starting therapy**	• **Mechanism of action:** **dopamine** receptor (D2) antagonism **(central)** • **Uses:-** emesis, CINV(mild to moderate by methotrexate) and **diabetic gastroparesis(as it induce gastric motility).** • **Adverse effects:-** sedation, headache, diarrhea, **extrapyramidal symptoms** (which limits long term and high-dose use)	• **Mechanism of action:** **dopamine** receptor Antagonism(central) • **Uses:** CINV,The butyrophenones are **moderately effective antiemetics**.(can be used in combination with other drugs) **• May prolong the QT interval** and should be reserved for patients with inadequate response to other agents. **Very important: don't give butyrophenones with ondansetron!!--> higher chances of QT prolongation.** "**High-dose haloperidol was found to be nearly as effective as high-dose metoclopramide** in preventing **cisplatin-induced emesis.**	• **Mechanism of action :** **Antagonizes the neurokinin receptor in the brain** and blocks the actions of the **natural substance P** • **Uses(important):** **only for CINV caused by highly/moderately emetogenic chemotherapy(like cisplatin)** •Important:- **Metabolized by CYP3A4,** and it **may affect the metabolism of other drugs that are metabolized by this enzyme, such as warfarin and oral contraceptives**. Side effects(not important)

typically due to problems in the basal ganglia or its connections.				

bonus drugs for CINV	
Benzodiazepines • Examples: lorazepam, alprazolam	**Corticosteroids** • Examples: dexamethasone and methylprednisolone
• **Low** antiemetic potential • Mainly anxiolytic/amnesic → **useful for the treatment of anticipatory vomiting**	• Unknown mechanism. • Effective against **mildly to moderately** emetogenic chemotherapy. • **They are used in combination with other agents(Synergistic effects(1+1=3)**



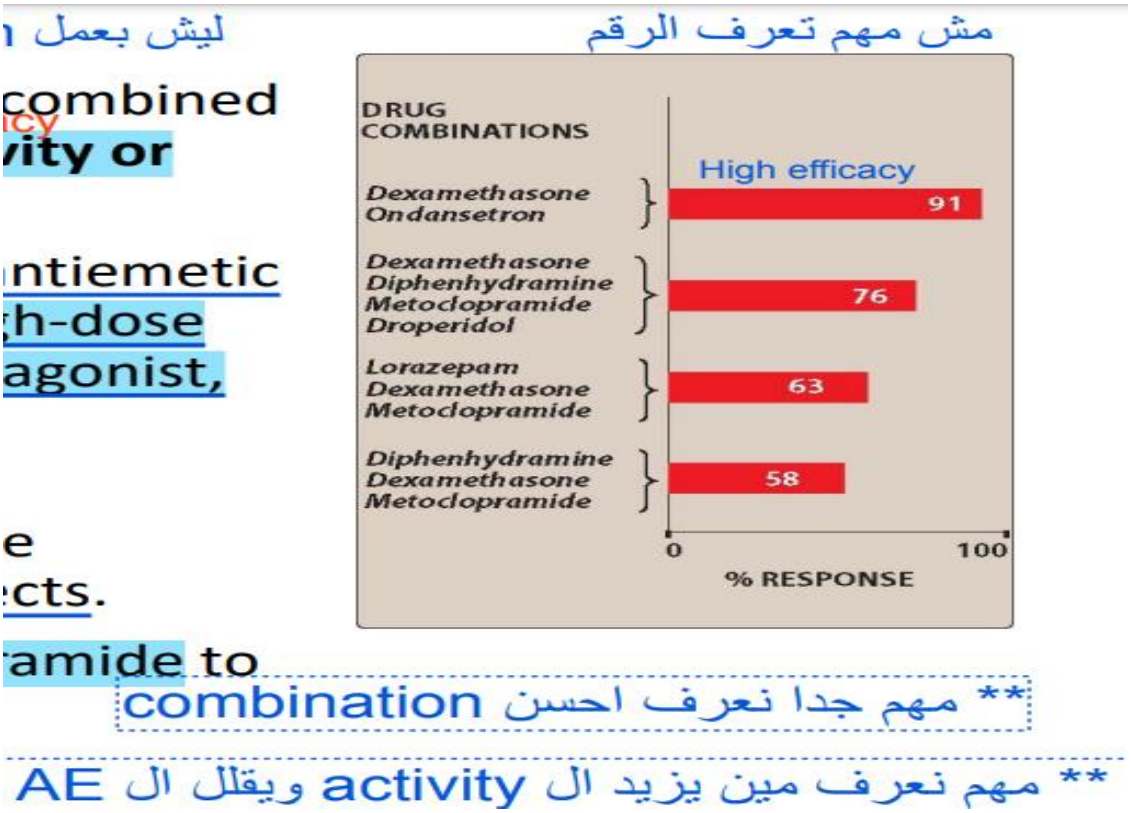
Combination Regimens(very important)

• Combinations either **increase antiemetic activity or decrease toxicity/adverse effects**

• **Dexamethasone(cortiscosteroids)** **increases antiemetic activity** when given with high-dose metoclopramide, 5-HT3 antagonist, butyrophenone, etc.

Dexamethasone also **reduces diarrhea adverse effect**

• **Antihistamine** + high-dose metoclopramide to **decrease extrapyramidal adverse effects.**



Cannabinoids (CB)

• In humans 2 subtypes of CB receptors have been exclusively identified namely CB 1 and CB 2.

• The antiemetic effects of cannabinoids like nabilone appear to be **due to the interaction of CB1 receptor**

• **Marijuana (medical marijuana) use as an antiemetic: controversial**

• **Synthetic e.g., nabilone: approved as second line or for the treatment of breakthrough(non-responsive) CINV**

• Additionally, nabilone may also **indirectly and partially manipulate 5-HT 3 and D 2 receptors.**

Antiemetic in pregnancy

• **Initial treatment is conservative(non-pharmacological)** and includes dietary changes, emotional support, and **vitamin B6 supplementation(pyridoxine).**

• **Combination therapy with vitamin B6 and doxylamine reduces nausea and vomiting by 70%.**

• If unsuccessful ,**use 5HT3 receptor blocker as ondansetron**