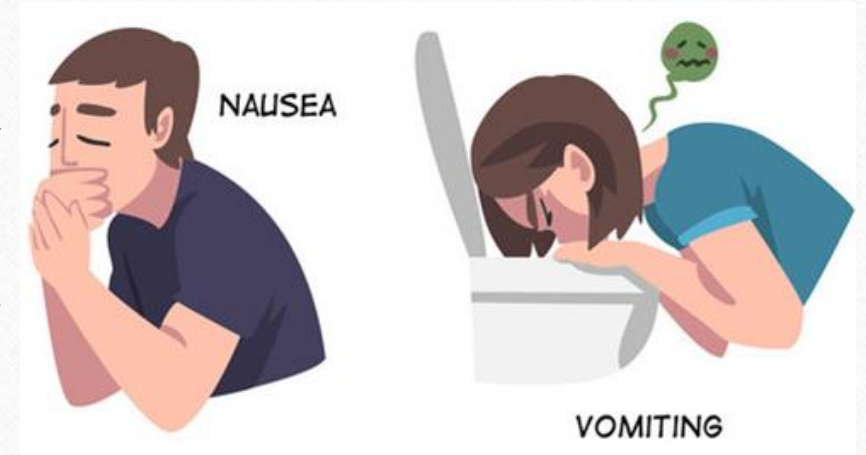


CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING (CINV)

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NAUSEA

- Nausea is a subjective, unpleasant sensation often felt in the back of the throat and epigastrium, commonly described as an urge to vomit.
- It is not directly observable and originates from a complex interplay between the gut and the central nervous system, often involving neurotransmitters like serotonin (5-HT₃), dopamine (D₂), and substance P (neurokinin-1, NK₁).



VOMITING (EMESIS)

- Vomiting is a forceful expulsion of stomach contents through the mouth, mediated by the vomiting center in the brainstem.
- Unlike nausea, it is an observable physical act, involving coordinated muscular contractions of the abdomen, diaphragm, and stomach.

EMETOGENICITY

- Emetogenicity refers to the capacity or tendency of a drug—particularly a chemotherapeutic agent—to cause nausea and/or vomiting.
- It is a critical concept in oncology because nausea and vomiting (together known as CINV: Chemotherapy-Induced Nausea and Vomiting) are among the most distressing side effects for patients undergoing cancer treatment.
- Emetogenic potential of chemotherapeutic agents, based on the modified Hesketh scale (as used by ASCO and NCCN).
- This classification helps guide the use of appropriate antiemetic prophylaxis depending on the risk of nausea and vomiting.

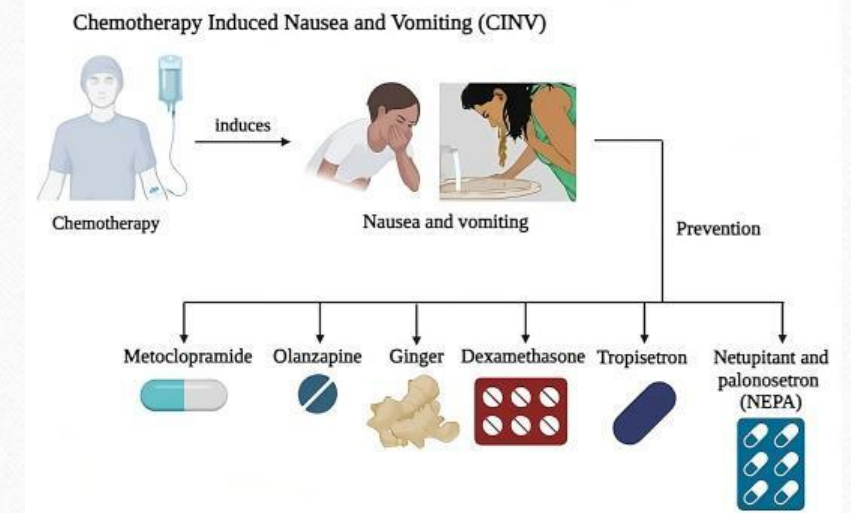
Category	Definition	Examples of Agents	Recommended Regimen
Highly Emetogenic	Agents that cause nausea and/or vomiting in >90% of patients	Cisplatin Cyclophosphamide (>1500 mg/m ²)- Dacarbazine-Carmustine	NK ₁ antagonist + 5-HT ₃ antagonist + Dexamethasone
Moderately Emetogenic	Agents that cause CINV in 30% to 90% of patients	- Doxorubicin- Cyclophosphamide (≤1500 mg/m ²)- Oxaliplatin- Irinotecan	5-HT ₃ antagonist + Dexamethasone (± NK ₁ antagonist)
Low Emetogenic	Agents associated with 10% to 30% incidence of CINV	- Etoposide- Paclitaxel- Docetaxel- Fluorouracil	Dexamethasone or 5-HT ₃ antagonist alone
Minimally Emetogenic	Agents that cause CINV in <10% of patients	- Vincristine- Vinblastine- Bleomycin- Methotrexate (low dose)	PRN antiemetics (e.g., metoclopramide, prochlorperazine)

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING (CINV)

- “CINV” is a broad term used to describe the many types of nausea and vomiting that can occur in patients with cancer.
- CINV refers to nausea and/or vomiting resulting from chemotherapy treatment.
- It is one of the most distressing and feared side effects of cancer therapy.
- CINV can significantly affect a patient’s quality of life, nutritional status, and willingness

Epidemiology

- Despite the introduction of new antiemetics, 30%–60% of patients undergoing chemotherapy still experience nausea or vomiting.
- Vomiting has decreased in prevalence due to improved pharmacological management, but nausea remains highly prevalent, often reported as the first or second most severe chemotherapy side effect.



Risk Factors for (CINV)

Patient Specific

1. Female sex
2. History of motion sickness
3. H/o pregnancy-induced emesis (morning sickness)
4. Younger age
5. Low alcohol consumption
6. High anxiety level

Treatment Specific

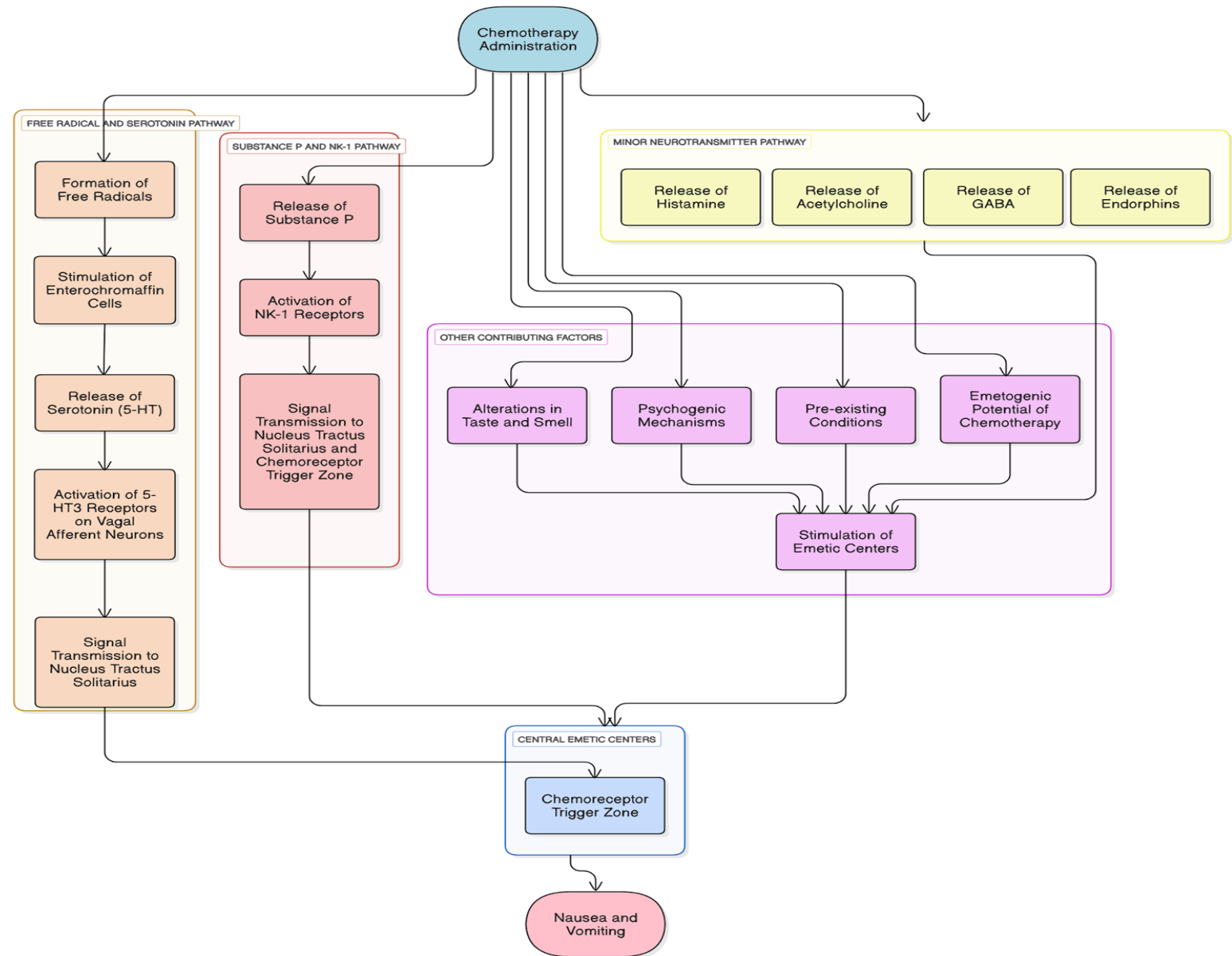
1. Highly emetogenic chemotherapy agents
2. Dose and schedule of chemotherapy
3. Site of radiation (in RINV)
4. Surgical factors (in PONV)

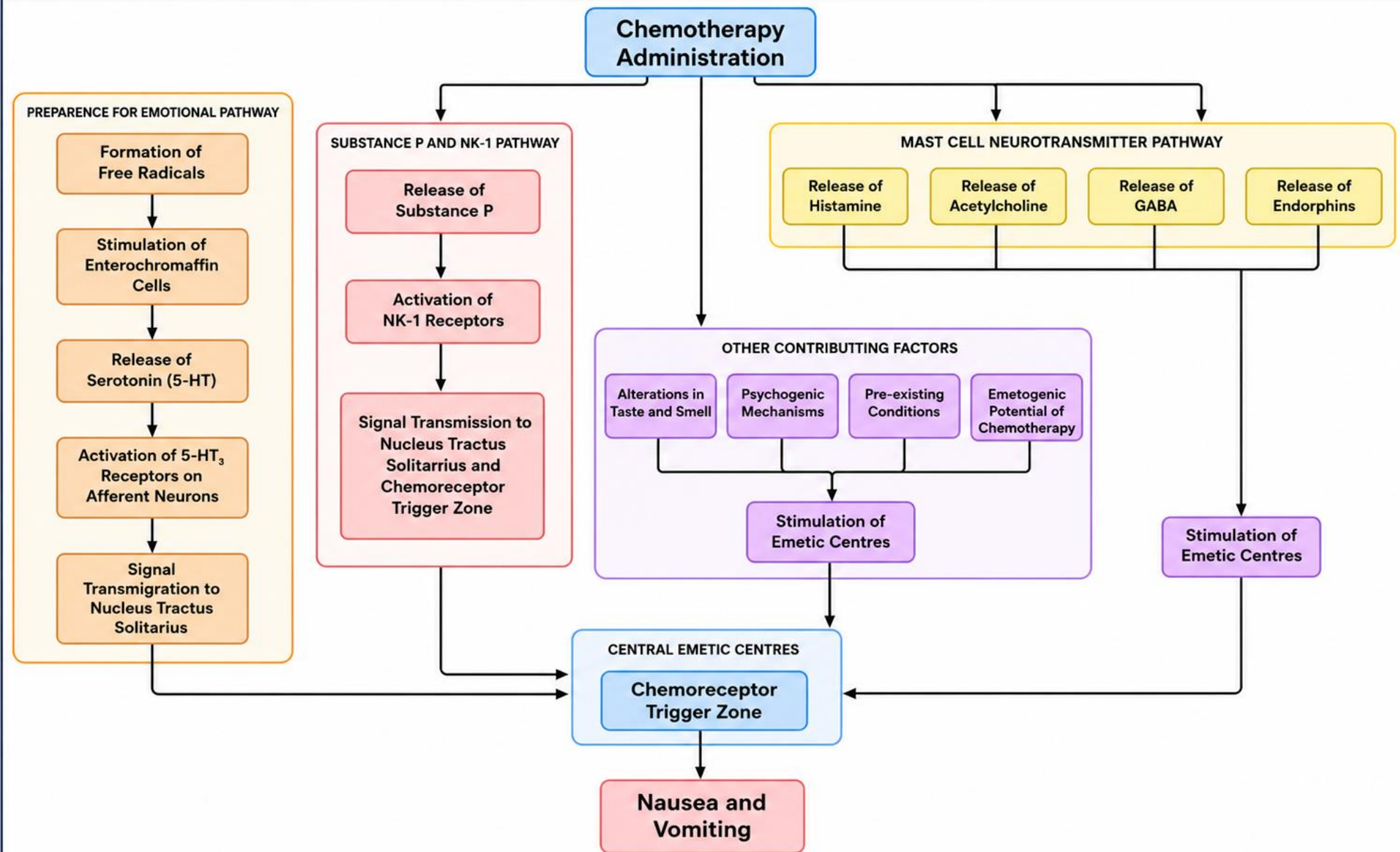
Types of CINV

Type of CINV	Timing of Onset	Incidence	Description & Key Features
Acute CINV	Within 24 hours of chemotherapy	Very common	Begins within minutes to hours after administration; peaks around 5–6 hours; subsides in 24h.
Late-Acute CINV	Between 12–24 hours after chemotherapy	Subtype of acute	Considered part of acute CINV, but onset occurs in the later part of the 24-hour window.
Delayed CINV	More than 24 hours post-chemotherapy (up to 5–7 days)	50–80% (especially with cisplatin, doxorubicin)	Often underreported and poorly controlled; occurs after patient leaves treatment site.

Anticipatory CINV	Before chemotherapy (conditioned response)	20–30% by 4th cycle; 8–20% per cycle	Triggered by sights, smells, or thoughts of chemo; due to prior negative experiences; behavioral therapy is most effective.
Breakthrough CINV	At any time, despite prophylactic antiemetics	Varies; requires rescue medication	Occurs when standard prevention fails; requires additional antiemetic therapy.
Refractory CINV	In subsequent cycles, when prior control was inadequate	<10% of patients	CINV that continues even after previous prophylaxis failed; difficult to manage.

Pathophysiology





Pharmacologic Management of Chemotherapy-Induced Nausea and Vomiting (CINV)

- Chemotherapy-induced nausea and vomiting (CINV) is a common and distressing side effect of cancer treatment. Effective management involves a combination of antiemetic agents targeting different pathways involved in emesis.
- The most effective regimen for CINV prevention is a combination of 5-HT₃ antagonists, NK₁ antagonists, and dexamethasone, tailored to the emetogenicity of the chemotherapy.

Classification of Antiemetic Agents

Antiemetics used for CINV are classified based on their mechanism of action:

1. **5-HT₃ Receptor Antagonists (Serotonin Antagonists)** : e.g. Ondansetron , Granisetron , Dolasetron, Palonosetron
2. **NK₁ Receptor Antagonists (Neurokinin-1 Antagonists)** : e.g. Aprepitant, Fosaprepitant, Rolapitant, Netupitant
3. **Corticosteroids** : e.g. Dexamethasone , Methylprednisolone
4. **Dopamine Receptor Antagonists**
 - a. Substituted Benzamides : e.g., Metoclopramide
 - b. Butyrophenones : e.g., Haloperidol, Droperidol
 - c. Phenothiazines : e.g., Prochlorperazine
5. **Atypical Antipsychotics** e.g., Olanzapine
6. **Cannabinoids** e.g., Dronabinol, Nabilone
7. **Benzodiazepines** e.g., Lorazepam, Alprazolam
-  8. **Antihistamines** e.g., Cyclizine, Diphenhydramine 

Triple Therapy for CINV

- Triple therapy is the gold-standard antiemetic regimen used to prevent nausea and vomiting in patients receiving highly emetogenic chemotherapy (HEC) (e.g., cisplatin, carmustine).
- Triple Therapy Recommended for:
 - Highly emetogenic chemo (HEC) (e.g., cisplatin, carmustine, cyclophosphamide $\geq 1,500$ mg/m²).
 - Some moderately emetogenic regimens (MEC) if patient has risk factors (e.g., prior CINV, female, young age).
- It combines three key drug classes to block multiple pathways involved in CINV:

Drug Class	Example Agents	Role in CINV Prevention
5-HT₃ Receptor Antagonist	Palonosetron (preferred), Ondansetron, Granisetron	Blocks acute-phase nausea/vomiting (first 24 hrs) by inhibiting serotonin in the gut and brain.
NK₁ Receptor Antagonist	Aprepitant, Fosaprepitant, Rolapitant	Prevents delayed-phase CINV (days 2–5) by blocking substance P in the brain.
Cortico steroid	Dexamethasone	Enhances efficacy of other drugs and reduces inflammation.

Dosing Schedule

Day 1 (Chemo Day):

- Palonosetron (0.25 mg IV) OR Ondansetron (8–16 mg oral/IV).
- Fosaprepitant (150 mg IV) OR Aprepitant (125 mg oral).
- Dexamethasone (12 mg oral/IV; reduced to 8 mg if combined with aprepitant).

Days 2–4 (Delayed Phase):

- Aprepitant (80 mg oral, days 2–3).
- Dexamethasone (8 mg oral, days 2–4).

5-HT₃ Receptor Antagonists:

- Block serotonin (5-HT₃) receptors in the gut (vagal afferents) and the chemoreceptor trigger zone (CTZ).
- First-line for acute CINV (first 24 hours post-chemotherapy).
- Most effective when combined with dexamethasone.
- Given 30–60 min before chemotherapy.
- Adverse Effects: Headache, constipation, dizziness., QTc prolongation (caution in cardiac patients)., Mild transaminase elevation.

NK₁ Receptor Antagonists

- Block substance P (a neurokinin) in the brainstem and gut.
- Aprepitant (oral, approved in 2003), Fosaprepitant (IV prodrug of aprepitant, approved in 2008), Rolapitant (long-acting, single-dose option)
- Highly effective for both acute and delayed CINV, especially with highly emetogenic chemotherapy (HEC).
- Used in combination with 5-HT₃ antagonists + dexamethasone.
- Given 30–60 min before chemotherapy.
- Adverse Effects: Fatigue, hiccups, diarrhea, elevated liver enzymes.
- Drug Interactions:
 - CYP3A4 inhibitor → increases dexamethasone levels
 - Weak CYP2C9 inducer → may decrease warfarin efficacy.

Corticosteroids

- modulate prostaglandins and serotonin.
- Key component in both acute and delayed CINV prevention.
- Enhances the effects of 5-HT₃ and NK₁ antagonists.
- Adverse Effects: Insomnia, hyperglycemia, mood changes, peptic ulcers.

Atypical Antipsychotics (Olanzapine)

- Blocks multiple receptors (5-HT₂, D₂, H₁).
- Effective for both acute and delayed CINV.
- Used as an adjunct in highly emetogenic regimens.
- Adverse Effects: Sedation, weight gain, hyperglycemia.

Cannabinoids (Dronabinol, Nabilone)

- Act on CB1 receptors in the CNS.
- Use: Refractory CINV (third-line).
- Adverse Effects: Euphoria, dizziness, hypotension, dependence.

Dopamine Receptor Antagonists

i. Substituted Benzamides (Metoclopramide)

- D₂ and mild 5-HT₃ blockade.
- Use: Rescue therapy for breakthrough CINV.
- Adverse Effects: Extrapyramidal symptoms (EPS), neuroleptic malignant syndrome (NMS).

ii. Butyrophenones (Haloperidol, Droperidol)

- Strong D₂ antagonism.
- Use: Less common due to sedation and EPS risk.

iii. Phenothiazines (Prochlorperazine, Promethazine)

- D₂ and histamine blockade.
- Use: Low-emetogenic chemotherapy or adjunct therapy.
- Adverse Effects: Sedation, hypotension, EPS.

CINV Prophylaxis

Emetogenic Risk	Recommended Regimen	Preferred Agents
High	3-drug: 5-HT3 RA + NK1 RA + Dexamethasone	Palonosetron preferred;
Moderate	2-drug: 5-HT3 RA + Dexamethasone	Palonosetron preferred
Low	Dexamethasone alone or alternatives	Alternatives: Metoclopramide, Prochlorperazine
Minimal	No prophylaxis recommended	—

Radiation-Induced Nausea and Vomiting (RINV)

Radiation Risk	Recommended Regimen	Preferred Agents
High (e.g., TBI)	5-HT3 RA ± Dexamethasone	Granisetron, Ondansetron
Moderate (e.g., upper abdomen)	5-HT3 RA ± Dexamethasone (fractions 1–5)	Same as above
Low (e.g., head/neck)	Rescue treatment only	5-HT3 RA or Metoclopramide, Prochlorperazine
Minimal (e.g., breast)	No routine prophylaxis	—
Combination of chemo + radiation	Based on chemo emetogenicity (or radiation if higher risk)	—

Table 2 Dosing Ranges for Antiemetics Used for Primary Prophylaxis of CINV

Antiemetic	Dose	Antiemetic	Dose
<i>NK₁ receptor antagonists</i>		Granisetron	2 mg oral or 1 mg oral twice daily; 1 mg IV or 0.01 mg/kg IV
Fosaprepitant	150 mg IV	Dolasetron	100 mg oral
Aprepitant	125 mg oral on day 1 and 80 mg oral on days 2 and 3	Palonosetron	0.25 mg IV
<i>5-HT₃ receptor antagonists</i>		<i>Corticosteroid</i>	
Ondansetron	16-24 mg oral; 8 mg IV	Dexamethasone	8-20 mg oral IV
5-HT indicates serotonin; CINV, chemotherapy-induced nausea and vomiting; IV, intravenous; NK, neurokinin.			

Table 1 Recommended Antiemetic Regimens for CINV Prophylaxis

Emetic risk	Treatment for acute phase ^a	Treatment for delayed phase
High	3-drug combination treatment with an NK ₁ receptor antagonist, a 5-HT ₃ receptor antagonist, and dexamethasone	NK ₁ receptor antagonist if oral route was used; dexamethasone
Moderate	2-drug combination treatment with a 5-HT ₃ receptor antagonist and dexamethasone	Dexamethasone
Low	Dexamethasone	
Minimal	No routine prophylaxis recommended	
^a All patients should have “as-needed” rescue medication available, which can include prochlorperazine, promethazine, or lorazepam, regardless of emetic risk level.		
5-HT indicates serotonin; CINV, chemotherapy-induced nausea and vomiting; NK, neurokinin.		

Table 3. Schedules for prevention of chemotherapy-induced nausea and vomiting

		Day 1	Day 2	Day 3	Day 4
High emetic risk	Aprepitant	125 mg	80 mg	80 mg	None
	Dexamethasone	12 mg po	8 mg po	8 mg po	8 mg po
	Ondansetron	32 mg iv	none	none	none
Moderate emetic risk	Day 1 Dexamethasone 12 mg po or iv and 5-HT ₃ antagonist Days 2–4 Dexamethasone 8 mg po or iv daily or 4 mg po or iv bd or 5-HT ₃ antagonist or metoclopramide 0.5 mg/kg po or iv 6-hourly or 20 mg po four times daily				
Low emetic risk	Dexamethasone 12 mg po or iv daily or metoclopramide 20–40 mg po 4–6-hourly or 1–2 mg/kg iv 3–4-hourly				
Minimal emetic risk	No routine prophylaxis				

5-HT₃ = 5-hydroxytryptamine 3; bd = twice daily; iv = intravenous; po = per oral