

Antiemetics 101

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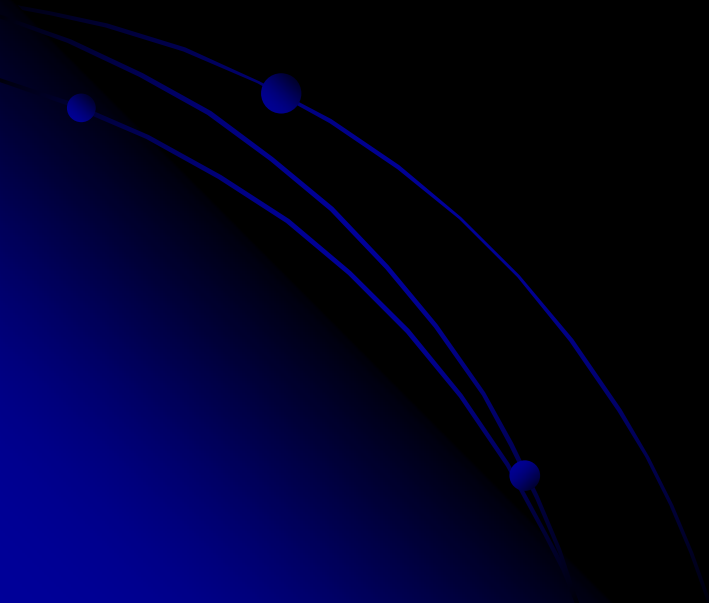
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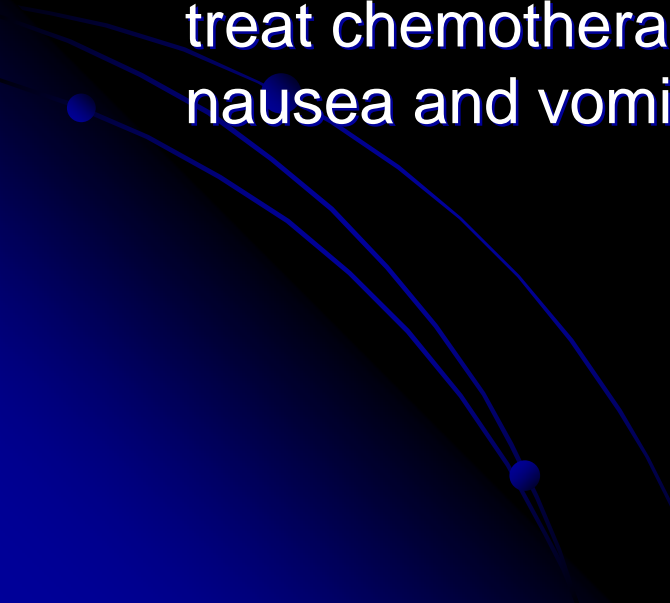
Disclosure of Conflict of Interest

- No conflict of interest with material presented



Objectives

By the end of the session the participant will:

- Understand the pathophysiology of nausea and vomiting
 - Know what medications are available to prevent and treat chemotherapy-induced and radiation-induced nausea and vomiting
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Outline

- Introduction
- Etiology and Prevalence
- Consequences
- Pathophysiology
- Risk Factors
- Prevention
- Treatment
- Review of Antiemetic Agents
- Conclusions

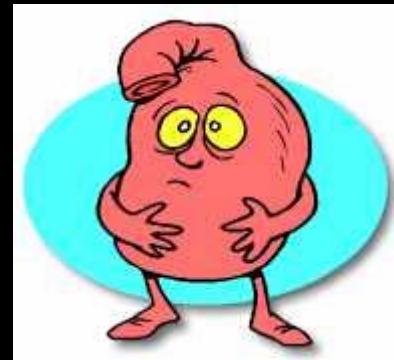
Nausea and Vomiting

- Nausea

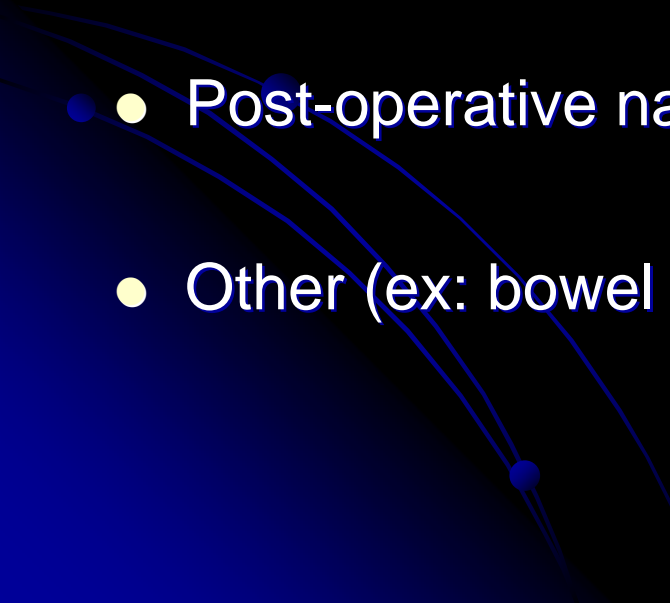
- Unpleasant sensation experienced in the back of the throat and/or epigastrium that may or may not culminate in vomiting

- Vomiting

- Forceful expulsion of the contents of the stomach through the oral cavity



Etiology of Nausea and Vomiting

- Chemotherapy-induced nausea and vomiting (CINV)
 - Radiation-induced nausea and vomiting (RINV)
 - Opioid-induced nausea and vomiting
 - Post-operative nausea and vomiting
 - Other (ex: bowel obstruction)
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Classification of Nausea and Vomiting

- Acute
 - Occurs within 24 hours after chemo or rads
- Delayed
 - Occurs more than 24 hours after chemo or rads
 - Can last up to 5 days
- Anticipatory
 - Occurs before chemo or rads begin
 - Conditioned response triggered by sensory stimuli
- Breakthrough
 - Occurs despite antiemetic prophylaxis
 - Requires rescue therapy

Incidence

- CINV
 - As high as 90% of patients
- RINV
 - As high as 67% of patients

Prevalence

- Dichotomy between health care providers' perceptions of nausea and vomiting and patients' actual experiences
- Oncology health care providers
 - Overestimated incidence of acute CINV
 - Underestimated incidence of delayed CINV
 - Underestimated incidence of RINV

Consequences

- Medical complications
 - Dehydration and electrolyte disturbances
 - Aspiration pneumonia
 - Malnutrition and weight loss
 - Delays in cancer therapy
- Patient quality of life
 - Distress, anxiety and fear
 - Negative effect on patient's activities of daily living
 - Refusal of treatment or non-compliance with cancer therapy
- Economic burden
 - Increased need for medical care (ER, hospital admissions)
 - Increased use of antiemetic medications

Pathways of Emesis

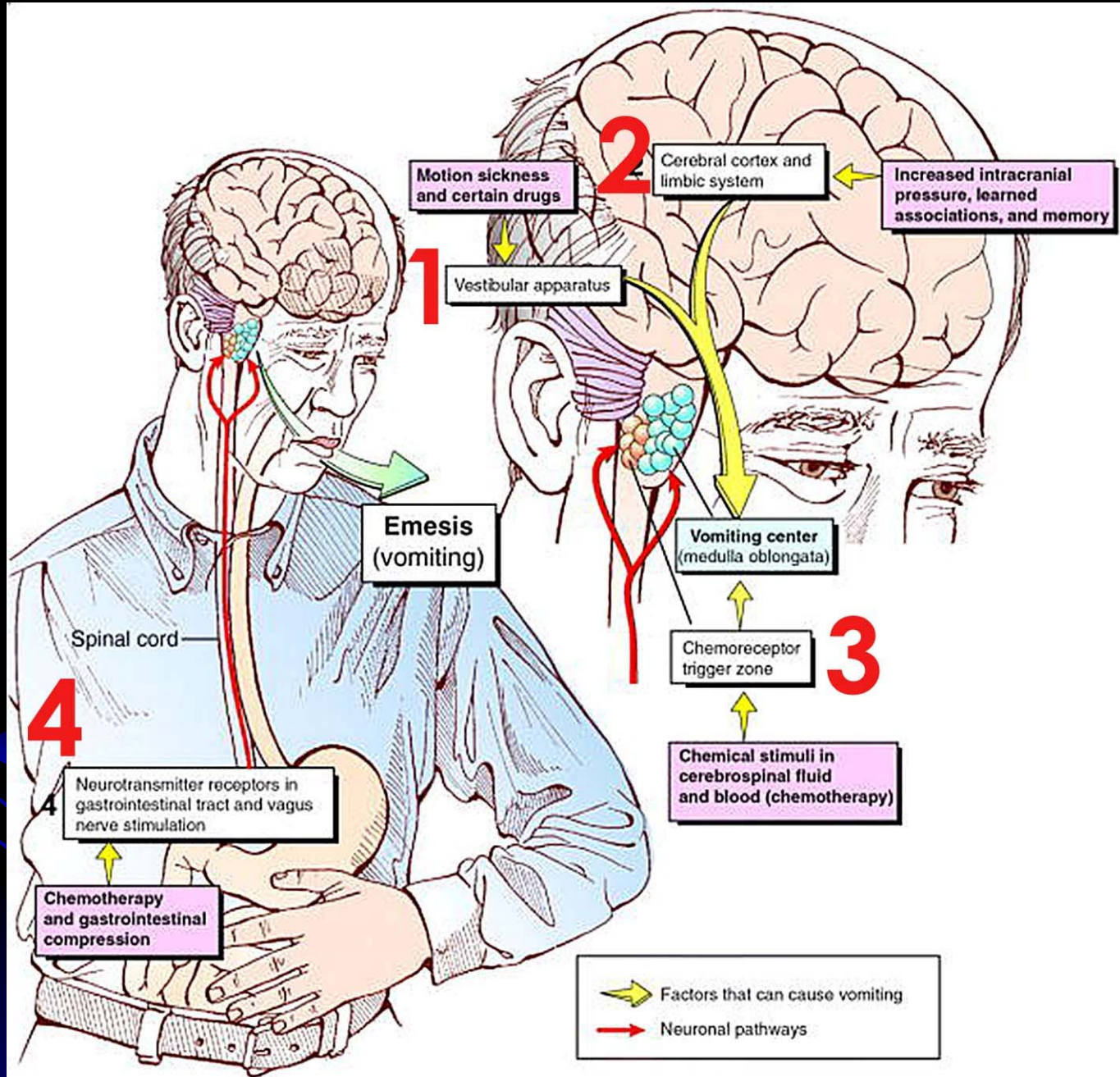


Central

- Vomiting Centre (VC)
- Chemoreceptor trigger zone (CTZ)
- Cortex
- Vestibular apparatus

Peripheral

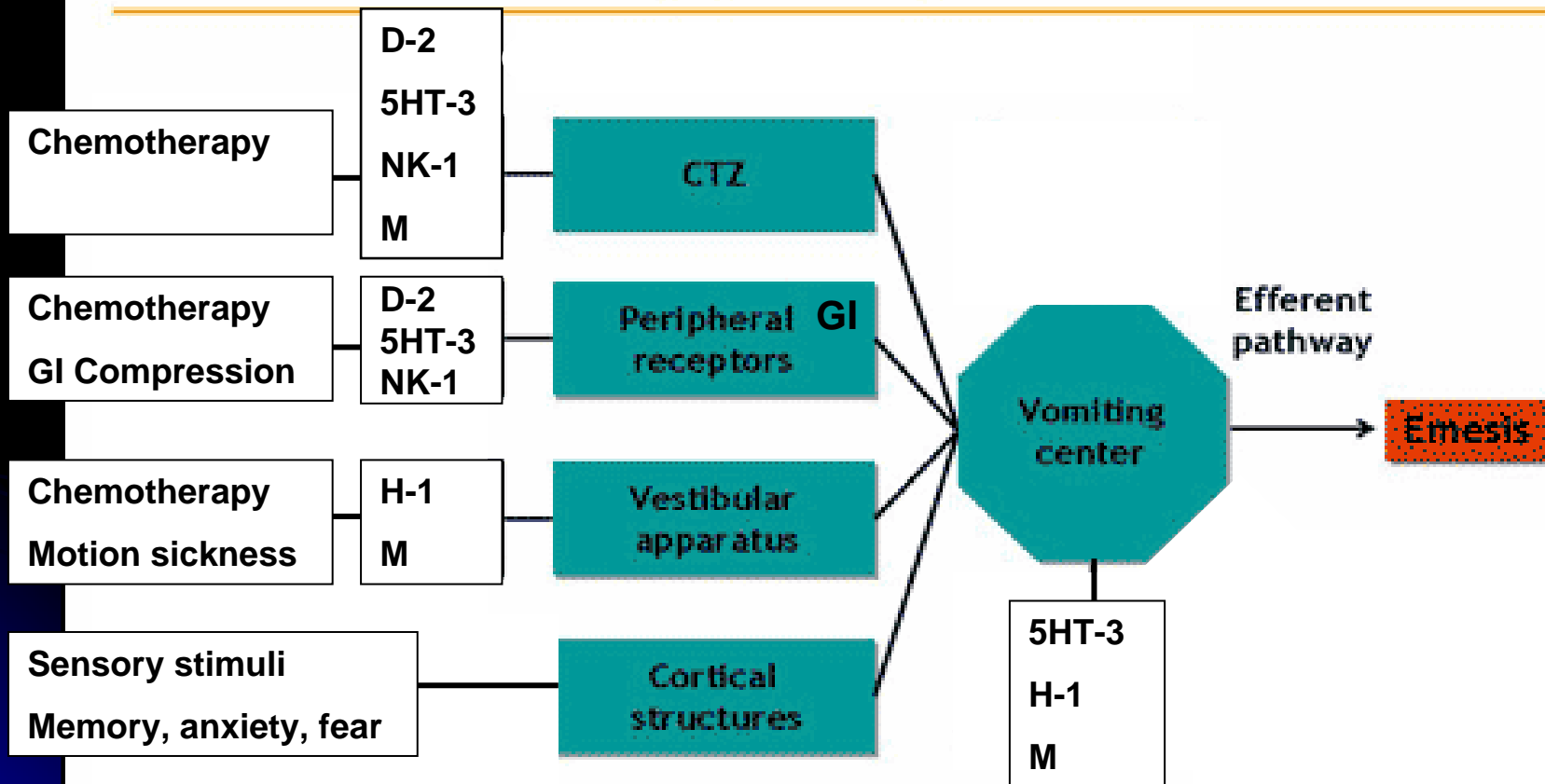
- GI tract



There are four primary pathways through which the vomiting center can be stimulated.

Receptors Involved in Emesis

Pathophysiology of Emesis



D-2=dopamine-2, 5HT-3=serotonin-3, NK-1=neurokinin-1, H-1=histamine-1, M=muscarinic

Patient-Specific Risk Factors

- Age
 - young patients > older patients
- Gender
 - women > men
- History
 - vomiting with prior chemotherapy or radiation
 - motion sickness
 - nausea and vomiting during pregnancy
- Low alcohol consumption
 - heavy alcohol use protective for CINV
- Inadequate hydration
- Surgery
- Anxiety

Treatment-Specific Risk Factors

- Emetogenicity of chemotherapy agent(s)
- Chemotherapy regimen
 - Combination chemotherapy > single agent
 - Rapid infusion rate
 - Repetitive daily doses
- Radiation field
 - Treatment site
 - Field exposure
 - Dose (per fraction and total)
- Combined modality > single modality
- Tumor stage

Emetogenicity of Chemotherapy

HESKETH LEVEL	INCIDENCE OF EMESIS* (% of patients)
5	>90%
4	60-90%
3	30-60%
2	10-30%
1	<10%

*Assuming absence of effective prophylactic antiemetics

Injectable Chemotherapy Agents

RISK GROUP	CHEMOTHERAPY	
5 (>90%)	Carmustine Cyclophosphamide (>1500 mg/m ²) Nitrogen mustard	Cisplatin >50 mg/m ² Dacarbazine Streptozocin
4 (60-90%)	Anthracyclines (ex: doxorubicin) Cisplatin <50 mg/m ² Cytarabine >1000 mg/m ² Methotrexate >1 g/m ² dose	Carboplatin Cyclophosphamide <1500 mg/m ² Irinotecan
3 (30-60%)	Asparaginase Cytarabine (<1000 mg/m ²) Mitoxantrone	Cyclophosphamide <750 mg/m ² Methotrexate < 1 g/m ² Topotecan
2 (10-30%)	Amsacrine 5-Fluorouracil Taxanes(ex: paclitaxel)	Etoposide Gemcitabine Trastuzumab
1 (<10%)	Bleomycin Fludarabine Vinca alkaloids (ex: vincristine)	Cladribine Rituximab

Oral Chemotherapy Agents

RISK GROUP	CHEMOTHERAPY	
5 (>90%)		
4 (60-90%)	Procarbazine	
3 (30-60%)	Cyclophosphamide Temozolamide	Lomustine
2 (10-30%)	Capecitabine Gefitinib	Etoposide Imatinib
1 (<10%)	Busulfan Fludarabine Melfhalan 6-Thioguanine	Chlorambucil Hydroxyurea Methotrexate

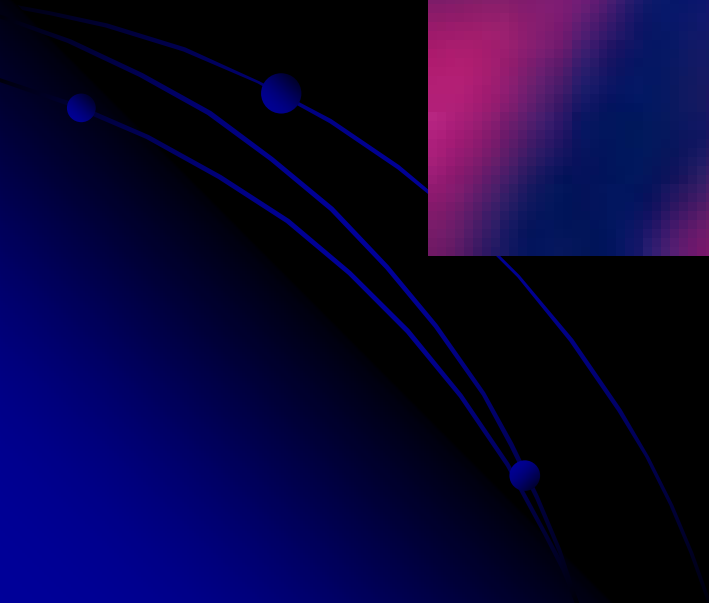
Source: Cancer Care Ontario

Emetogenicity of Radiation

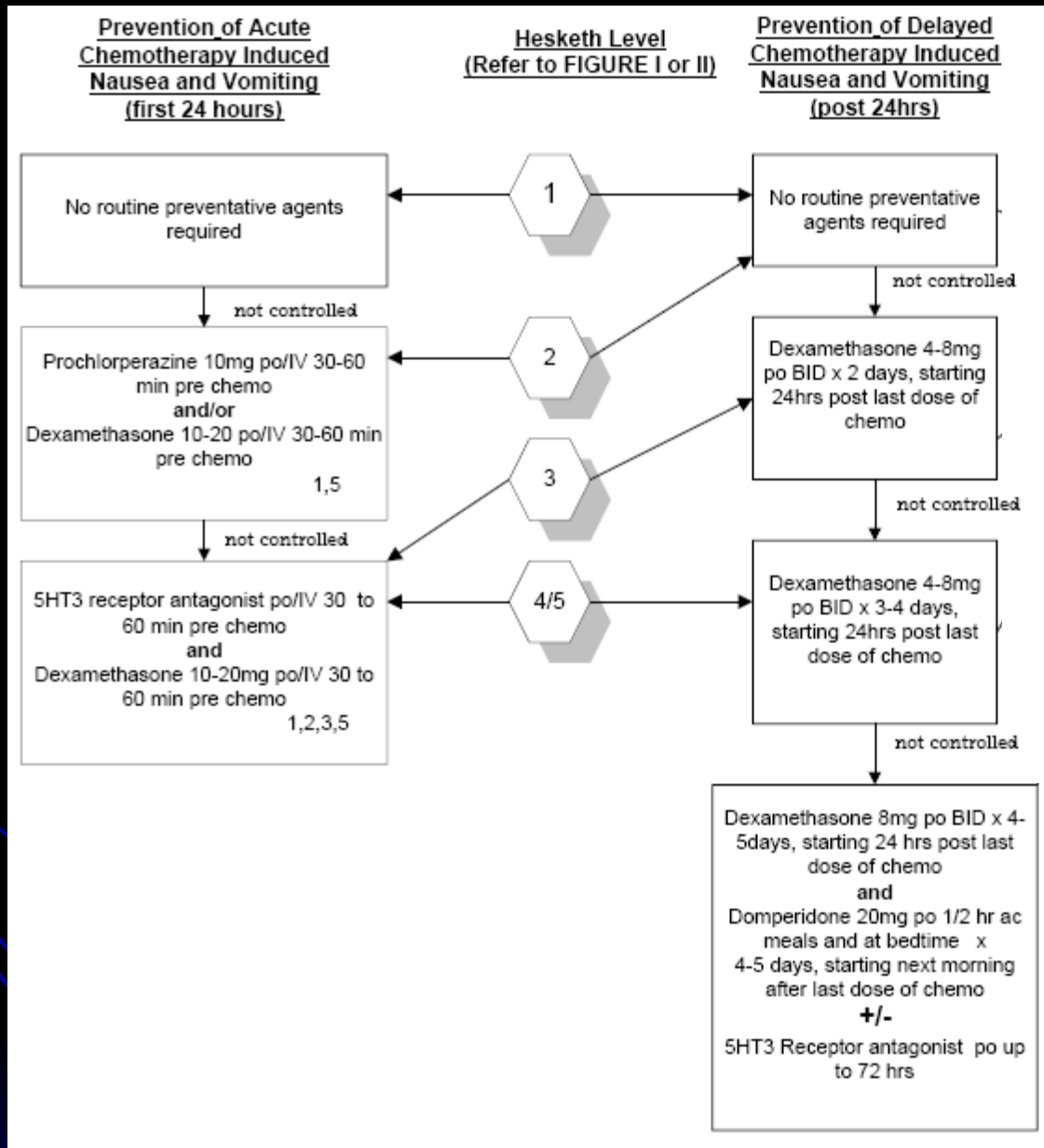
Table 1. Emetogenic Risk Groups According to Radiation Site

Risk Level	Area of Treatment
High	Total-body irradiation
Moderate	Upper abdomen
Low	Lower thorax region, pelvis, cranium (radiosurgery), craniospinal
Minimal	Head and neck, extremities, cranium, breast

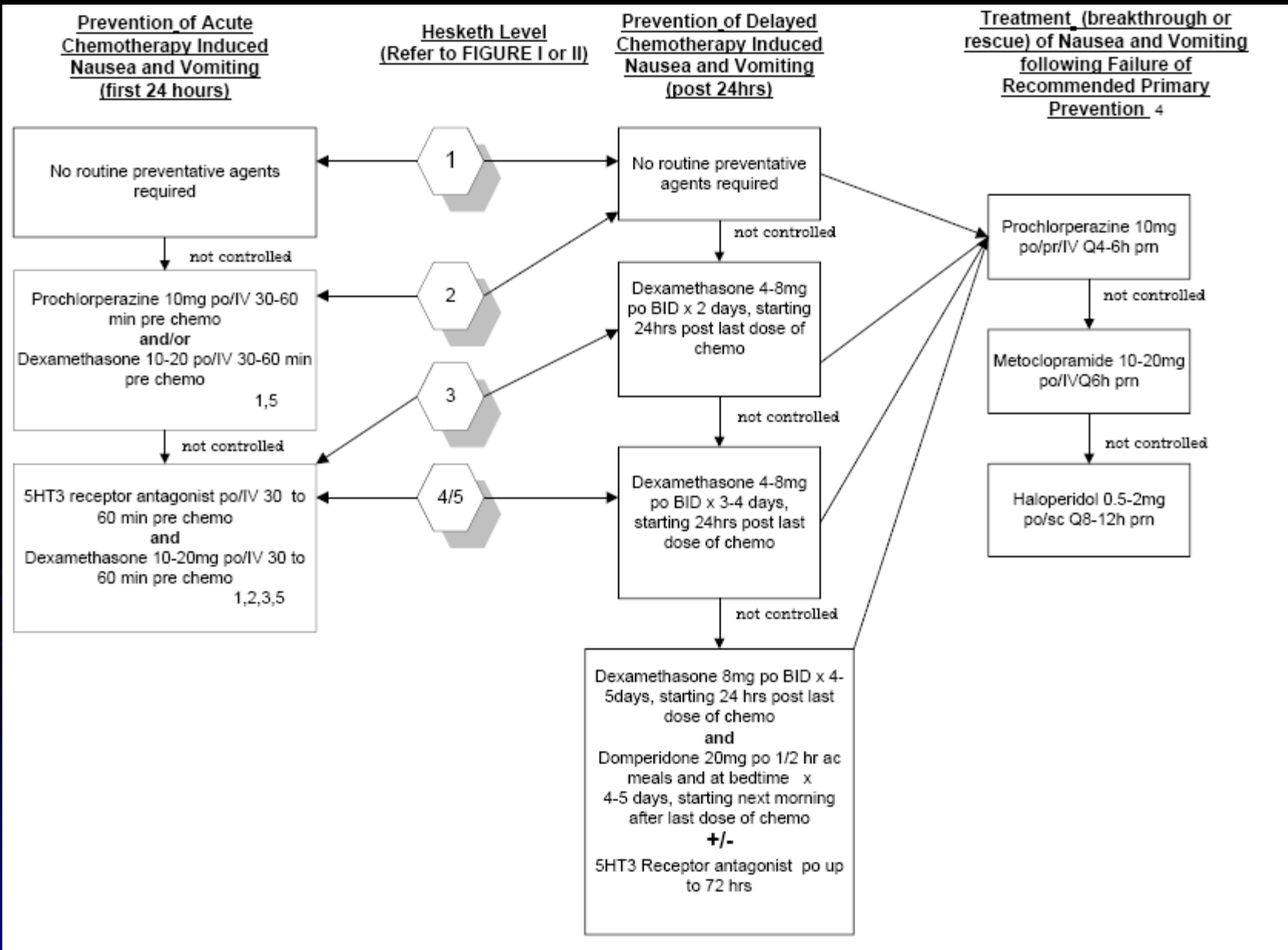
Prevention and Treatment



Prevention of CINV



Treatment of CINV



Prevention and Treatment of CINV

- Continue 5HT-3 receptor antagonists x 24 hours post chemotherapy
- Control of acute CINV appears to minimize development of anticipatory and delayed CINV
- For treatment of breakthrough CINV
 - Select antiemetic from different pharmacological class
 - Modify prophylactic antiemetic regimen for next cycle of chemotherapy

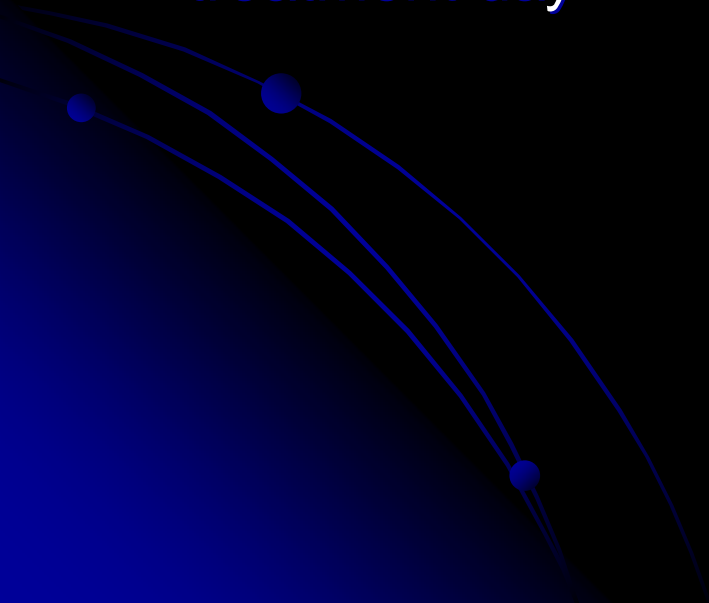
Prevention and Treatment of RINV

Table 2. Treatment Recommendations for RINV

Level of Radiation Emetogenicity	Recommended Therapy
Highly emetogenic	5-HT ₃ -receptor antagonist plus dexamethasone
Moderately emetogenic irradiation of upper abdomen	5-HT ₃ -receptor antagonist
Low emetogenic	<ul style="list-style-type: none">• Rescue with a 5-HT₃-receptor antagonist if a patient experiences NV• Prophylaxis with a 5-HT₃-receptor antagonist before future radiation therapy
Minimally emetogenic	No routine use of antiemetics unless patient has a history of NV

Prevention and Treatment of RINV

- For high risk, continue 5HT-3 receptor antagonists x 24 hours post radiation
- For patients with breakthrough RINV, continue antiemetics prophylactically for each remaining radiation treatment day



Antiemetic Drugs

CLASS	SITE OF ACTION	DRUG	DOSAGE	ADVERSE EFFECTS
5HT-3 receptor antagonists	5HT-3 receptors in GI mucosa and CTZ	Ondansetron	8 mg PO/IV	Headache Constipation Transient increase in LFTs
		Granisetron	1 mg PO/IV	
		Dolasetron	100 mg PO/IV	
Corticosteroids	Unknown	Dexamethasone	10-20 mg PO/IV pre chemo 4-8 mg PO BID post chemo	Insomnia, anxiety Hyperglycemia Heartburn
Prokinetic Agents	D-2 receptors (low dose) 5HT-3 receptors (high dose)	Metoclopramide	10-20 mg PO/IV pre and q6h PRN	Extrapyramidal effects Diarrhea Mild sedation
	D-1 and D-2 receptors	Domperidone	20 mg PO AC and HS	Extrapyramidal effects (rare, does not cross blood brain barrier)
Phenothiazines	D-2 receptors	Prochlorperazine	10 mg PO/IV q4-6h PRN	Extrapyramidal effects Anticholinergic effects Decreased seizure threshold
	D-2 receptors	Chlorpromazine	25-50 mg PO q4-6h PRN	
	D-2 and H-1 receptors	Promethazine	25 mg PO q4-6h PRN	

Antiemetic Drugs

CLASS	SITE OF ACTION	DRUG	DOSAGE	ADVERSE EFFECTS
Butyrophenones	D-2 receptors	Haloperidol	0.5-2 mg PO/IM q8-12h PRN	Sedation Extrapyramidal effects Q-T prolongation
Benzodiazepines	Unknown Useful in anticipatory CINV	Lorazepam	0.5-1 mg SL/PO pre chemotherapy and q6h PRN	Sedation Confusion Dependence
Antihistamines Anticholinergics	H-1 receptors M receptors	Dimenhydrinate Scopolamine	25-50 mg PO/IM q4-6h PRN 1 patch behind ear 4 h pre chemo; change q3days	Sedation Anticholinergic effects
Cannabinoids	Unknown May be useful in refractory CINV	Nabilone Dronabinol	1 mg PO BID 5 mg/m ² (~7.5-10 mg) PO pre chemo then q2-4h PRN post chemo for total of 4-6 doses/day	Sedation Dizziness, ataxia Euphoria Withdrawal syndrome
Neurokinin-1 receptor antagonists	Substance P/NK-1 receptors in GI tract and brain	Aprepitant (currently not available in Canada)	125 mg PO pre chemo then 80 mg PO qAM x 2 days Use with 5HT-3 antagonist + dexamethasone	Fatigue, dizziness Diarrhea Hiccoughs Headache Inhibits CYP3A4

Conclusions

Assess risk factors

- Patient-specific
- Treatment-specific

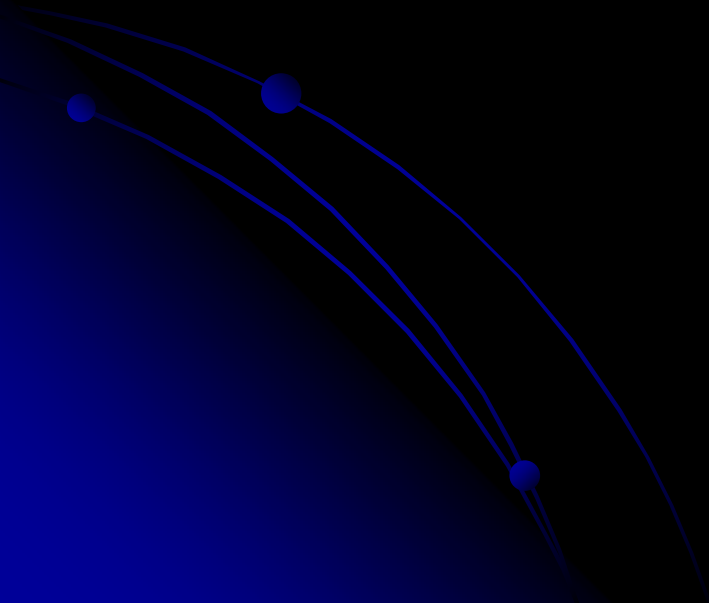
Develop institutional guidelines

Follow evidence-based guidelines

- Prevention
- Treatment

Websites

- www.cancercare.on.ca
- www.oncologyse.com
- www.asco.org



Questions



