Management of Nausea and Vomiting in Palliative Care

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Faculty/Presenter Disclosure

- **Presenter: Grace Ma**
- **Relationships with commercial interests:**
  - **none**

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- **Presenter: Andrea Weiss**
- **Relationships with commercial interests:**
  - **none**

Disclosure of Commercial Support

- **This program has not received any financial or in-kind support**

- **<u>Potential for conflict(s) of interest</u>:**
  - none

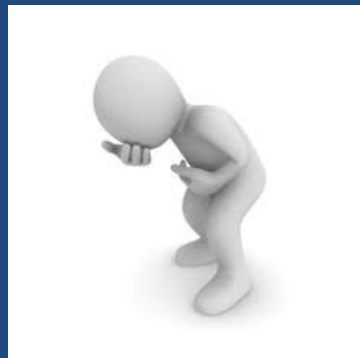
Mitigating Potential Bias

No conflict of interest to declare

Objectives

By the end of this session, you will be able to:

1. identify common causes of nausea and vomiting in palliative care
2. determine the receptor pathways based on the etiology of nausea and vomiting
3. confidently choose an effective anti-emetic



Prevalence - Nausea and Vomiting

- Prevalence
  - 30-60% of patients with advanced cancer
  - 40-50% of patients with AIDS
  - 15-50% of patients with HF
  - 30-40% of patients with CKD
  - 20% of patients with COPD

Blinderman CD, Homel P, Billings JA, Tennstedt S, Portenoy RK. Symptom distress and quality of life in patients with advanced chronic obstructive pulmonary disease. J Pain Symptom Manage 2009;38:115-23.

Solano JP, Gomes B, Higginson IJ. A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. J Pain Symptom Manage 2006;31:58-69.

Consequences of N/V

- Increased inpatient hospitalization
- Interference with treatment

- Metabolic/Physical
  - Dehydration
  - Metabolic alkalosis
  - Electrolyte derangement
  - Malnutrition/weight loss
  - Exhaustion
  - Aspiration pneumonia
- Psychological
  - Impact quality of life (QOL)

CASE 1 – Heart Failure

- Summer, 23 yo F with ESCHF 2° to congenital cardiac malformation.
  - She is admitted to hospital, where ongoing medical management of her HF is occurring, but she is declining. Her PPS is 30%. High likelihood of dying on this admission.
  - There are no further surgical options.
  - Her dyspnea is managed for the past several months with hydromorphone. Besides dyspnea, her other main complaint is nausea.

- **What is the etiology of her nausea?**
- **What would you choose to manage her nausea?**

Steinberg L, White M, Arvanitis J, Husain A, Mak S. Approach to advanced heart failure at the end of life. Can Fam Physician 2017;63:674-80.

Assessment/Management

- History and Physical
  - What are the patient's goals of care? What is his/her performance status?
- Relevant investigations
- Treat the underlying cause

Etiologies – Presentation

- **Acute onset** - Multiple causes, including:
- Chemotherapy induced (within 5 days of last chemo):
  - Acute - within 24h of chemo
  - Delayed - > 24h from chemo
  - Anticipatory - sensory triggers; after 3-4 rounds
- Radiation
- **Chronic** - advanced cancer and/or end stage organ failure

Etiologies – a mechanistic approach

PERIPHERAL

- GI
- Respiratory
- Cardiac

CENTRAL

- High CNS
- Vestibular
- Chemoreceptor Trigger Zone
- Raised intracranial pressure

Peripheral Causes - GI

GI IRRITATION

- Chemical
  - Blood, Medications
- Physical
  - Tumor, ulcer, radiation
- Distention
  - Stasis, ascites, hepatomegaly, tumor
- Infection
  - gastroenteritis

GI OBSTRUCTION

- Mechanical
- Functional
  - Gastroparesis, chronic pseudo-obstruction

Central Causes

HIGH CNS

- Sensory – sights, smells, pain
- Cerebral – anticipatory nausea, memories, fear

VESTIBULAR

- Medications
- Cerebellar tumor
- Menieres, labyrinthitis
- Motion sickness

CHEMORECEPTOR TRIGGER ZONE (CTZ)

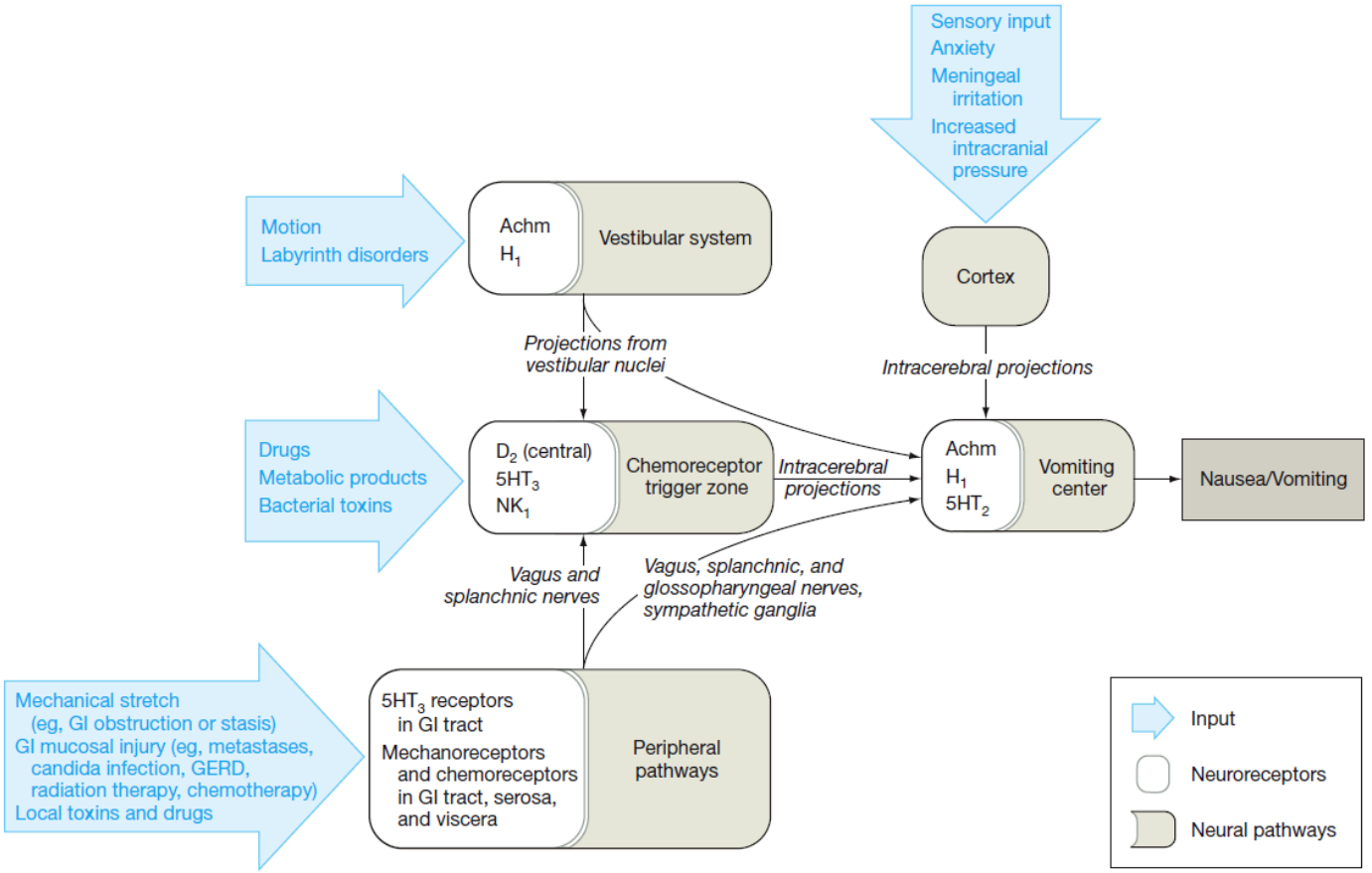
- Meds
- Toxins – Sepsis
- Metabolic – Uremia, hypercalcemia

RAISED ICP

- Brain tumor – primary or metastatic

Pathophysiology of common etiologies of N/V

Figure. Interrelationships Between Neural Pathways That Mediate Nausea and Vomiting



Achm indicates muscarinic acetylcholine receptor; D_2, dopamine type 2 receptor; GERD, gastroesophageal reflux; GI, gastrointestinal; H_1, histamine type 1 receptor; NK_1, neurokinin type 1 receptor; $5HT_2$, 5-hydroxytryptamine type 2 receptor; and $5HT_3$, 5-hydroxytryptamine type 3 receptor.

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Management: Non-pharmacologic (If applicable)

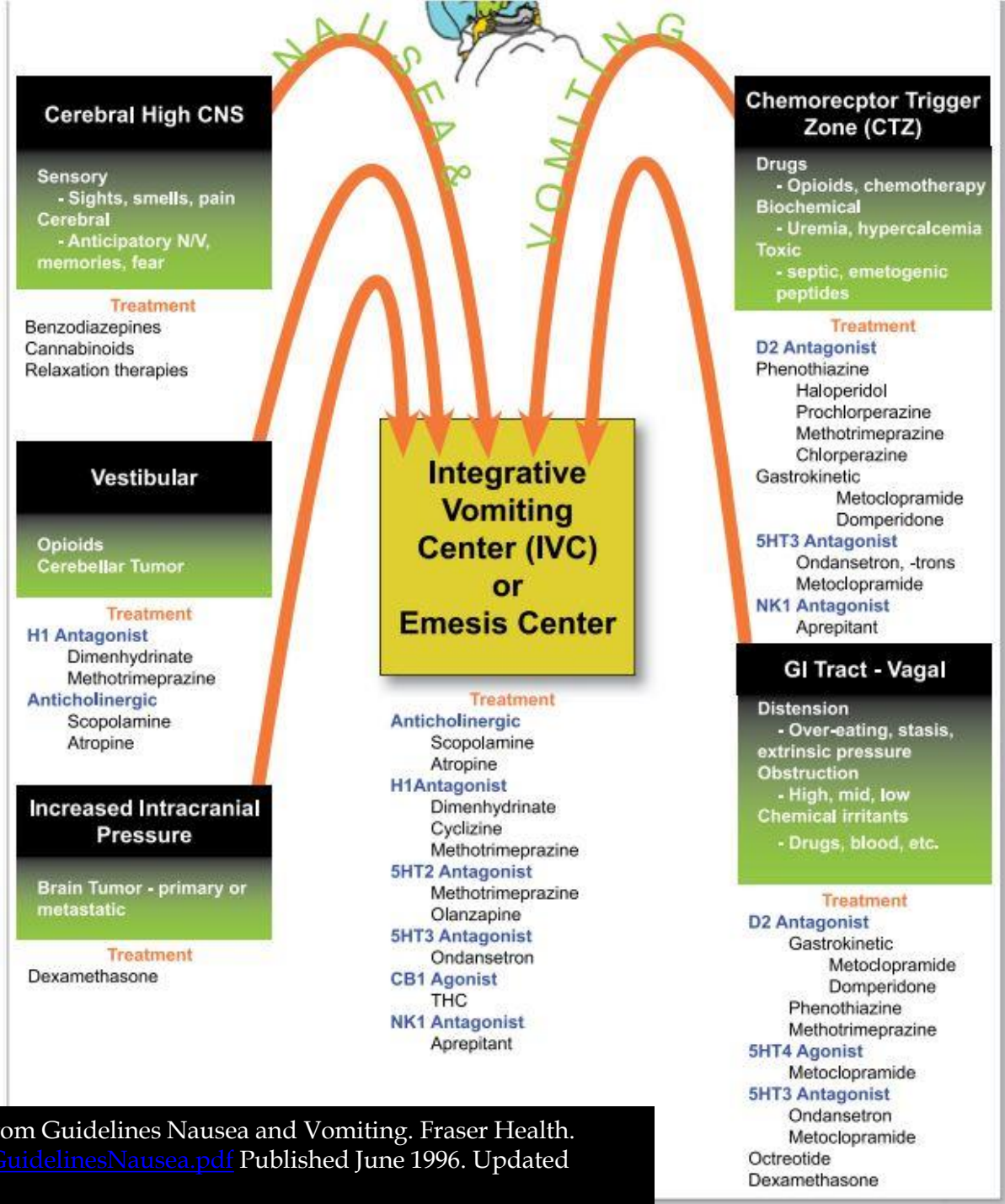
- Distraction/relaxation
- CBT
- Environmental modification
- Remove noxious stimulus, ventilation
- “Small, frequent meals”
- Dietician consult
- Fluids & electrolyte replacement
- Treat obstruction - stents, NG, venting G-tube, ostomies, surgical resection, percutaneous drainage

Pharmacologic Management

First consider the receptors involved in the N/V pathways:

- Histamine (H1)
- Acetylcholine (ACh)
- Serotonin (5HT2, 5HT3, 5HT4)
- Dopamine (D2)
- Cannabinoid (CB1, CB2)
- Neurokinin 1 (NK1)

Pharmacologic Management



Fraser Health. Hospice Palliative Care Program Symptom Guidelines Nausea and Vomiting. Fraser Health. https://www.fraserhealth.ca/media/14FHSymptomGuidelinesNausea.pdf Published June 1996. Updated January 2016. Accessed November 7, 2017.

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CASE 1 – Heart Failure

- Etiology likely multifactorial
  - Intestinal edema
  - Hepatic congestion
  - Reflux
  - Hepatic and/or renal dysfunction
  - Drugs
- Considerations
  - QT prolongation risk
- Rx
  - Cardiology prescribed: dimenhydrinate (Gravol®) 25-50 mg IV q4h prn
  - Palliative care suggests: Metoclopramide 10 mg po TID
  - Other options: Olanzapine 2.5mg po/sc qhs, benzos
  - Avoid: dexamethasone – promotes Na and fluid retention

H1 Antagonists and Anticholinergics

- Usually for vestibular etiology
- Antihistamine:
  - Dimenhydrinate (Gravol®) 25-50 mg po/iv/sc q4-6h prn
- Anticholinergic:
  - Hyoscine hydrobromide (Scopolamine®) (1.5 mg) transdermal patch post auricular q3d
- SEs
  - Dry mouth, drowsiness, sedation, other anticholinergic effects

Case 2.1

Fred, 68 y.o. male with non-small cell lung cancer

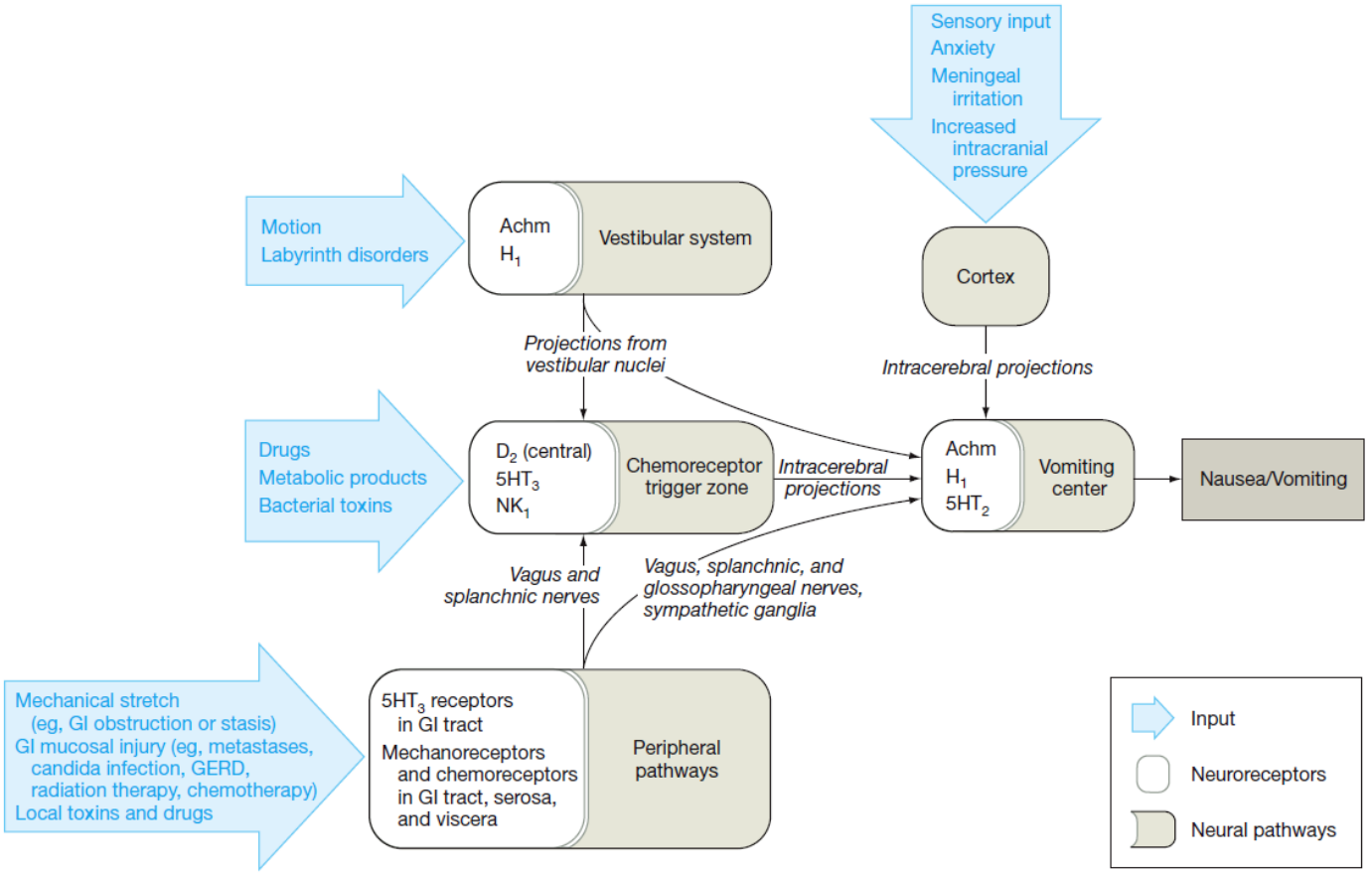
- Received his first dose of chemotherapy 3 days ago
- Anxious
- Was given a script for anti-emetics, but did not fill it
- Complains of nausea, no vomiting
- Feels ++ fatigued
- Poor appetite
- Regular bowel movements
- Analgesic needs met by acetaminophen

Etiology

- **Chemotherapy-induced N/V**
- **Rx?**

Pathophysiology of common etiologies of N/V

Figure. Interrelationships Between Neural Pathways That Mediate Nausea and Vomiting



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CINV - Guidelines

- Depends on emetogenecity and regimen
- High-emetic risk → offer prophylaxis:
  - a four-drug combination of a
    - NK1 receptor antagonist,
    - Serotonin (5-HT3) receptor antagonist
    - dexamethasone
    - olanzapine
- Lower emetic risk → anti-emetics recommended as prophylaxis
  - If N/V despite optimal prophylaxis, may use olanzapine

Roila F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol 2016;27:v119-v33.

5HT3 Antagonist

"Setrons"

- Ondansetron (Zofran®) 4-8 mg po/iv one to three times daily
- Granisetron (Kytril®) 1-2 mg po/iv/sc in one or two doses
- Most effective for chemotherapy-induced N/V and radiotherapy-induced N/V
- Usually given on days 0-1 post-chemotherapy (no evidence for > day 1)
- Side Effects:
  - Constipation, QT prolongation

NOTE: Olanzapine also has some 5HT3 antagonism

Neurokinin-1 Receptor Antagonists

- Aprepitant (Emend®)
- Used primarily in CINV for prevention of N/V with highly emetogenic chemotherapy
- 125 mg prior to chemotherapy on day 1, followed by 80 mg once daily on days 2 and 3 (in combination with dexamethasone and a 5-HT3 antagonist antiemetic on day 1, followed by dexamethasone for 3 to 4 more days)
- Capsule and suspension form

CASE 2.2

Fred, 68 y.o. male with non-small cell lung cancer

- Now completed chemotherapy
- New bony mets found in rib and chest wall
- Receives radiation therapy
- Complains of nausea, no vomiting

Etiology

- **Radiation induced N/V**
- **Management?**

Radiation-Induced N/V - Guidelines

- Mechanism not clear, but thought to be related to CINV
- High emetic risk XRT - offer combination of the following before each # and on the day after each #:
  - 5-HT3 receptor antagonist – useful when massive release of 5HT/serotonin from enterochromaffin cells or platelets as can occur with radiation
  - Dexamethasone

Table 4. Emetic Risk in Adults by Site of Radiation Therapy

Risk Level	Site
High (> 90%)	Total body irradiation
Moderate (30%-90%)	Upper abdomen, craniospinal irradiation
Low (10%-30%)	Brain, head and neck, thorax, pelvis
Minimal (< 10%)	Extremities, breast

Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2017;35:3240-61.
Twycross R, Wilcock A, Howard P, eds. Palliative care formulary. Fifth edition. Nottingham, UK: Palliativedrugs.com Ltd; 2014.

CASE 2.3

Fred, 68 y.o. male with non-small cell lung cancer

- Chemotherapy and radiation completed
- Now has increased pain, requiring regular opioids
  - Hydromorphone long-acting (Hydromorph Contin®) 9 mg po BID and hydromorphone 2 mg po q1h prn
- Complains of nausea
- BMs q1-2 days
- Normal mentation
- Endorses premature satiety
- Attributes his decreased appetite to nausea
- **Etiology?**
- **Management?**

D2 Antagonists - Prokinetics

- Consider for early satiety, opioid-induced N/V, chronic nausea
  - Domperidone 5-10 mg po TID prn
    - Does not cross the blood-brain barrier
    - May try if EPS from Metoclopramide
  - Metoclopramide 5-10 mg po/iv/sc q6h prn
    - Acts peripherally in the upper GI tract
      AND
      Acts centrally in the chemoreceptor trigger zone
    - Also a 5HT4 agonist in the upper GI tract
    - Consider routine ac meals and qhs if persistent N/V

D2 Antagonists

- Effective and generally well-tolerated
- Common examples:
  - Prochlorperazine (Stemetil®) 5-10 mg po/iv q6h prn
    - May be useful in delayed CINV
  - Haloperidol (Haldol®) 0.5-1 mg po/iv/sc q4h prn
  - Olanzapine (Zyprexa®, Zyprexa Zydis®) 2.5-5 mg po/ODT/sc qhs +/- q4h prn
    - May cause hyperglycemia
  - Methotrimeprazine (Nozinan®) 5-10 mg po or 6.25-12.5 mg po/sc/iv q4h prn
- SEs:
  - EPS, sedation, prolonged QT, lower seizure threshold

CASE 2.4

Fred, 68 y.o. male with non-small cell lung cancer

- Wife calls - she's worried because he seems confused and has been complaining of headache
- Now has nausea, vomiting 2-3x per day
- No BM x 3 days, not sure about flatus
- Also complains of overall aches; has been taking more hydromorphone breakthroughs

- **What is your differential diagnosis?**
- **What do you want to do?**

Steroids

- Dexamethasone
- For reduction of edema associated with brain metastases
  - 4-8 mg/24h for patients with mild symptoms
  - For severe symptoms or risk of herniation use doses ≥ 16 mg/24h
- General antiemetic effect
  - May be mediated by a:
    - corticosteroid-induced reduction in permeability of the chemoreceptor trigger zone and BBB to emetogenic substances
    - Reduction in the neuronal content of GABA in the brain stem.

Twycross R, Wilcock A, Howard P, eds. Palliative care formulary. Fifth edition. Nottingham, UK: Palliativedrugs.com Ltd; 2014.

- But Doctor, what about marijuana? My cousin's friend took it and says it really helps...

Cannabinoids

- Not first line
- Consider if D2 antagonists or 5HT3 antagonists are ineffective
- Examples:
  - Nabilone (Cesamet®)
  - Dronabinol (Marinol®)
  - Nabiximols (Sativex®)
  - Marijuana

CASE 3

Maria, 58 yo F with metastatic ovarian cancer

Maria's husband calls you re: Maria being "severely constipated"

- No BM x 1 wk, no flatus
- Nauseous, vomiting 2-3x/d
- Very poor oral intake
- Abdominal pain, "crampy"
- **What's going on?**
- **What are your next steps?**


OBSTRUCTION
AHEAD

Malignant Bowel Obstruction

Epidemiology

- 20-50% of ovarian ca
- 10-28% of GI ca
- Median survival: 30-90 days
- Pancreatic cancer, cholangiocarcinoma → duodenal obstruction
- Colon cancer, ovarian cancer → distal obstruction

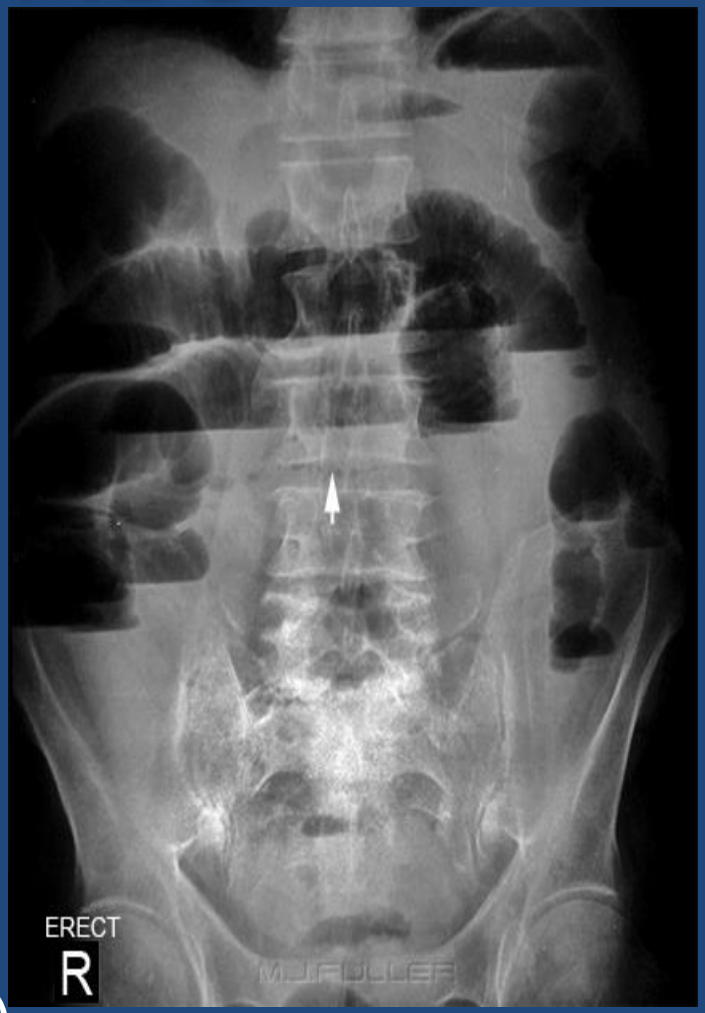
Symptoms MBO

Typical symptoms

- Nausea/vomiting
- Colic/abdominal pain
- Obstipation

Symptoms result from:

- Increased GI secretion
- Gut edema
- Increased peristalsis (initial)



Management MBO

Reduce intestinal distension

- Medical
- Surgical

Conservative Management

- NPO/bowel rest
- NGT for emesis
- Replace with fluids IV prn

Pharmacologic Management MBO

- Nausea/Vomiting
  - D2-antagonst prokinetic agents, metoclopramide, domperidone:
    - contraindicated in complete obstruction
    - indicated in partial obstruction
  - D2-antagonists:
    - Haloperidol, olanzapine, methotrimeprazine appropriate
  - 5HT3 antagonist may worsen constipation

Pharmacologic Management MBO

- Reduce secretions/decrease edema
  - Octreotide 300 mcg sc q8h or 10 mcg/hr continuous infusion
  - Octreotide long-acting (Sandostatin LAR®)
    - Use if proven benefit on octreotide
    - 10-20 mg IM q monthly
    - Covered by Ontario Drug Benefit and RAMQ (depends on your location of practice)
    - Need to overlap with octreotide sc x 2 weeks after first IM dose
- Reduce edema/nausea
  - Dexamethasone 4-16 mg sc daily, trial of 5-7 days
    - Anti-inflammatory; can reduce edema

Major P, Figueredo A, Tandan V, Bramwell V, Charette M, Oliver T, et al. The role of octreotide in the management of patients with cancer. Cancer Care Ontario. https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34421
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Management MBO

Constipation

- If partial obstruction, consider laxatives e.g. sennosides
- If complete obstruction, no laxatives (po/pr)

Palliative Surgical Management MBO

Stenting - duodenal/colonic

- Success: 90% GOO, 88-93% colonic

Venting G-tube

- Prognosis < 30d
- Multi-level obstruction

N/V Summary

Nausea – a systematic approach to management

- Pathophysiology
  - Pathways
  - Receptors
- Etiologies
- Assessment
- Management
  - Pharmacologic
  - Non-pharmacologic

Objectives

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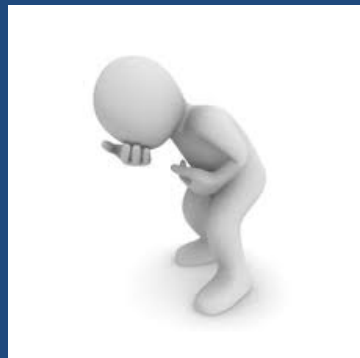

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