

Painweek.

ADVANCED EDUCATION

CERTIFICATION SERIES



PALLIATIVE CARE

Gastrointestinal Symptoms – Part 2

Alexandra McPherson, PharmD, MPH

Titles and Affiliations

Alexandra McPherson, PharmD, MPH

Palliative Care Clinical Pharmacist

MedStar Washington Hospital Center

Disclosures



Learning Objectives

At the conclusion of this presentation the participant will be able to:

List five potential causes of nausea/vomiting (N/V).

Recognize signs that a patient may be suffering from total nausea.

Design an appropriate treatment regimen, including both nonpharmacologic and pharmacologic treatment, to manage a given patient's N/V based on the etiology.

Meet RK

- 69-year-old female with a PMH of hypertension, diabetes, stage IV ovarian cancer (metastatic to abdominal wall), and recent hospitalization for UTI who presents with worsening abdominal pain and N/V x 5 days
- Per patient, she had been very constipated and after taking a “cocktail of laxatives,” developed diarrhea and subsequent dehydration which prompted her to seek medical attention
- CT abdomen/pelvis revealed disease progression; no evidence of bowel obstruction
- Palliative care consulted to assist with pain and nausea

PMH: past medical history; UTI: urinary tract infection

Meet RK (continued)

Home Medications

- Amlodipine 10 mg po daily
- Docusate 100 mg po BID
- Ibuprofen 800 mg po TID PRN (takes 2-3x/day on average)
- Metformin 1000 mg po BID
- Multivitamin 1 tab po daily
- Ondansetron 4 mg po q8h PRN nausea/vomiting
- Oxycodone 5 mg po q4h PRN moderate pain (takes 1x/day on average)
- Oxycodone 10 mg po q4h PRN severe pain (takes 5x/day on average)

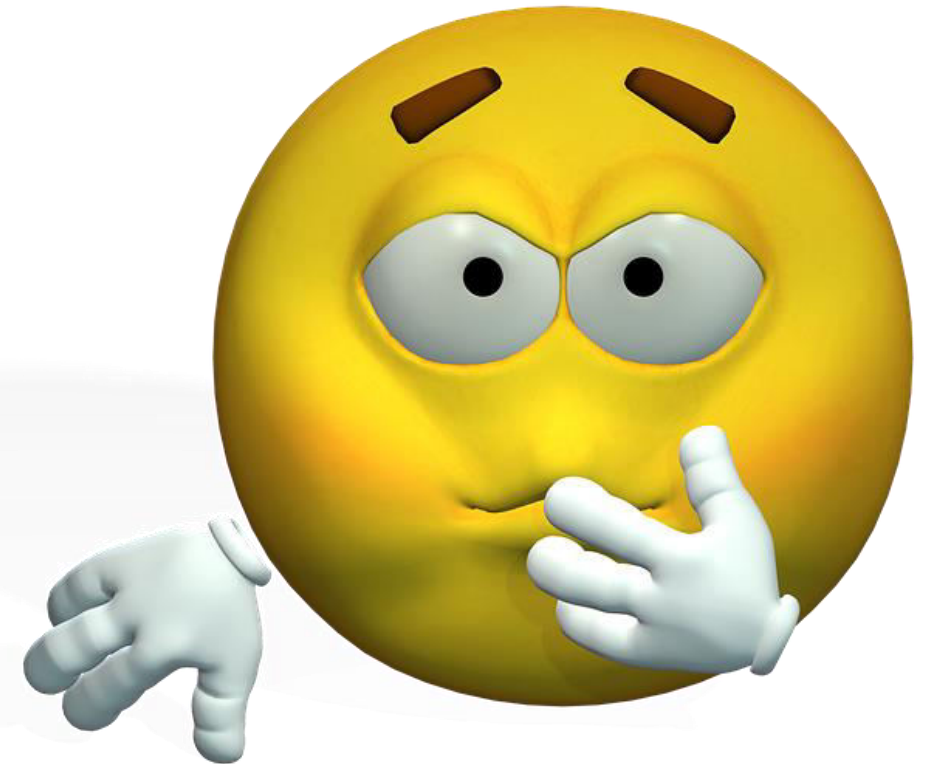
The Basics

What is nausea?

- The unpleasant sensation of feeling the need to vomit, which may be accompanied by abdominal discomfort, sweating, or tachycardia
- Can be acute, anticipatory, delayed, or chronic
- Subjective experience

What is vomiting?

- The process of ejection of gastric contents through the mouth as a result of prolonged contraction of the diaphragm & abdominal muscles
 - Usually (but not always) preceded by nausea
- **Retching** is defined as the spasmodic movements of the esophagus and gastric muscles, without vomiting



The Basics (continued)

Regurgitation

- Passive, retrograde flow of esophageal contents into the mouth
- Occurs with gastroesophageal reflux (GERD) or esophageal obstruction

Dyspepsia

- Chronic or recurrent pain or discomfort centered in the upper abdomen
- Can be classified as structural (acid-related) or functional (dysmotility-related)
 - Functional dyspepsia in cancer patients is called the cancer-associated dyspepsia syndrome, characterized by nausea, vomiting, early satiety, bloating, and constipation

Prevalence

- Up to 71% of **palliative care patients** will develop nausea and vomiting
 - 40% will experience these symptoms in the last six weeks of life
- ~20-30% of patients with **advanced cancer** experience nausea
 - 70% report nausea in the last week of life
- Up to 33% of patients with **ESRD** experience nausea and vomiting
- **Less common** in patients > 65 years old
- **More common** in females, specific tumor types (gynecological,* stomach, esophageal, breast), metastases (to lung, pleura, or mediastinum), GI pathology or intestinal obstruction, and those on opioids

Wilson, Plourde, Marshall, et al. *J Pall Care*. 2002;18(2):84-91.

Stern, Koch, Andrews. *Nausea: Mechanisms and Management*. New York, NY: Oxford University Press 2011.

Walsh, Davis, Ripamonti, et al. *Support Care Cancer*. 2017 Jan;25(1):333-340.

Back to RK

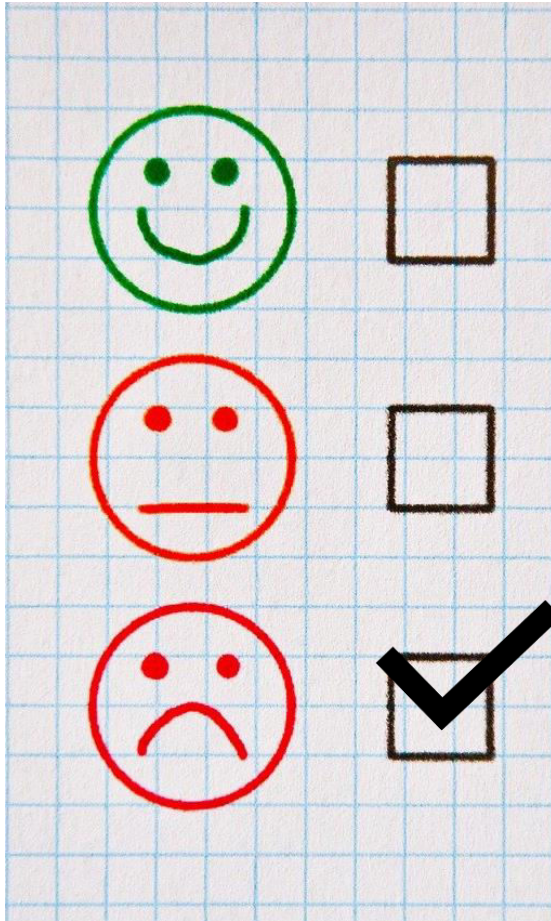
Which of the
“more common”
factors listed on
the previous
slide are true for
RK?

Back to RK

Which of the
“more common”
factors listed on
the previous
slide are true for
RK?

Female
Gynecological tumor
Opioids

Complications of Nausea and Vomiting



Dehydration

Metabolic disturbances

Poor oral intake → malnutrition

Aspiration

Esophageal tears

Gotfried. Nausea and Vomiting. 2020. *The Merck Manual of Diagnosis and Therapy*.

Causes of Nausea and Vomiting: 13 M's of Emesis

Above the neck

- Masses
- Meningeal irritation
- Migraine/other headaches
- Movement

Below the neck

- Motility
- Mucositis
- Mechanical obstruction
- Myocardial infarction
- Maternity


Systemic

- Mentation
- Medication
- Microbes
- Metabolic

Causes of Nausea and Vomiting

Medication-Related

- Chemotherapy
 - Highly-emetogenic agents include AC combination, carboplatin $AUC \geq 4$, cisplatin, cyclophosphamide $> 1,500 \text{ mg/m}^2$, doxorubicin $\geq 60 \text{ mg/m}^2$
- Analgesics
 - Opioids, NSAIDs
- Antiarrhythmics
 - Digoxin, quinidine
- Antibiotics
- Oral contraceptives
- Metformin
- Antiparkinsonians
 - Bromocriptine, L-DOPA
- Anticonvulsants
 - Phenytoin, carbamazepine
- Antihypertensives
- Theophylline
- Anesthetic agents
- Iron supplements



For full list of emetogenic potential of antineoplastic agents, visit:
NCCN Clinical Practice Guidelines in Oncology: Antiemesis

AC: doxorubicin + cyclophosphamide; NSAIDs: nonsteroidal anti-inflammatory drugs

Self-Assessment!



WHAT HAVE YOU LEARNED?











- Which of the following medications are commonly associated with medication-related nausea/vomiting?

- A. Naproxen
- B. Hydromorphone
- C. Amoxicillin/clavulanate
- D. A and B
- E. All of the above

Self-Assessment!

WHAT HAVE YOU LEARNED?











- Which of the following medications are commonly associated with medication-related nausea/vomiting?

- A. Naproxen
- B. Hydromorphone
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- E. All of the above

Back to RK

Is RK taking any medications that might cause nausea/vomiting?

Back to RK

Is RK taking any medications that might cause nausea/vomiting?

Opioids



Oxycodone

NSAIDs



Ibuprofen

Antihypertensives

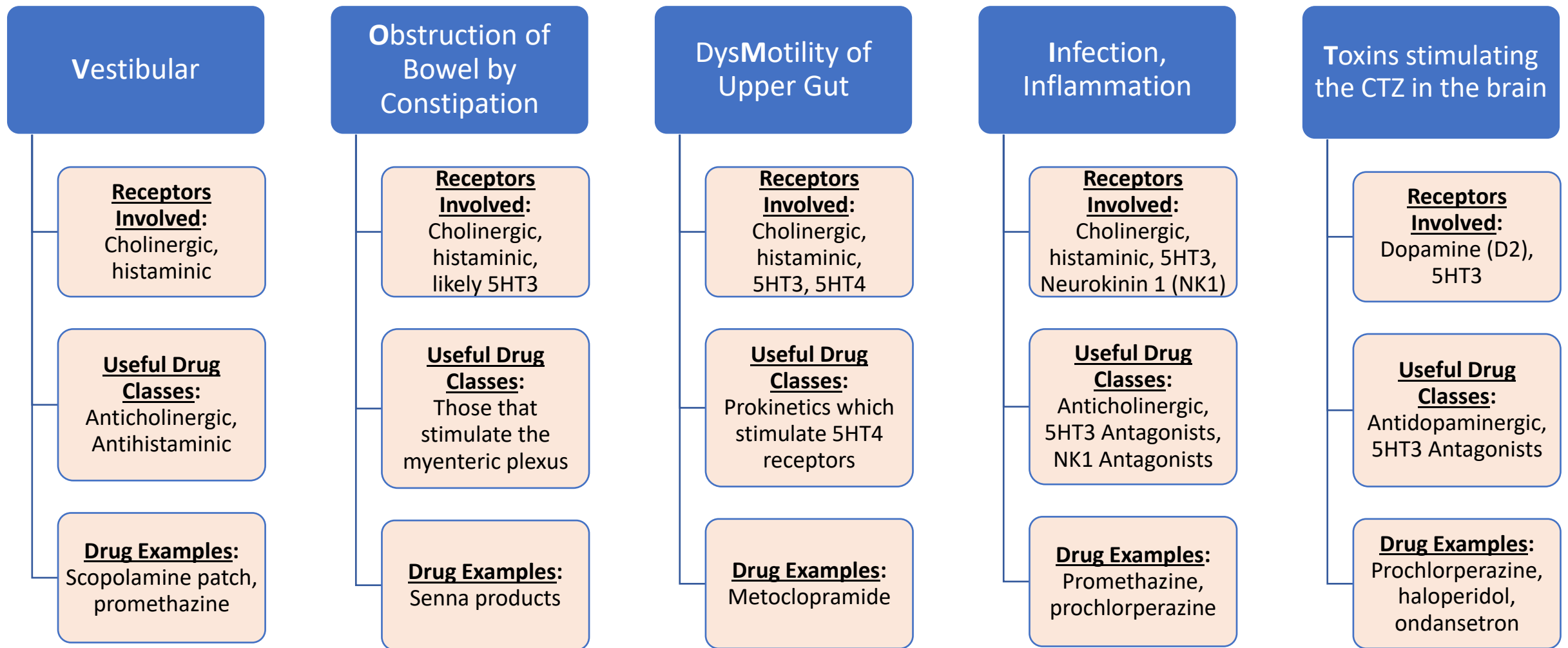


Amlodipine

Metformin

Antibiotics?

Causes of Nausea and Vomiting: VOMIT



CTZ: Chemoreceptor Trigger Zone

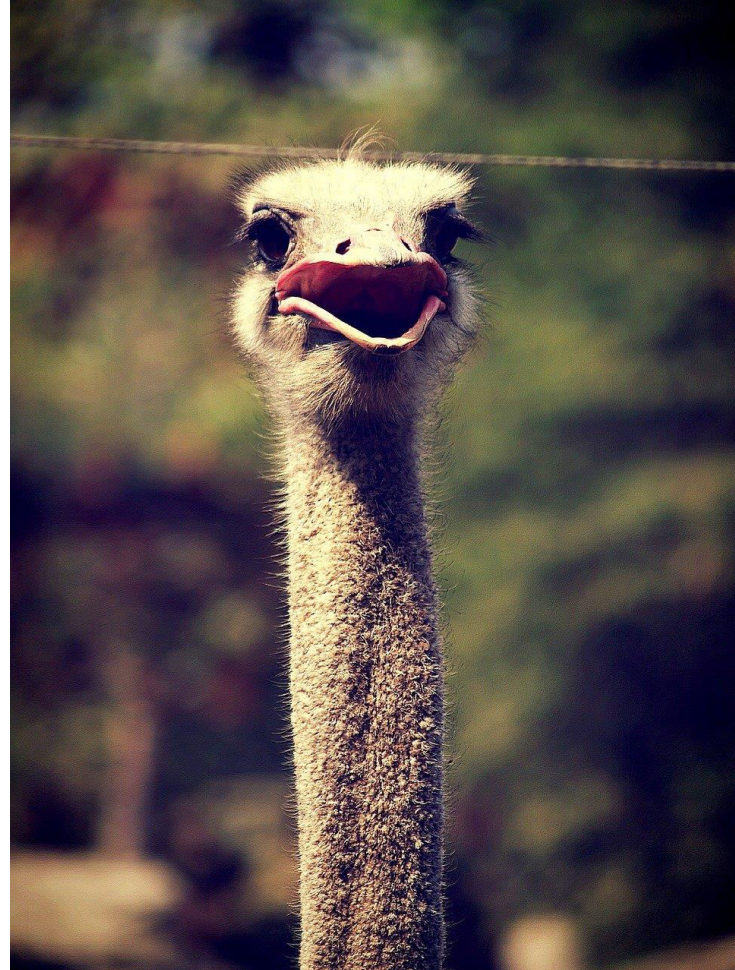
Back to RK



- Reports **severe abdominal pain** (9/10)
 - Mainly located in LLQ
 - Improves somewhat when she lies on her left side
 - Uncontrolled on home pain regimen (PRN oxycodone, doesn't last long enough)
- Reports "**constant nausea**," denies vomiting at present
 - Cannot identify any precipitating or alleviating factors off the top of her head
 - Maybe worse with eating? Has been going on for a while, but has gotten worse
 - Does not think ondansetron (home med) is helping
- Very **anxious**, waiting to hear whether further surgery is an option

Now what?

What else do
you want to
know?



P²QRS²TU: Assessment of Nausea and Vomiting

Precipitating

- What (if anything) aggravates or triggers nausea/vomiting?

Palliating

- What (if anything) alleviates nausea/vomiting?
- What has the patient (or team) tried to treat their symptoms? Has it been effective?

Quality

- How do they describe their nausea/vomiting?

Recent changes

- Have there been any recent changes (eg, new medications) and can these be related to the start of symptoms?

Severity

- How do they rate their nausea/vomiting? 0-10?

Symptoms

- Are they experiencing any other associated symptoms?
- Examples: dyspepsia, early satiety, constipation, diarrhea, flatus, headache, confusion, fever

Temporal

- When did symptoms start?
- Are they constant or intermittent?
- Are symptoms worse at a particular time of day?

(Yo)u

- How do the patient's symptoms affect their quality of life?

Assessment of Nausea and Vomiting

Onset of Symptoms	
Abrupt	Cholecystitis, food poisoning, gastroenteritis, illicit drugs, medications, pancreatitis
Insidious	GERD, gastroparesis, medications, metabolic disorders, pregnancy
Timing of Symptoms	
Before breakfast	Alcohol, increased intracranial pressure, pregnancy, uremia
During or directly after eating	Psychiatric causes, less likely peptic ulcer disease or pyloric stenosis
1-4 hours after a meal	Gastric outlet obstruction (eg, from PUD or neoplasms), gastroparesis
Continuous	Conversion disorder, depression
Irregular	Depression
Nature of Vomited Matter	
Undigested food	Achalasia, esophageal disorders (diverticulum, strictures)
Partially digested food	Gastric outlet obstruction, gastroparesis
Bile	Proximal small bowel obstruction
Feculent or odorous	Fistula, obstruction with bacterial degradation of contents
Large volume	Suggests organic rather than psychiatric causes

Scorza, Williams, Phillips, et al. *Am Fam Physician*. 2007;76(1):76-84.

Assessment of Nausea and Vomiting

Abdominal Pain

Right upper quadrant	Biliary tract disease, cholecystitis
Epigastric	Pancreatic disease, peptic ulcer disease
Severe pain	Biliary disease, pancreatic disease, peritoneal irritation, small bowel obstruction
Severe pain that precedes vomiting	Small bowel obstruction

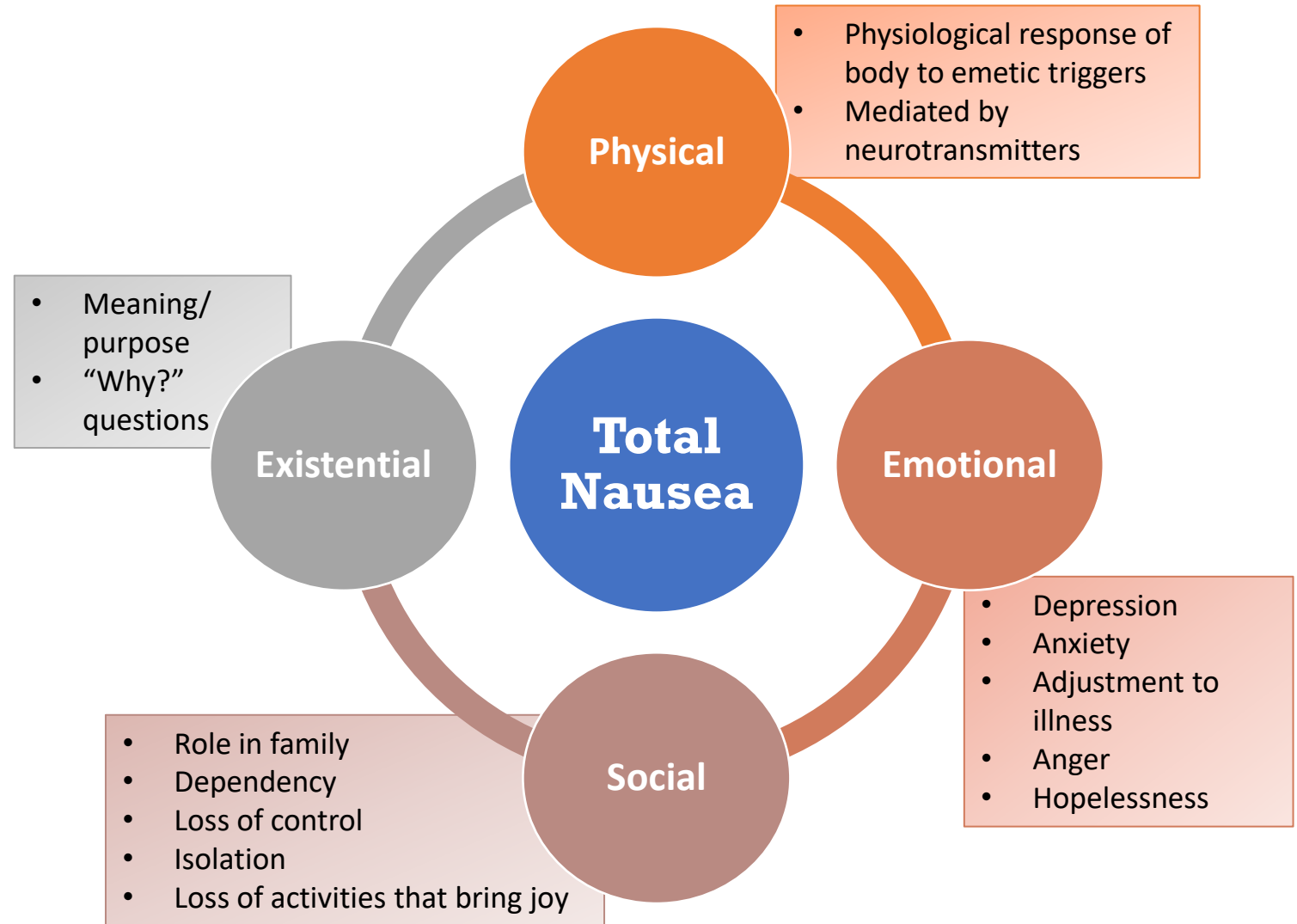
Associated Symptoms/Findings

Weight loss	Malignancy, gastric outlet obstruction, peptic ulcer disease
Diarrhea, myalgias, malaise, headache, contact with ill persons	Viral etiologies
Headache, stiff neck, vertigo, focal neurologic deficits	Central neurologic causes (eg, encephalitis, meningitis, head injury, mass lesion, or other cause of increased intracranial pressure, migraine)
Early satiety, postprandial bloating, abdominal discomfort	Gastroparesis
Repetitive migraine headaches or symptoms of irritable bowel syndrome	Cyclic vomiting syndrome

Scorza, Williams, Phillips, et al. *Am Fam Physician*. 2007;76(1):76-84.

Total Nausea

- Nausea is typically managed using a biomedical approach, emphasizing medication management
- Similar to total pain, total nausea involves physical, emotional, social, and existential components
- Best approached from a transdisciplinary perspective
- Utilizes multiple complementary interventions to address suffering



Darrah, Goldberg. *J Pain Symptom Manage*. 2018;55(1):e3-e5.

Back to RK

What do you think could be contributing to the patient's nausea/vomiting?

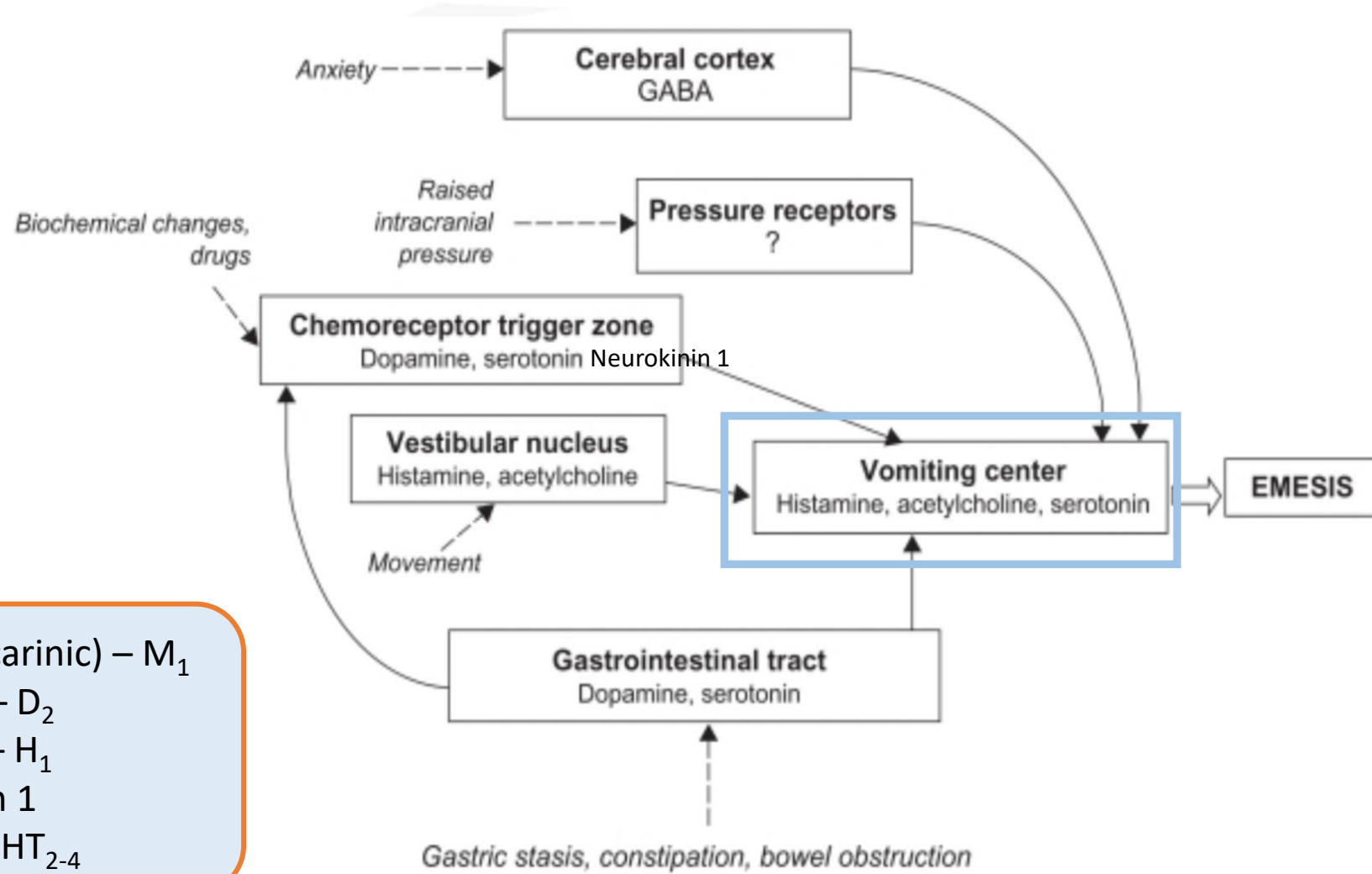


Back to RK

What do you think could be contributing to the patient's nausea/vomiting?

Diabetes – gastroparesis
Constipation
Medications
Disease progression
Uncontrolled pain
Anxiety

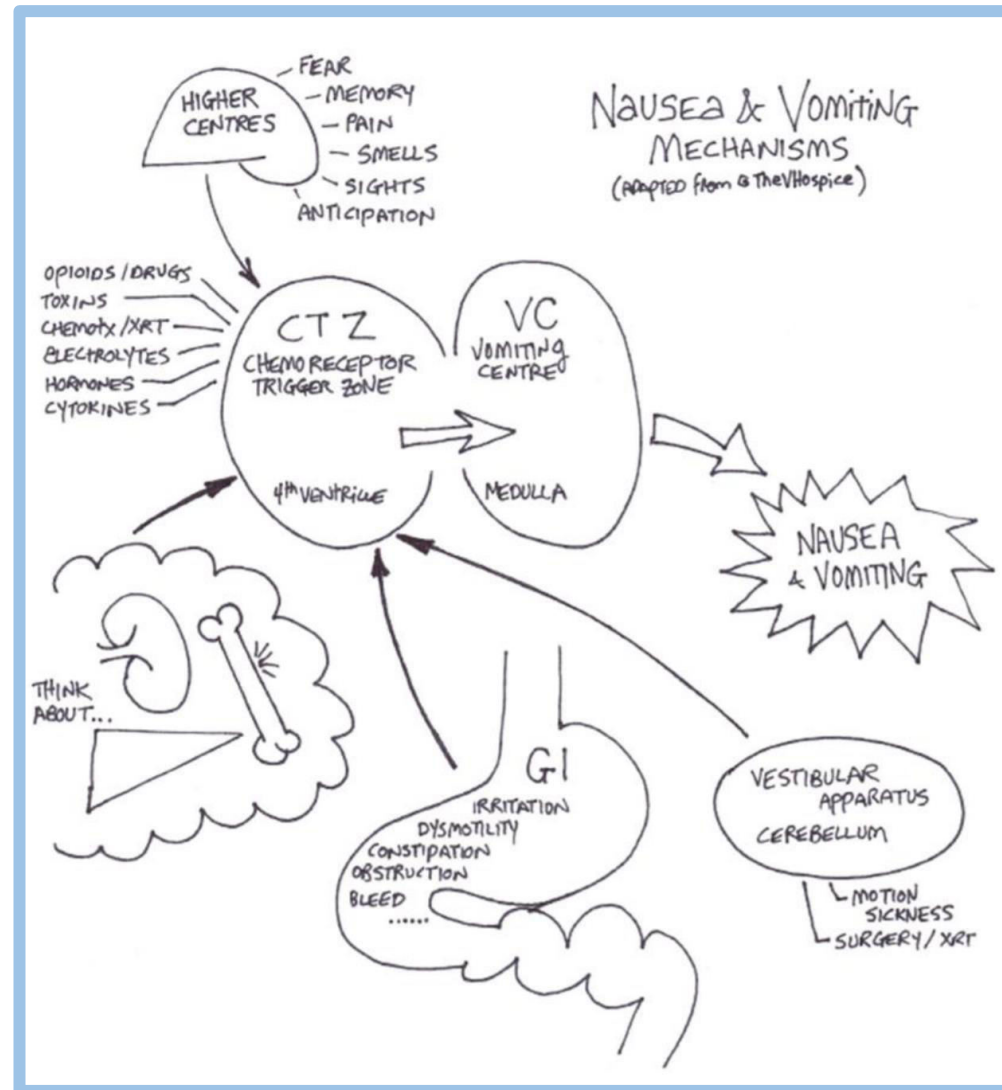
Neurotransmitters and the Emetic Pathway



Acetylcholine (muscarinic) – M₁
Dopamine – D₂
Histamine – H₁
Neurokinin 1
Serotonin – 5HT₂₋₄

Glare, Miller, Nikolova, et al. *Clin Interv Aging*. 2011;6:243-259.

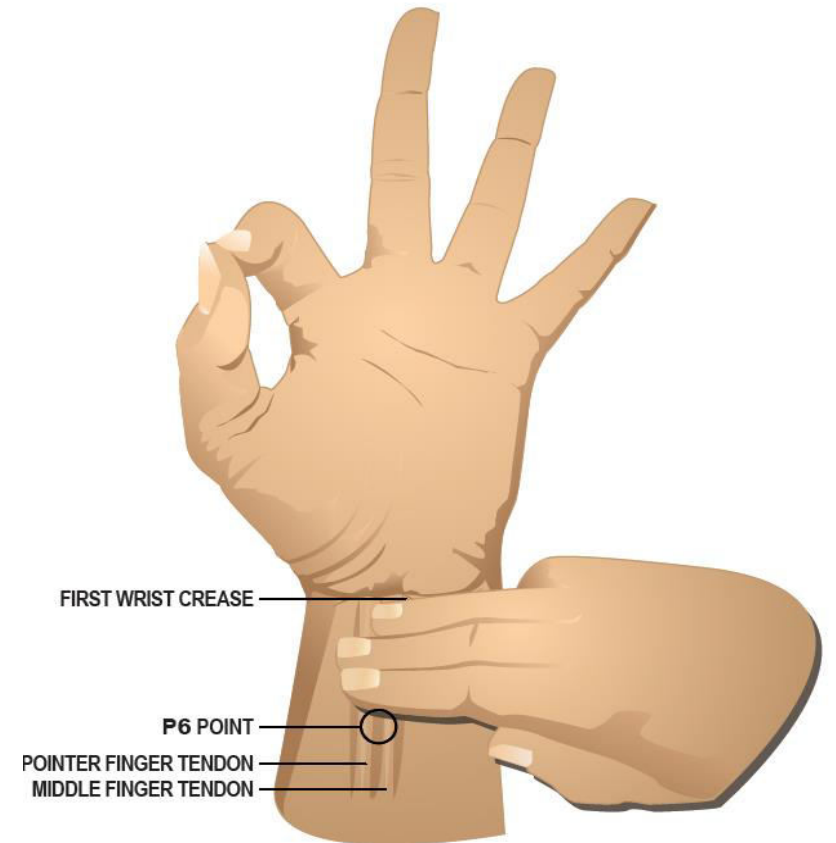
Nausea and Vomiting Mechanisms



Management of Nausea and Vomiting

Nonpharmacologic Treatment

- Acupressure, acupuncture
- Relaxation exercises
- Avoidance of strong odors, foods, or other known triggers
- Promoting good oral care
- Offer clear liquids, educate patients to sip liquids slowly (don't gulp)
- Eat small, frequent meals that patient desires
 - Cold and bland foods often better tolerated
 - Avoid greasy, fried, or spicy foods



Management of Nausea and Vomiting

Pharmacologic Treatment

- Dopamine antagonists
- Histamine antagonists
- Serotonin antagonists
- Substance P (NK1) antagonists
- Acetylcholine antagonists
- Benzodiazepines
- Corticosteroids
- Cannabinoids
- Other



Pharmacologic Management

Dopamine Antagonists

• Medications

- Haloperidol (Haldol®)
 - Starting dose: 0.5-1 mg PO/SC/IV q12h
- Metoclopramide (Reglan®)
 - Starting dose: 5-10 mg PO/SC/IV q6h
- Prochlorperazine (Compazine®)
 - Starting dose: 10 mg po q6h; 25 mg PR q12h
- Olanzapine (Zyprexa®)
 - Starting dose: 5 mg po qhs

• Indications

- Opioid-induced nausea/vomiting
- Unknown etiology
- Gastroparesis/ileus/functional obstruction
 - Metoclopramide

• Adverse Effects

- Extrapyrimalidal symptoms/movement disorders
 - Akathisia
 - Dystonic reactions
 - Parkinsonism
 - Tardive dyskinesia
- QTc prolongation

Haloperidol. In: Lexi-Drugs Online. Hudson, OH : Lexi-Comp, Inc.; [Updated September 18, 2021; Accessed September 19, 2021].

Metoclopramide. In: Lexi-Drugs Online. Hudson, OH : Lexi-Comp, Inc.; [Updated September 18, 2021; Accessed September 19, 2021].

Prochlorperazine. In: Lexi-Drugs Online. Hudson, OH : Lexi-Comp, Inc.; [Updated September 18, 2021; Accessed September 19, 2021].

Olanzapine. In: Lexi-Drugs Online. Hudson, OH : Lexi-Comp, Inc.; [Updated September 10, 2021; Accessed September 19, 2021].

Pharmacologic Management

Dopamine Antagonists

- **Adverse Effects (continued)**

- To screen for movement disorders, watch for **PUR**:

- **P**ostural abnormalities

- Pregnancy stance
- Pelvic thrust
- Altered gait

- **U**nintentional movements

- Finger tap
- Mouth, tongue, and leg movement

- **R**estlessness

- Hands, arms, and legs

Chlorpromazine
Thioridazine
Haloperidol
Clozapine
Risperidone
Olanzapine
Quetiapine



Olanzapine

- **Study Design**

- Double-blind, placebo-controlled RCT

- **Patient Population**

- N = 30 patients (15 in each arm) with advanced cancer who had persistent N/V without having had chemotherapy or XRT in the prior 14 days

- **Intervention**

- Patients received olanzapine 5 mg or placebo daily for 7 days

- **Outcome**

- Δ in nausea numeric rating scores from baseline to the last treatment day (primary endpoint)

- **Results**

- Baseline median nausea scores (all patients): 9/10
- Olanzapine group: 2/10 (day 1), 1/10 (day 7)
- Placebo group: 9/10 (day 1 and day 7)

Research

JAMA Oncology | [Brief Report](#)

Olanzapine for the Treatment of Advanced Cancer-Related Chronic Nausea and/or Vomiting A Randomized Pilot Trial

Rudolph M. Navari, MD; Cameron M. Pywell, MD; Jennifer G. Le-Rademacher, PhD; Patrick White, MD; Andrew B. Dodge, MS; Costantine Albany, MD; Charles L. Loprinzi, MD

Pharmacologic Management

Histamine Antagonists

• Medications

- Dimenhydrinate (Dramamine®)
- Diphenhydramine (Benadryl®)
 - Starting dose: 25-50 mg PO/SC/IV
- Meclizine (Antivert®)
 - Starting dose: 25-50 mg PO q6h
- Promethazine (Phenergan®)
 - Starting dose: 25 mg PO/PR q6h;
12.5-25 mg IV q6h

• Indications

- Vestibular, motion sickness, or movement-related
- Nausea/vomiting of pregnancy (specifically dimenhydrinate)

• Adverse Effects

- Sedation
- Confusion

Dimenhydrinate. In: Lexi-Drugs Online. Hudson, OH : Lexi-Comp, Inc.; [Updated September 2, 2021; Accessed September 19, 2021].

Diphenhydramine. In: Lexi-Drugs Online. Hudson, OH : Lexi-Comp, Inc.; [Updated September 17, 2021; Accessed September 19, 2021].

Meclizine. In: Lexi-Drugs Online. Hudson, OH : Lexi-Comp, Inc.; [Updated September 18, 2021; Accessed September 19, 2021].

Promethazine. In: Lexi-Drugs Online. Hudson, OH : Lexi-Comp, Inc.; [Updated September 10, 2021; Accessed September 19, 2021].

Pharmacologic Management

Serotonin Antagonists

• Medications

- Ondansetron (Zofran®)
 - Starting dose: 4 mg PO/SC/IV q6h
- Palonosetron (Aloxi®)
 - Starting dose: 0.25 mg PO/IV daily
- Granisetron (Kytril®)
 - Starting dose: 1 mg PO/IV q12h or daily
- Dolasetron (Anzemet®)
 - Starting dose: 200 mg PO/IV daily

• Indications

- Chemotherapy-induced nausea/vomiting

• Adverse Effects

- Constipation
 - Consider providing prophylactic bowel regimen
- QTc prolongation

Ondansetron. In: Lexi-Drugs Online. Hudson, OH : Lexi-Comp, Inc.; [Updated September 18, 2021; Accessed September 19, 2021].

Palonosetron. In: Lexi-Drugs Online. Hudson, OH : Lexi-Comp, Inc.; [Updated August 6, 2021; Accessed September 19, 2021].

Granisetron. In: Lexi-Drugs Online. Hudson, OH : Lexi-Comp, Inc.; [Updated September 4, 2021; Accessed September 19, 2021].

Dolasetron. In: Lexi-Drugs Online. Hudson, OH : Lexi-Comp, Inc.; [Updated May 29, 2021; Accessed September 19, 2021].

Pharmacologic Management

Substance P (NK1) Antagonists

• Medications

- Aprepitant (Emend®)
- Fosaprepitant (Emend IV®)
- Aprepitant injectable emulsion (Cinvanti®)
- Rolapitant (Varubi®)

• Indications

- Chemotherapy-induced nausea/vomiting

• Adverse Effects

- Varies based on the individual product/formulation
- Infusion site reactions
- Drug-drug interactions

Aprepitant. In: Lexi-Drugs Online. Hudson, OH : Lexi-Comp, Inc.; [Updated September 18, 2021; Accessed September 19, 2021].

Fosaprepitant. In: Lexi-Drugs Online. Hudson, OH : Lexi-Comp, Inc.; [Updated September 18, 2021; Accessed September 19, 2021].

Rolapitant. In: Lexi-Drugs Online. Hudson, OH : Lexi-Comp, Inc.; [Updated September 10, 2021; Accessed September 19, 2021].

Pharmacologic Management

Acetylcholine Antagonists

• Medications

- Scopolamine (Transderm Scop®)
 - Starting dose: 1 patch q72h
 - Patches cannot be cut
 - Injectable product withdrawn in 2015
- Glycopyrrolate (Robinul®)
 - Starting dose: 0.2-0.4 mg SC q6h PRN
 - Low oral bioavailability (<15%)
 - Fewer CNS effects than other anticholinergics

• Indications

- Vestibular nausea
- Adjuvant to control symptoms of malignant bowel obstruction

• Adverse Effects

- Sedation
- Blurred vision
- Urinary retention
- Dry mouth
- Constipation
- Delirium

Scopolamine. In: Lexi-Drugs Online. Hudson, OH : Lexi-Comp, Inc.; [Updated September 13, 2021; Accessed September 19, 2021].

Glycopyrrolate. In: Lexi-Drugs Online. Hudson, OH : Lexi-Comp, Inc.; [Updated September 9, 2021; Accessed September 19, 2021].

Pharmacologic Management

Benzodiazepines

- **Medications**

- Lorazepam (Ativan®)
 - Starting dose: 0.5-1 mg PO/SC/IV q8h

- **Indications**

- Anticipatory nausea/vomiting in patients receiving chemotherapy
- Total nausea, where anxiety plays a role

- **Adverse Effects**

- Confusion
- Sedation
- Delirium

Pharmacologic Management

Corticosteroids

• Medications

- Dexamethasone (Decadron®)
 - Starting dose:
4 mg po daily or BID
 - Daily or BID dosing preferred; no added benefit to q6h dosing due to long half-life

• Indications

- Chemotherapy-induced nausea/vomiting
- Increased intracranial pressure
- Meningeal irritation
- Unknown etiology

• Adverse Effects

- Anxiety
- Delirium
- Insomnia

Pharmacologic Management

Cannabinoids

• Medications

- Dronabinol (Marinol®)
 - 5 mg po 1-3 hours prior to chemotherapy, then 5 mg/m² q2-4h after chemotherapy for a total of 4-6 doses/day (max 15 mg/m²/dose)
- Dronabinol (Syndros®)
- Nabilone (Cesamet®)
 - 1 mg po BID; first dose given 1-3 hours prior to chemotherapy.
 - May also be helpful to administer 1-2 mg the night prior to chemotherapy; continue for up to 48 hours after last dose of chemotherapy
 - Max. dose 6 mg/day in 3 divided doses
 - *No longer available in the US*

• Indications

- Chemotherapy-induced nausea/vomiting
 - Generally less effective than other antiemetics, and with more side effects

• Adverse Effects

- Confusion
- Dizziness
- Sedation
- Ataxia

Dronabinol. In: Lexi-Drugs Online. Hudson, OH : Lexi-Comp, Inc.; [Updated September 18, 2021; Accessed September 19, 2021].

Nabilone. In: Lexi-Drugs Online. Hudson, OH : Lexi-Comp, Inc.; [Updated September 2, 2021; Accessed September 19, 2021].

Pharmacologic Management

Other

- **Medications**

- Erythromycin

- Antibiotic, pro-kinetic agent
- Starting dose:
250 mg po TID before meals
- Beneficial if patient cannot tolerate metoclopramide 2/2 EPS
- Tachyphylaxis can occur with duration of therapy > 4 weeks

- Octreotide

- Starting dose:
100 mcg SC/IV q8h
- Beneficial in patients with inoperable bowel obstruction

Erythromycin. In: Lexi-Drugs Online. Hudson, OH : Lexi-Comp, Inc.; [Updated September 9, 2021; Accessed September 19, 2021].

Octreotide. In: Lexi-Drugs Online. Hudson, OH : Lexi-Comp, Inc.; [Updated August 26, 2021; Accessed September 19, 2021].

What's New?

Supportive Care in Cancer
<https://doi.org/10.1007/s00520-021-06437-w>

SPECIAL ARTICLE

MASCC antiemetics in advanced cancer updated guideline

Mellar Davis¹  • David Hui² • Andrew Davies³ • Carla Ripamonti⁴ • Andreia Capela⁵ • Giulia DeFeo⁴ • Egidio Del Fabbro⁶ • Eduardo Bruera²

Received: 11 June 2021 / Accepted: 12 July 2021

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MASCC level of evidence and panel consensus

First Line: Metoclopramide (II) multiple small RCTs including a placebo-controlled trial, **haloperidol** (II) multiple non-placebo-controlled RCTs, high consensus.


Second line: Methotrimeprazine (II) 1 well-powered non-placebo-controlled RCT, **olanzapine** (II) 1 placebo-controlled pilot RCT, high consensus.

Third line: Tropisetron (II) large unblinded lower quality non-placebo-controlled RCT, **levosulpiride** (III) 1 blinded small non-placebo-controlled pilot RCT, high consensus.

Supportive Care in Cancer
<https://doi.org/10.1007/s00520-021-06438-9>

SPECIAL ARTICLE

Medical management of malignant bowel obstruction in patients with advanced cancer: 2021 MASCC guideline update

Mellar Davis¹  • David Hui² • Andrew Davies³ • Carla Ripamonti⁴ • Andreia Capela⁵ • Giulia DeFeo⁴ • Egidio Del Fabbro⁶ • Eduardo Bruera²

Received: 11 June 2021 / Accepted: 12 July 2021

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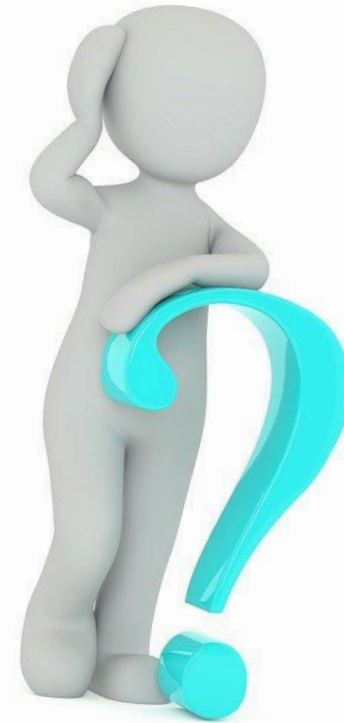


Octreotide remains the drug of choice in managing MBO.

Metoclopramide and olanzapine may be effective.

Let's Help RK

How should
we manage
RK's nausea/
vomiting?



Let's Help RK!

How should we manage RK's nausea/vomiting?

Gastroparesis – metoclopramide 5 mg IV q6h (transitioned to PO at discharge)

Constipation – D/C'd docusate, started senna 2 tabs po BID, Miralax PRN

Medications – UTI abx D/C'd, rechecked A1c (below goal) D/C'd metformin

Disease progression/uncontrolled pain – optimized pain regimen, started LA

Anxiety – psychosocial support, lorazepam 0.5 mg po BID PRN

LA: long acting

Summary



- Nausea and vomiting are prevalent in our patient population
- Thorough assessment and history taking is essential! Everyone on the team has a role to play here
- Treatment should target the underlying cause
 - Hint: ondansetron is rarely the answer!
- Patients should be reassessed regularly to determine efficacy and toxicity of antiemetic therapy

Self-Assessment!



- Which of the following statements is true regarding the Medicare Hospice Benefit?
 - A. Patients have a prognosis of 6 months or less (if disease follows trajectory)
 - B. Patient forgoes curative therapy, focuses on comfort measures
 - C. If the patient lives longer than 6 months, they are automatically discharged from hospice
 - D. A and B
 - E. All of the above

Self-Assessment!

WHAT HAVE YOU LEARNED?











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Painweek.

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GI Symptoms (Part 2)

Alexandra McPherson, PharmD, MPH