PAINWEEK®

Taming of the Spew!

Managing Opioid-Induced Nausea and Vomiting

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Rockford, IL

Disclosure

- None

Learning Objectives

- Recognize risk factors predictive of opioid-induced nausea and vomiting.
- Describe the possible mechanisms responsible for opioid-induced nausea and vomiting.
- Discuss strategies for managing opioid-induced nausea and vomiting, including the role of anti-emetic therapies.

Abbreviations Key

- 5-HT3: 5-hydroxytryptamine type 3 receptor
- 5-HT2: 5-hydroxytryptamine type 2 receptor
- Ach-M: muscarinic acetylcholine receptor
- CINV: chemotherapy-induced nausea and vomiting
- CNS: Central Nervous System
- COPD: chronic obstructive pulmonary disease
- CTZ: chemoreceptor trigger zone
- D2: dopamine type 2 receptor
- EPS: extrapyramidal symptoms
- GAD: generalized anxiety disorder
- GERD: gastroesophageal reflux disease
- H1: histamine type 1 receptor
- ICP: intracranial pressure
- MASCC/ESMO: Multinational Association of Supportive Care in Cancer/European Society of Medical Oncology
- MOR: Mu Opioid Receptor
- NCCN: National Comprehensive Cancer Network
- NK1: neurokinin type 1 receptor
- NTS: Nucleus tractus solitarius or nucleus of the solitary tract
- NSAID: Nonsteroidal anti-inflammatory drugs
- N/V: Nausea/Vomiting
- OINV: Opioid induced nausea and vomiting
- PONV: postoperative nausea and vomiting
- PUD: peptic ulcer disease
- RIE: radiation induced emesis
- VC: “vomiting center”

Opioid-Induced Nausea and Vomiting (OINV)

- Incidence of OINV within 72 hours after opioid administration
  - Nausea ~30-40%
  - Vomiting ~15-25%
- Not uncommon with initiation of opioid therapy or with dose titration
  - Generally, tolerance develops within 3-7 days (at the same opioid dose)
- Chronic OINV?

MJA 1999; 170: 68-71

JPSM 1991; 6(6): 389-393

J Pain Symptom Manage. 1991;6(7):428-430

Weissman DE. Fast Fact: Opioids and Nausea, 2015; https://www.mypcnow.org/fast-fact/opioids-and-nausea/

Current Pharmaceutical Design 2012; 18: 6043-6052

JAMA.2007;298(10):1196-1207

J Am Assoc Nurse Pract 2017; 29: 704-710

Risk Factors for Nausea and Vomiting

- **Female**
- **Adults <**50-60 **years old**
- Minimal to no alcohol consumption
- Anxiety
- History of nausea and vomiting
  - Motion-sickness
  - Pregnancy-related
- **Worsening performance status**
- **Gynecologic Cancer**
- **Opioid other than transdermal fentanyl**

Anxious patients are hyperalert to any type of threat.

Extreme anxiety would be expected to lower their threshold for the detection of toxins.

Bolded terms specific to opioid-induced N/V in cancer patients

Eur J Cancer 2011;47: 1682–1691

Critical Reviews in Oncology/Hematology 2009; 71: 214–221

Clinical Journal of Oncology Nursing 1999; 3(3): 113-119

Stern RM, Koch KL, Andrews PL, eds. *Nausea: Mechanisms and Management.* New York, New York: Oxford Press; 2011

Consequences of Nausea and Vomiting

- **Reduced quality of life***
- **Barrier to effective pain management***
- **Nutritional deterioration***
- Anorexia
- Increased pain intensity (wound dehiscence, esophageal tears)
- Dehydration
- Electrolyte imbalances
- Withdrawal from anticancer treatment
- **Decline in functional ability or performance status***
- Decline in mental status
- **Impact postoperative recovery***
- **Increased healthcare utilization***

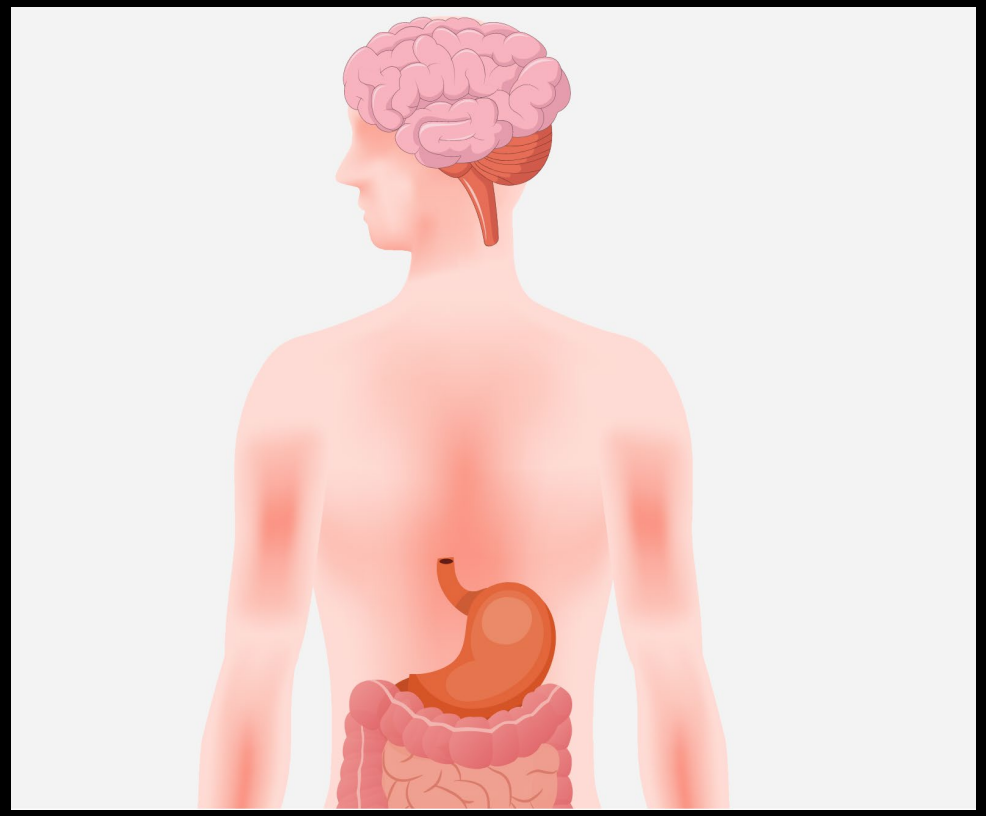
*** Specific to opioid-related N/V**

JAMA.2007;298(10):1196-1207

National Comprehensive Cancer Network (NCCN). NCCN Guideline Version 1.2021. Antiemesis. NCCN.org

Journal of the American Association of Nurse Practitioners 2017 (29): 704–710

Why do We Experience Nausea and Vomiting?

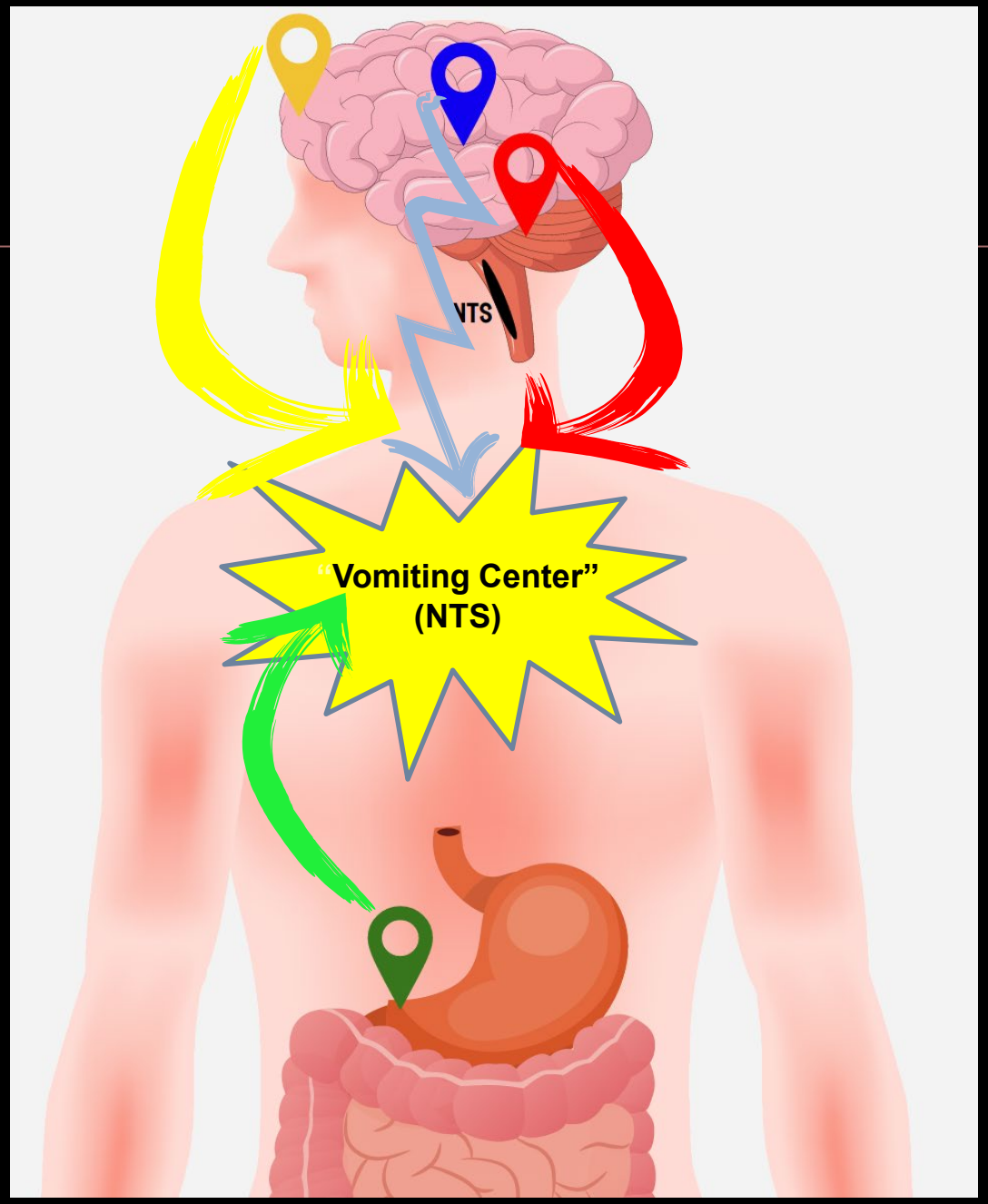


Koch KL, Hasler WL, eds. Nausea and Vomiting: Diagnosis and Treatment. Cham, Switzerland: Springer International Publishing; 2017.

- **To protect against ingesting toxic substances**
- **Warning signal of:**
  - danger in our environment related to motion or food
  - Damage/dysfunction of digestive tract or other organ systems
- **Levels of Defense:**
  - External cues from the senses (to evoke disgust and avoid toxic food)
  - Ingested toxins stimulate N/V to limit absorption
  - Toxins in bloodstream sensed by the brain
  - Memory of N/V associated with that substance

Hallenbeck, JL. *Palliative Care Perspectives.* NY, NY: Oxford Press, 2003.

4 Neural Pathways for Nausea and Vomiting

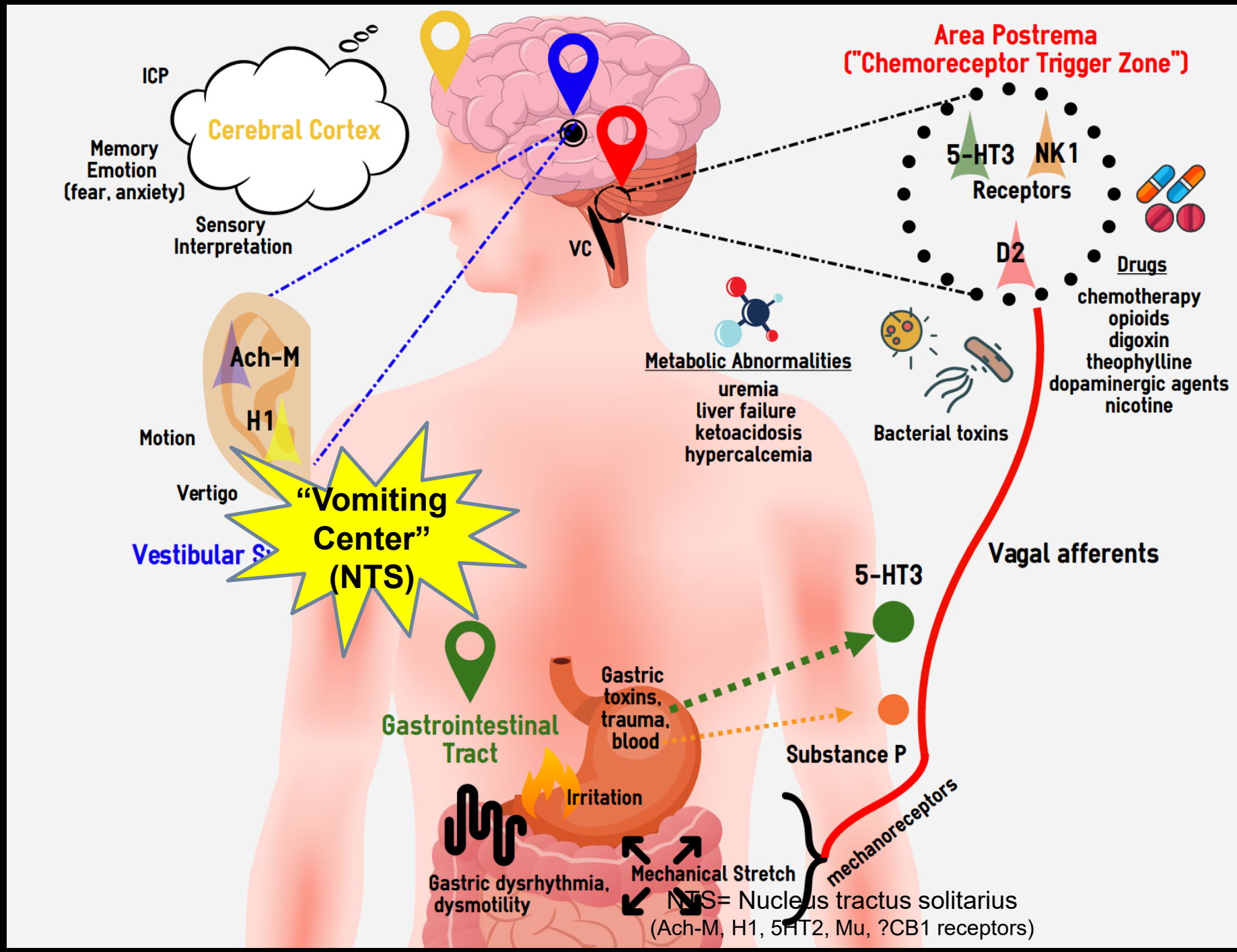


Cortical

Gastrointestinal

Vestibular

Chemical



JAMA.2007;298(10):1196

NEJM 2005; 352:817-82

Ann Palliat Med 2012; 1(2):137-142

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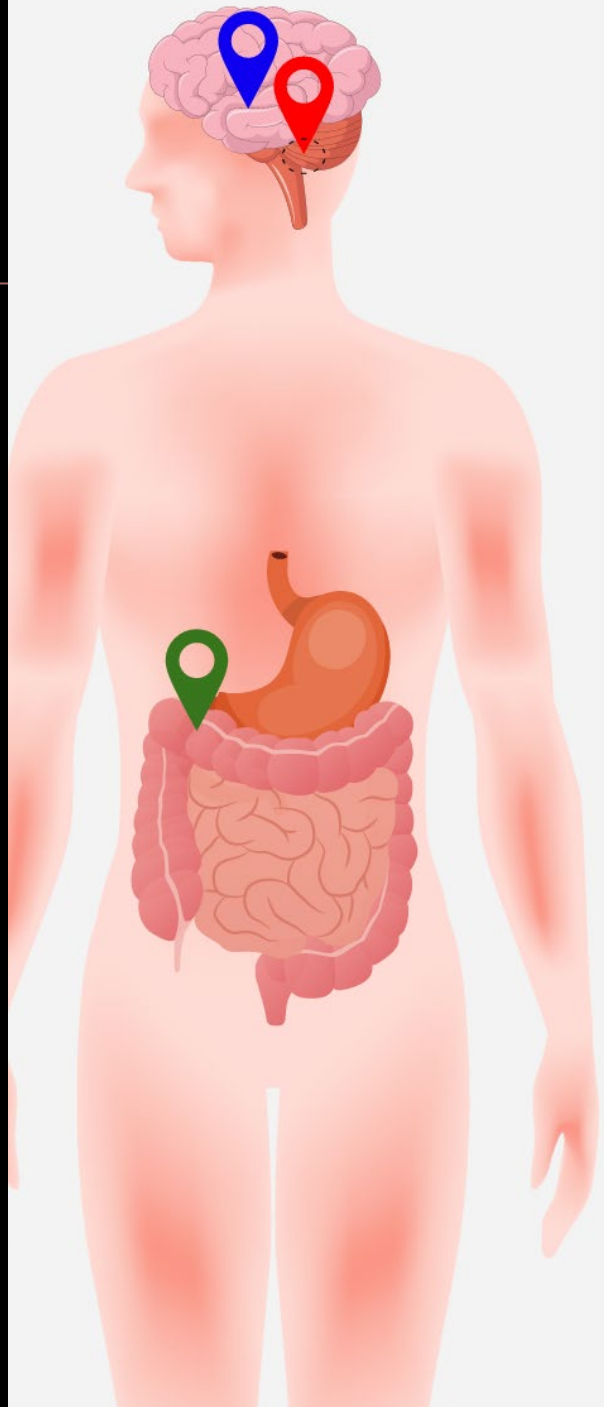
The Trifecta!

OINV

Vestibular Source

Chemical Source (CTZ)

Gastrointestinal Source



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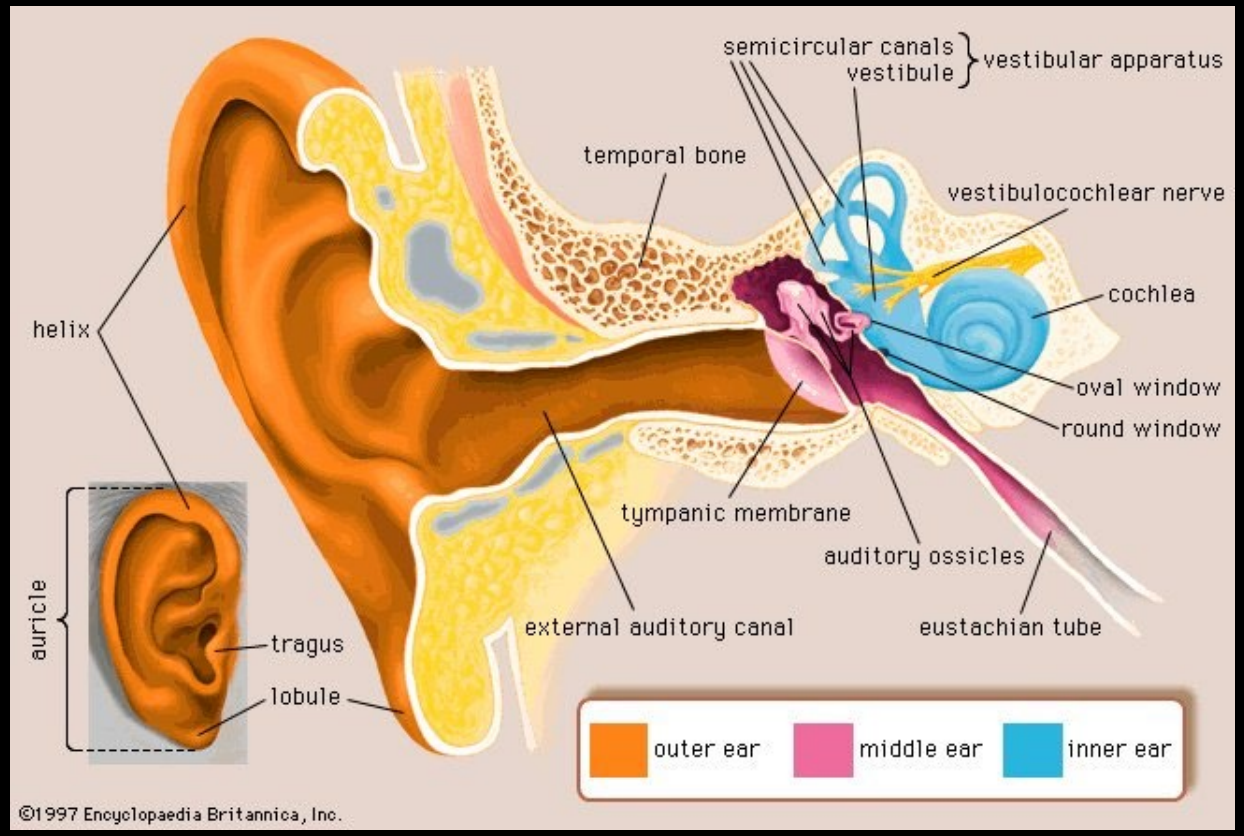
Current Pharmaceutical Design 2012; 18: 6043-6052

Opioid Stimulation of the Vestibular Apparatus



https://www.britannica.com/science/ear/images-videos#Images

- Opioids can directly stimulate the vestibular apparatus
  - non-auditory portion of the inner ear
  - Key role in sensation of motion and spatial orientation of the head
- Mechanism largely unknown
  - Activation of *mu opioid receptors (MOR) on the vestibular epithelium* → increase vestibular sensitivity
- Through ***cholinergic (Ach M)*** and ***histamine (H1)*** pathways, the vestibular apparatus provides direct input into the vomiting center

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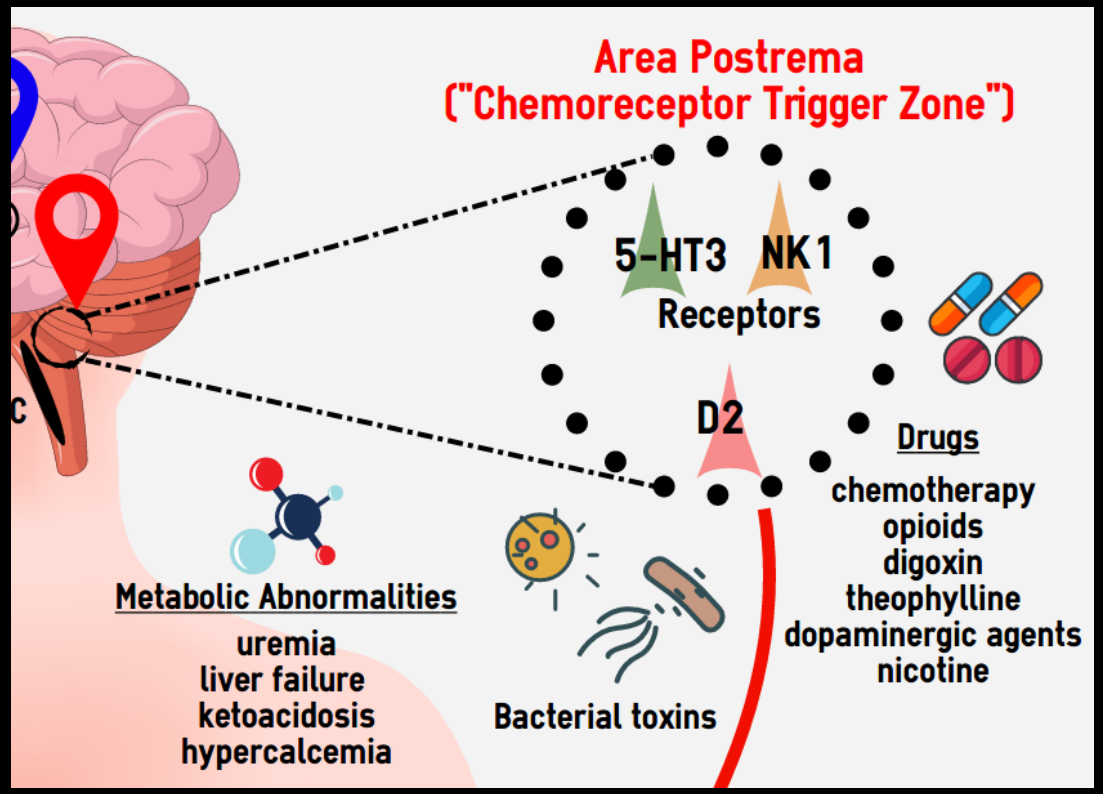
Current Pharmaceutical Design 2012; 18: 6043-6052
European Journal of Pharmacology 2014; 722: 67-78

Opioid Stimulation of the Chemoreceptor Trigger Zone (CTZ)

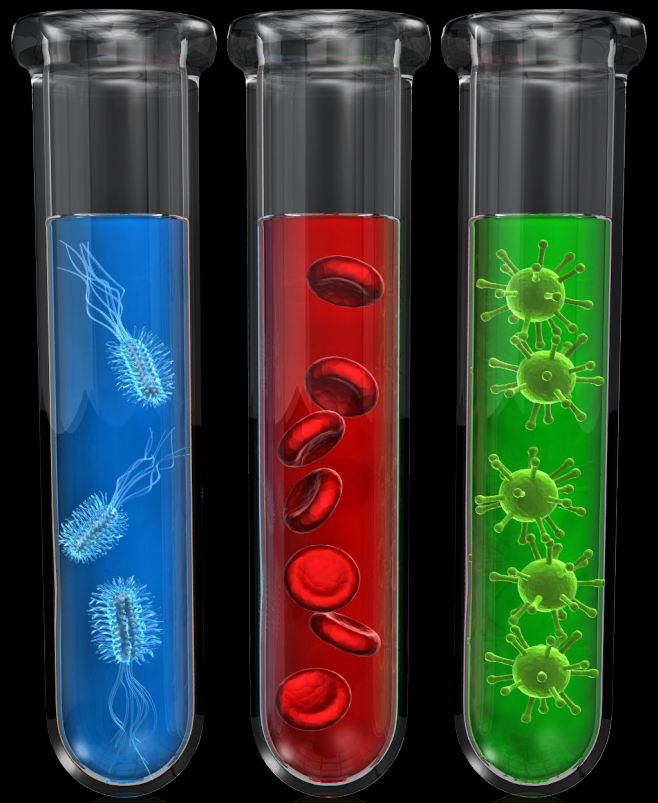


- The CTZ lies outside the blood brain barrier to detect potentially toxic substances in the blood
- Opioids directly stimulate the CTZ via:
  - Mu and delta opioid receptors
- Signaling to the vomiting center occurs via:
  - **The dopamine D2 receptor, *primarily***
  - Serotonin (5HT3) receptor

Hallenbeck, JL. *Palliative Care Perspectives.* NY, NY: Oxford Press, 2003.

Current Pharmaceutical Design 2012; 18: 6043-6052
European Journal of Pharmacology 2014; 722: 67-78

CTZ, the Peripheral "Sampling Port"



- The CTZ is sensitive to ***rising*** blood levels of substances
  - –Opioid initiation
  - –Opioid titration
- Emetogenic effects caused by CTZ stimulation often decrease ***rapidly***
  - –With repeated opioid administration
  - –Tolerance develops at a constant opioid dose (likely dependent on PK/PD characteristics and possibly choice of opioid?)

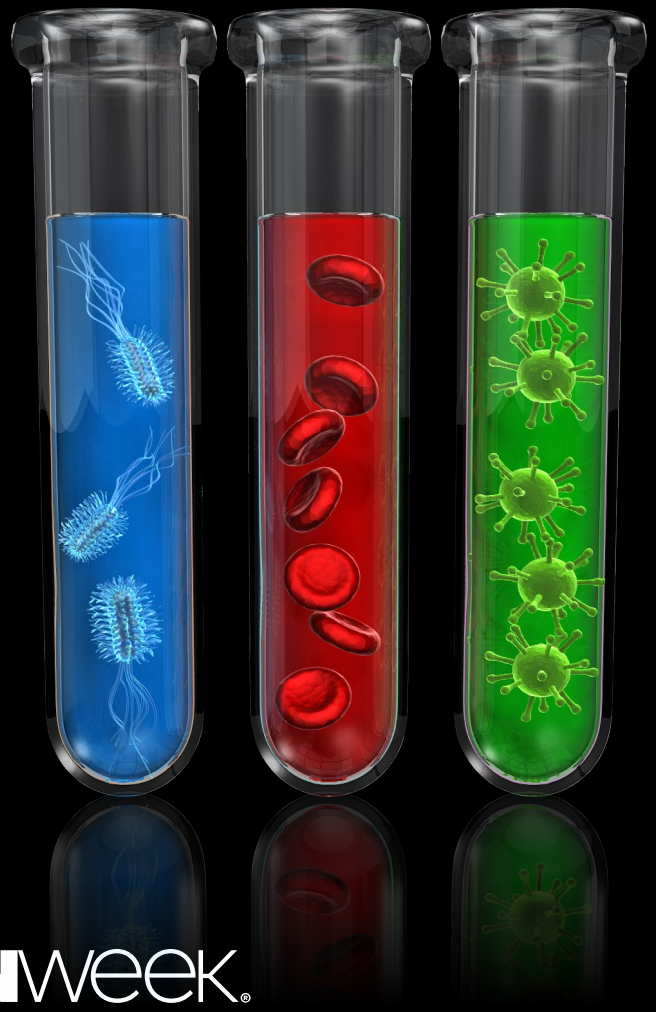
Current Pharmaceutical Design 2012; 18: 6043-6052

Pain Medicine 2009; 10(4): 654-662

Hallenbeck, JL. *Palliative Care Perspectives.* NY, NY: Oxford Press, 2003.

European Journal of Pharmacology 2014; 722: 67-78

CTZ and the Emetic Effect of Opioids



- ***It has been suggested that…*** low opioid doses activate MOR in the CTZ but "high doses" may suppress emesis by a ***central*** mechanism in the vomiting center
- Emetogenic potential of various opioids may then be related to ***lipid solubility*** of the opioid
  - Fast penetration in the vomiting center may reduce emetic effect
- Morphine is the ***least*** lipid soluble opioid and is often cited as **more emetogenic** vs other opioids
- Fentanyl is the ***highly*** lipid soluble, and transdermal fentanyl is sometimes suggested to be **less emetogenic**

J Pain Symptom Manag 1997;13:254–61.

Pain Medicine 2009; 10(4): 654-662

J Pharmacol Exp Ther 1977; 203: 222-230

Weissman DE. Fast Fact: Opioids and Nausea, 2015; https://www.mypcnow.org/fast-fact/opioids-and-nausea/

Can We Rank the Emetogenicity of Opioids?

- Limited research on the incidence of OINV with specific opioids
- From select studies in cancer patients:

Retrospective Study of Mod-Severe Nausea 72 hours after Oral Opioid Initiation	Nausea in Cross-Over Randomized Controlled Trials(RCT)	Nausea/Vomiting in Open-label Trial of Outpatients with Cancer on Long Term Opioid Therapy	Nausea and Vomiting in RCT of Cancer Patients on Weak Opioids
• Morphine ≈ Codeine > Oxycodone > Buprenorphine	• Morphine > oxycodone • Oral morphine > IV morphine PCA • Oral morphine sustained release > transdermal fentanyl (TDF)*	• Oral morphine > oral hydromorphone • Oral hydromorphone CR > transdermal fentanyl > transdermal buprenorphine**	• Tramadol > Codeine > Hydrocodone
J Pain Symptom Manage 1991; 6(7):428-430	*Clin Pharmacol Ther* 1990; 47: 639-646 *J Pain Symptom Manage* 1997; 13(5): 254-261	*Support Care Cancer* 2008; 16: 999-1009 *Eur J Pain* 2009: 13: 737-743	*J Palliat Med* 2007; 10: 56-60

*constipation also better with TDF

**for vomiting only; no difference in nausea

Chronic OINV

OINV ***may not*** always be a *short-lived* side effect:

- 3 year U.S. registry study of 233 patients on oxycodone CR (mean: 52.5 mg/day) for *non-cancer pain* (*Clin J Pain* 2007; 23: 287-299)
  - The most common adverse effects were constipation (15%) and nausea (12%)
  - Nausea greatest within the first 3 months
  - Small majority had persistence of nausea over years

- Prospective, open-labeled studies of outpatients with *cancer pain* on stable doses
  - 33% of patients on hydromorphone or morphine had nausea and emesis over 4-5 months (*Support Care Center* 2008; 16:999-1009)
  - 21% of patients taking transdermal buprenorphine, fentanyl, or controlled release hydromorphone had nausea/emesis despite long term therapy (*Eur J Pain* 2009: 13: 737-743)

Current Pharmaceutical Design 2012; 18: 6043-6052

European Journal of Pharmacology 2014; 722: 38-47

Is there a Concentration-Effect Relationship of Opioid Metabolites and Chronic Nausea?

YES, with chronic renal impairment

Chronic Nausea and Morphine-6-Glucuronide

Neil A. Hagen, MD, Kathleen M. Foley, MD, Daniel J. Cerbone, BS, Russell K. Portenoy, MD, and Charles E. Inturrisi, PhD
Pain Service and Department of Neurology (NAH, KMF, RKP), Memorial Sloan-Kettering Cancer Center, New York, New York; Department of Pharmacology (DJC, CEI), Cornell University Medical College, New York, New York

J Pain Symptom Manag 1991; 6: 125-128

Plasma Morphine and Glucuronide (M3G and M6G) Concentrations in Hospice Inpatients

Michael Ashby, FRACP, Beverley Fleming, RN, BN, Michael Wood, PhD, and Andrew Somogyi, PhD

J Pain Symptom Manage l997;14:157-167.

NO, without chronic renal impairment

Palliative Medicine 2003; **17:** 679–687

Routine drug monitoring of serum concentrations of morphine, morphine-3-glucuronide and morphine-6-glucuronide do not predict clinical observations in cancer patients

Palliative Medicine 2003; 17: 679-687

Opioid-induced effects on the Gastrointestinal (GI) System

Opioid receptors
- Ubiquitously distributed throughout the GI Tract

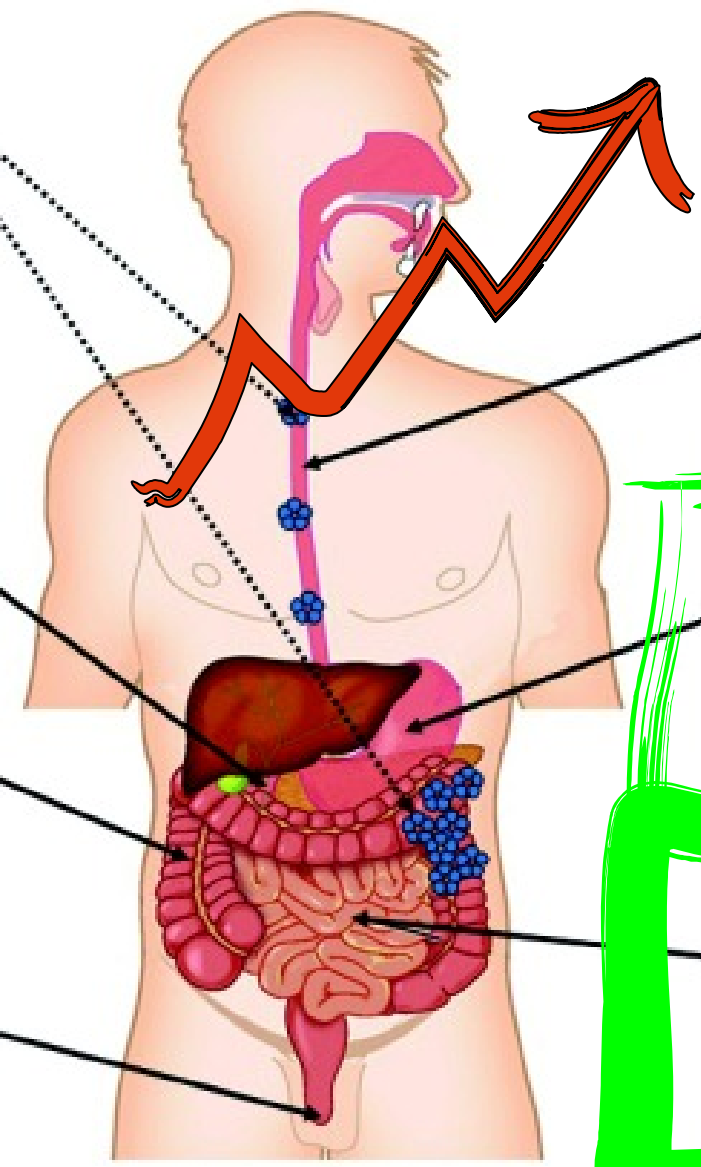
Gallbladder, sphincter of oddi & pancreas
- Sphincter of Oddi dysfunction
- Decreased pancreatic secretion of bicarbonate
- Maldigestion of lipids

Colon — **Constipation**
- Delayed transit
- Harder drier stools

- Constipation

Internal anal sphincter*
- Incomplete relaxation

- Straining
- Incomplete evacuation



Stimulation of Mechanoreceptors

Oesophagus
- Dysmotility
- Achalasia type picture

- Dysphagia

Stomach — **GI Emptying Time**
- Gastroparesis

- Early satiety
- Heartburn, reflux
- Nausea and vomiting

Small bowel — **Gut Distention**
- Dysmotility
- Fluid balance disturbance
- Small intestinal bacterial overgrowth

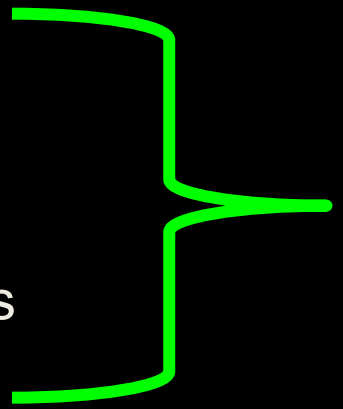
- Bloating and distension
- Postprandial discomfort

United European Gastroenterol J 2019; 7(1): 7–20 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6374652/

Abnormal GI Motility May Contribute to Chronic Nausea

Chronic opioid use results in:

- Uncoordinated bowel activity
  - repeated activation of mu opioid receptors in myenteric and submucosal plexi
- Reduced peristalsis
  - Decreasing GI secretions
  - Relaxing longitudinal muscle in the colon
  - Stimulating contractions of the circular muscles



Stools are hard and dry

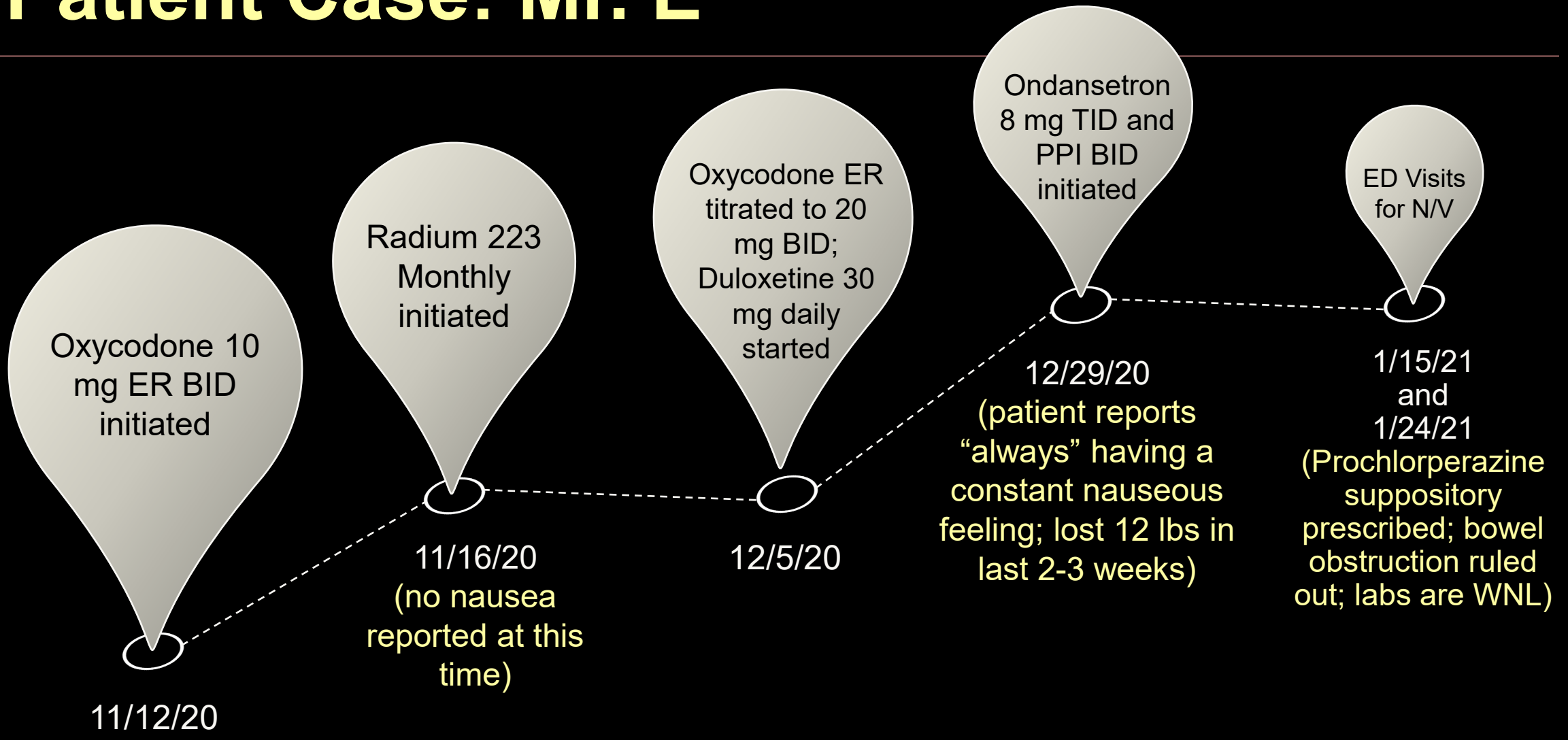
Bowel distention and cramping

J Pain Symptom Manage 2004;28:381–388
Pharmacotherapy 2002; 22(2):240-250
Current Pharmaceutical Design 2012; 18: 6043-6052
European Journal of Pharmacology 2014; 722: 67-78

Patient Case: Mr. E

- 78 year old male patient struggling with nausea, constipation and pain control
- His past medical history is significant for:
  - Metastatic prostate cancer (widespread bony mets to the pelvis, hip, sternum, lumbar spine, right scapula and left greater trochanter)
    - Received chemotherapy 2018-2019; palliative radiation to the left hip, L2 spine, and sacrum and right hip/proximal femur, completed 2020 (~6 months ago)
    - Radium 223 (radioisotope)-completed 3 of 6 doses (initiated 11/16/20 and given monthly)
  - Diabetes
  - Anxiety
  - Hypertension
  - GERD
  - Peripheral Vascular Disease
  - Hypothyroidism
  - Coronary Artery Disease
  - Recent history of C.diff and completion of po vancomycin

Patient Case: Mr. E



Patient Case: Mr. E

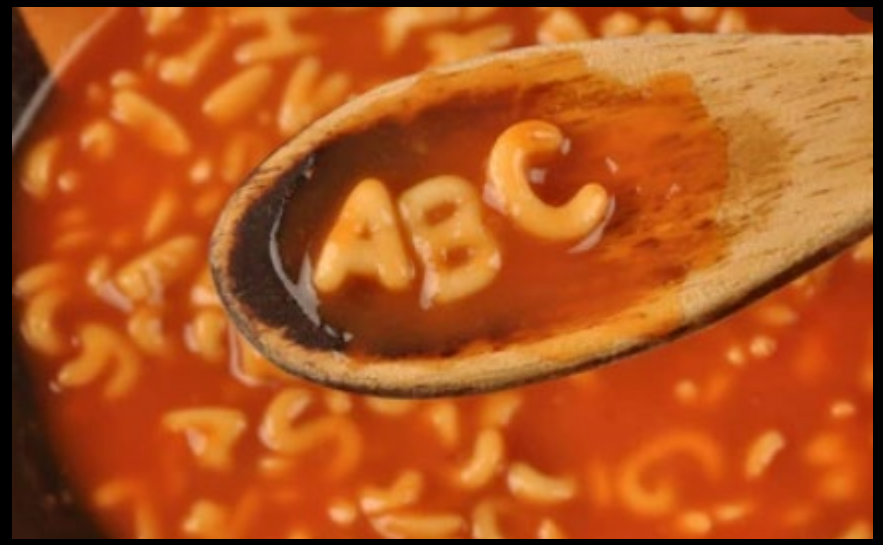
- Medications:
  - Ondansetron 8 mg TID
  - Prochlorperazine suppository 25 mg PR q 12h prn
  - Amlodipine 10 mg daily
  - Aspirin 81 mg daily
  - Atenolol 25 mg daily
  - Atorvastatin 80 mg daily
  - Leuprolide 22.5 mg IM q 3 months
  - Pantoprazole 40 mg BID
  - Omega 3 fatty acids 1000 mg daily
  - Glipizide 10 mg daily
  - Duloxetine 30 mg daily
    - Initiated on 11/30/20 for anxiety/depression
- Analgesics:
  - Hydrocodone/acetaminophen 5/325 mg, 1-2 tablets q 4 h prn
  - Oxycodone ER 20 mg BID
    - Initiated as ER 10 mg BID on 11/12/20
    - Increased to ER 20 mg BID on 11/30/20
  - Ibuprofen 200 mg, 2 tablets q 6 h prn

Patient Case: Mr. E

- Patient is seen in Supportive Oncology Clinic on 1/26/2021
  - Patients states that N/V and abdominal pain has worsened over the last 3 months
- Over the past 2 weeks, he had been self-reducing his medications
  - On 1/7, he reduced his opioid use by stopping use of prn hydrocodone/acetaminophen
  - On 1/21, he reduced his oxycodone ER 20 mg BID to once daily
  - On 1/24 following ED visit, he stopped ***all*** medications:
    - Except: ibuprofen, acetaminophen, and ondansetron (which he takes prior to the ibuprofen and APAP)
- Today, he states he feels his nausea better off his medications
- He is very anxious and tearful
- His pain is “ok” as long as he stays “still.” His primary concern is the N/V

Is OINV? Or CINV? RIE? PONV?

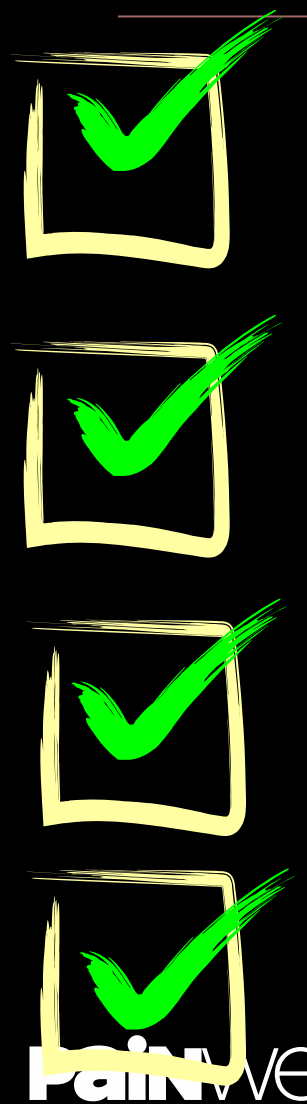
- OINV can be difficult to “tease” apart from other etiologies of nausea:
  - Chemotherapy-induced nausea and vomiting (CINV)
  - Radiation-induced nausea and vomiting (RIE)
  - Postoperative nausea and vomiting (PONV)
- In patients with palliative care or advanced cancer, etiology of N/V could be multifactorial:
  - Brain metastases
  - Bowel obstruction
  - Dehydration
  - Electrolyte abnormalities
  - Drug or opioid-induced
- So…OINV *alone* has not been robustly studied



Journal of Palliat 2019; 22(1): 90-96

Pharmacotherapy 2002; 22(2):240-250
European Journal of Pharmacology 2014; 722: 38-47

Assessment of Nausea and Vomiting in Cancer Patients



Onset	• When did it begin? How often does it occur in a day? • Does nausea always come before vomiting?
Aggravating and Ameliorating Factors	• What brings it on? (smells, food, medications, anxiety, ambulating) • What makes it better? (sleep, relaxation, vomiting, food, medications) • What makes it worse?
Quality	• Can you describe it? • Is it associated with *abdominal pain, bloating, early satiety, vertigo, headache, hiccups, or any other symptoms*?
Effect of Treatment	• What medications/doses/treatments are you using? • How effective are they? What side effects?

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Current Pharmaceutical Design 2012; 18: 6043-6052

Searching for "Clues"– Bowel Obstruction vs Gastroparesis

It sounds like…	It could be…
Abdominal PAIN • With descriptors: "crampy," "colicky," "getting worse" • AND **diminishing or absent bowel movements** -Large amounts of post-prandial bilious, watery emesis (with little to no odor) -Small volume emesis with foul **odor**	**A bowel obstruction** **Gastric or small bowel** obstruction (proximal obstruction) Distal small bowel or colon obstruction (distal obstruction)
Small volume emesis with "undigested" or "chewed" food • **PLUS post-prandial "bloating or fullness" and "early satiety"** • **AND presence of bowel movements**	**Impaired gastric emptying**

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Stern RM, eds. *Nausea: Mechanisms and Management.* New York, New York: Oxford Press; 2011
Koch KL, eds. Nausea and Vomiting: Diagnosis and Treatment. Cham, Switzerland: Springer International Publishing; 2017.
Eur J Cancer 2008; 44:1105-1115 *Clinical Interventions in Aging* 2011: 6: 243-259

Searching for "Clues"– Temporal Relationship with Food

It sounds like…	It could be…
Nausea upon awakening **before ingestion of food**… • With or without typical acid reflux symptoms (such as heartburn) • "Worse in the morning" and may be "relieved by breakfast"	**Mucosal inflammation (GERD, PUD, H. pylori infection, NSAIDs-induced, etc)**
Vomiting **right after** food is swallowed	**Anxiety-related or a cortical-learned response**
Vomiting **45 minutes to 1 hour after eating**	**Delayed gastric emptying or external compression of the stomach**
Vomiting **hours after eating**	**Intestinal or bowel involvement**

Koch KL, Hasler WL, eds. Nausea and Vomiting: Diagnosis and Treatment. Cham, Switzerland: Springer International Publishing; 2017.

EPEC-O. Nausea and vomiting.

Stern RM, Koch KL, Andrews PL, eds. *Nausea: Mechanisms and Management.* New York, New York: Oxford Press; 2011

Searching for "Clues"– Temporal Relationship with Food

It sounds like…	It could be…
Nausea upo **food**… • With or v (such as h • "Worse i breakfast'	on fection, tc)
Vomiting	al-learned
Vomiting	r external mach
Vomiting **hours after eating**	**Intestinal or bowel involvement**

Vomiting Relieves Nausea

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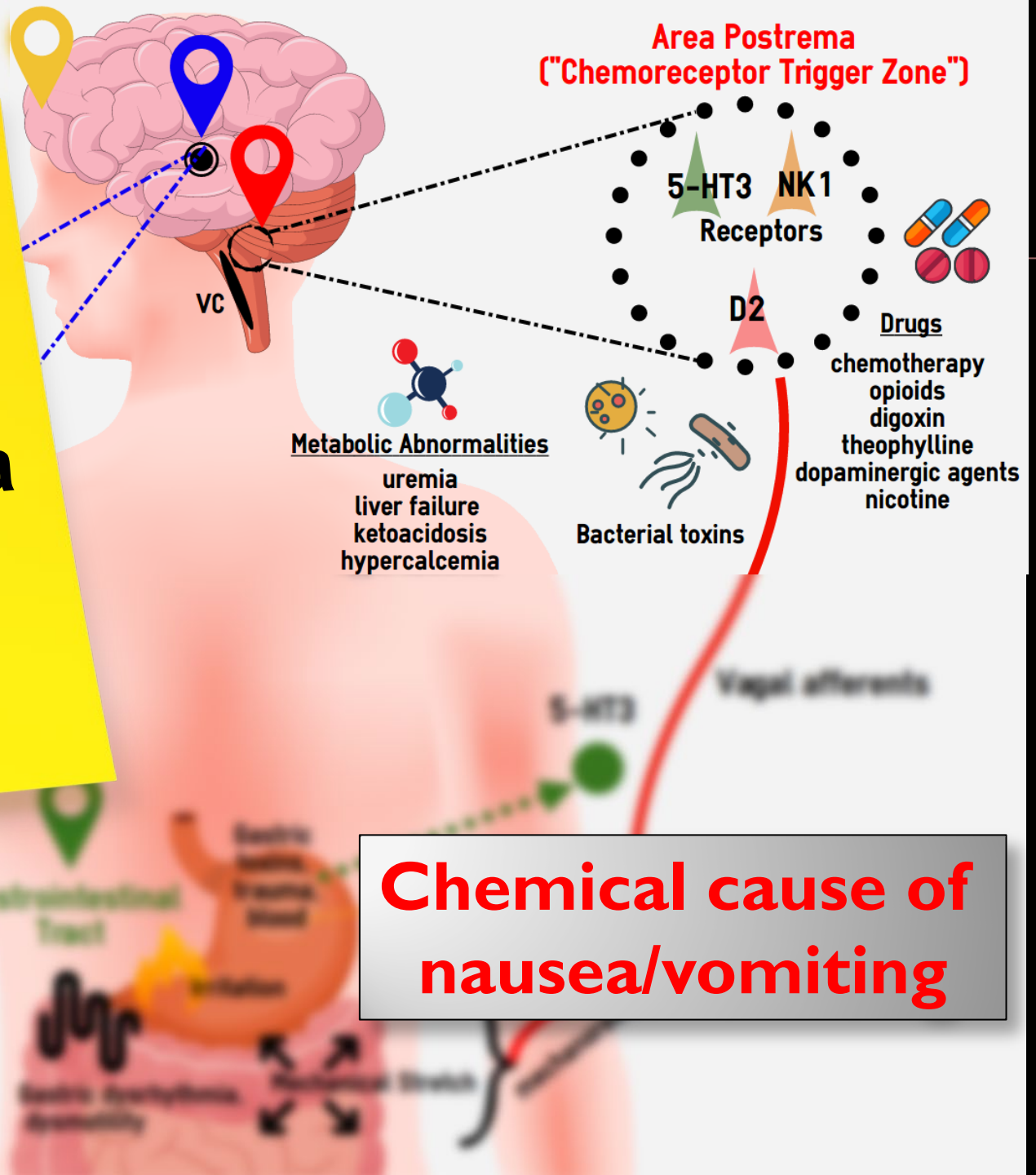
Koch KL, Hasler WL, eds. Nausea and Vomiting: Diagnosis and Treatment. Cham, Switzerland: Springer International Publishing; 2017.

EPEC-O. Nausea and vomiting.

Stern RM, Koch KL, Andrews PL, eds. *Nausea: Mechanisms and Management.* New York, New York: Oxford Press; 2011

CTZ notes

Persistent nausea not relieved by vomiting



Chemical cause of nausea/vomiting

Clinical Interventions in Aging 2011: 6: 243-259

N Engl J Med 2005; 352:817-82

JAMA.2007;298(10):1196-1207

Ann Palliat Med 2012;1(2):137-142

PainWe

Medications that Cause Nausea and Vomiting

Mechanism of N/V	Drug Class	
Stimulation of the CTZ	Acetylcholinesterase inhibitors Antibiotics *Chemotherapy* Dopaminergic Agents Digoxin	Nicotine Opioids Theophylline SSRIs/SNRIs
Gastric irritation and activation of vagal afferent nerves	Alcohol abuse Antibiotics Corticosteroids (also due to adrenal insufficiency)* Erythromycin Iron supplements	NSAIDs Potassium supplements Salicylates
Activation of 5-HT3 receptors on vagal afferent nerves	Antibiotics *Chemotherapy* SSRIs/SNRIs	
Gastric Stasis (may be cause of chronic nausea)	Anticholinergics Glucagon-like peptide (GLP)-1 agonists Opioids	

Curr Ther Res Clin Exp 2003; 64(4): 216–235
J Support Oncol 2013;11:8 –13
https://www.palliativedrugs.com/formulary/en/anti-emetics.html
Koch KL, Hasler WL, eds. Nausea and Vomiting: Diagnosis and Treatment. 2017.
Gastroenterology 2001; 120: 263-86

Which of the following are possible sources of Mr. E's nausea and vomiting?

A. GI mucosal irritation (**gastrointestinal source**)
B. Gastric dysmotility—delayed gastric emptying; or mechanical stretch—constipation (**gastrointestinal source**)
C. Metabolic abnormality (**chemical source**)
D. Opioid-induced nausea and vomiting **(gastrointestinal, chemical, vestibular source)**
E. Other drug-induced nausea and vomiting (**chemical or gastrointestinal source**)
F. Anxiety or other learned response (**cortical source**)
G. All of the above?

OINV: Management Strategies

Three Approaches to Managing OINV

In general, there are three approaches to opioid-induced nausea and vomiting:

1. Dose Adjustment

2. Opioid Switching

3. Changing the Opioid Route of Administration

3. Use of Antiemetics

J Palliat Med 2019; 22(1): 90-97

Dose Adjustment

- If the patient has acceptable pain relief but with OINV, opioid dose reduction may be tried to reduce OINV while maintaining analgesia
  - A 10-20% reduction in daily opioid dose may be considered.

- <u>Supporting Principles:</u>
  1. OINV appears to increase in a dose-dependent manner. This may be due to effects on the CTZ or GI tract.

JAMA.2007;298(10):1202
BMJ 1998;317 (7150):81
Weissman DE. Fast Fact: Opioids and Nausea, 2015; https://www.mypcnow.org/fast-fact/opioids-and-nausea/
Anesth Analg 2005; 101: 1343-1348
Anesth Analg 2020; 131: 411-448
Pharmacotherapy 2002; 22(2):240-250

Opioid Switching

- Opioid rotation may be considered in patients on stable opioid regimens experiencing OINV

- <u>Supporting Principles:</u>
  1. Given incomplete opioid cross-tolerance, opioid rotation may facilitate a lower dose of another opioid and potentially reduce incidence of OINV
  2. Specific opioids *may* be associated with a lower incidence of OINV

Pharmacotherapy 2002; 22(2):240-250

Opioid Switching

- **Morphine → Oxycodone**
  - *Clin Pharmacol Ther* 1990; 47: 639-646: Double-blind, crossover RCT of 20 patients with cancer pain with morphine and oxycodone given orally and as an intravenous PCA for 48 hours (and then switched). *Greater OINV with morphine*
  - *Pain* 1997; 73: 37-45: Double-blind, crossover RCT of oxycodone CR and morphine SR in 45 patients with cancer pain. *Greater OINV with morphine.*
  - *J Pain Symptom Manage* 1996; 12: 182-189: Prospective study of 13 patients with morphine-induced adverse effects had *improvement in OINV with oxycodone.*

- **Morphine or Oxycodone → Methadone**
  - *Eur J Cancer* 2011; 47: 2463-2470: randomized phase II study *suggests improvement of OINV* with three day switch method to methadone

- **Transdermal Fentanyl → Methadone**
  - *J Clin Oncol* 2005; 23: 5229-5234: Prospective study of 18 patients with *improvement of OINV with switch to methadone*

Palliative Medicine 2011; 25(5): 442-453

J Palliat Med 2019; 22(1): 90-97

Opioid Switching in Cancer Patients with OINV: Recommendations from Systematic Reviews

J Palliat Med 2019; 22(1): 90-97	*Palliative Medicine* 2011; 25(5): 442-453
Morphine→Oxycodone (*weak recommendation*)	Morphine→Oxycodone or Hydromorphone (*weak recommendation*)
Tramadol→Codeine or Hydrocodone (*weak recommendation*)	Transdermal Fentanyl→Methadone (*weak recommendation*)
Morphine or oxycodone→methadone using three-day switch method (*weak recommendation*)	

Changing the Route of Administration

- Changing the route of administration of the same opioid may partially alleviate symptoms of OINV

- Supporting Principles:
  1. Oral opioids theoretically may have a local effect on the GI tract, and therefore parenteral (intravenous or subcutaneous) or transdermal opioids may reduce symptoms of OINV
  2. Due to first pass metabolism, oral morphine may produce greater plasma concentrations of metabolites (M6G) versus parenteral administration.

J Pain Symptom Manage 1997;14:157-167 *Eur J Clin Pharmacol* 1990; 38:121-124 *Pharmacotherapy* 2002; 22(2):240-250

Changing the route of administration

- **Oral→ Subcutaneous (SC)**
  - *Palliat Med* 1991; 5: 323-329: Prospective study of 164 patients with advanced cancer, changing from *oral morphine to intermittent (q4h) SC dosing reduced OINV*
- **Intermittent SC → Continuous SC**
  - *Pain* 1989; 36: 169-176: Prospective controlled study of 36 inpatients with severe nausea or drowsiness on intermittent oral or subcutaneous (SC) morphine had *improvement in OINV with continuous subcutaneous morphine*
- **Oral → Transdermal**
  - *Eur J Pain* 2009: 13: 737-743: Open-label trial of outpatients with cancer; *less emesis observed with transdermal products (buprenorphine and fentanyl) than controlled release oral hydromorphone*
- **Oral → Rectal**
  - *J Clin Oncol* 1995; 13: 1004-1008: Double-blind, cross-over RCT of 34 patients with cancer. *OINV was not different based on route of administration of morphine.*
- **SC → Rectal**
  - *J Clin Oncol* 1995; 13: 1520-1527: Double blind, cross-over RCT of 30 patients with cancer pain. *OINV was not different based on route of administration of morphine.*

Palliative Medicine 2011; 25(5): 442-453

J Palliat Med 2019; 22(1): 90-97

Changing Route of Opioid Administration: Recommendations from Systematic Reviews

J Palliat Med 2019; 22(1): 90-97	*Palliative Medicine* 2011; 25(5): 442-453
No recommendations could be made based on available literature	Oral morphine→ SC morphine (*weak recommendation*)

Use of Antiemetics

- Treatment of OINV or prophylaxis should be based on knowledge of neural pathways for OINV and other possible etiologies of N/V.

- <u>Supporting Principles:</u>
    1. Limited randomized controlled studies exist to guide antiemetic selection. Dopamine D2 receptor may be most important target for OINV for acute OINV whereas abnormal GI motility/constipation may be the target for chronic OINV.

    2. Prophylaxis may be considered in patients with a history of OINV or in patients with significant risk factors for OINV.
        1. Risk factors (i.e. such as in PONV) and history of OINV may guide decision to use antiemetic prophylaxis.
        2. Match duration of prophylaxis to suspected duration of OINV (2-3 days after opioid initiation or titration)

J Pain Symptom Manage 1997;14:157-167 *Eur J Clin Pharmacol* 1990; 38:121-124 *Pharmacotherapy* 2002; 22(2):240-250

Antiemetic Selection for OINV: Recommendations from Systematic Reviews

J Palliat Med 2019; 22(1): 90-97	*Palliative Medicine* 2011; 25(5): 442-453
"None of these studies provided sufficient evidence to formulate any recommendations."	"Current evidence is too limited to give evidence-based recommendations for the use of antiemetics for opioid-induced nausea or vomiting in cancer patients." "Recommendations must…be based upon knowledge about etiologies for nausea/vomiting and expert opinion."

Antiemetic Selection for OINV: Mechanistic Based Approach

"Clues" from Assessment	*Possible Source of OINV*	*Drug Action Needed*	*Antiemetic Selection*
OINV with opioid initiation or dose increases **(*Acute OINV*)**	Direct stimulation of the CTZ with rising opioid levels (chemical source)	D2 blockade in the CTZ (preferentially)	*Butyrophenones* (Haloperidol) *Phenothiazines* (Prochlorperazine, Promethazine) *Atypical Antipsychotics* (Olanzapine, Risperidone) *Prokinetic Agents* (metoclopramide)*
		5HT3 blockade in the CTZ (in refractory cases or PONV prevention)	*Serotonin antagonists* (ondansetron, dolasetron, granisetron, palonesteron)

Pharmacotherapy 2002; 22(2):240-250
European Journal of Pharmacology 2014; 722: 67-78

* At higher doses?

Current Pharmaceutical Design 2012; 18: 6043-6052

Antiemetic	Dose (lower end for older adults)	Receptor Affinities (lower number= tighter binding)				Side Effects
		D2	5HT3	H1	Ach-M	
Prokinetics						
Metoclopramide	5-10 mg PO/IV/SC QID	++ (270)	+ (319)	- (1100)	- (10000)	Restlessness, drowsy, involuntary movement
Phenothiazines						
Promethazine	12.5-25 mg PO/ 25 mg PR q6h	++ (240)	- (-)	++++ (3)	+++ (21)	Sedation, anticholinergic SE, orthostasis
Prochlorperazine	2.5-10 mg IV/PO, 25 mg PR 3-4 x/day	+++ (15)	- (-)	++ (100)	+ (2100)	Sedation, orthostasis, involuntary movement
Atypical Antipsychotic						
Olanzapine	2.5-10 mg PO at bedtime	+++ (30)	++ (57)	+++ (7)	++ (76)	Sedation, orthostasis, anticholinergic & metabolic SE, ↑appetite
Butyrophenones						
Haloperidol	0.5-2 mg TID SC/IV = ½ PO	**++++ (4.2)**	- (-)	- (1600)	- (10000)	EPS, ↑QTc, ↑ mortality in dementia patients

NCCN Guideline Version 2.2021. Palliative Care. NCCN.org

Lancet 1982; 1 (8273): 658-659 *JAMA*.2007;298(10):1202 https://kidbdev.med.unc.edu/databases/pdsp.php

Palliative Care Perspectives,2003. *Clinical Inter in Aging* 2011: 6: 249 *Drugs* 1992; 43 (3):295-315

Antiemetic	Dose (lower end for older adults)	Receptor Affinities (lower number= tighter binding)				Side effects
		D2	5HT3	H1	Ach-M	
5-HT3 Antagonists						
Ondansetron	4-8 mg PO/IV q6-8 h	- (-)	++++ (4)	- (10000)	- (10000)	Constipation, headache, ↑QTc
Agents for Vestibular Source						
Scopolamine	1.5 mg TD q 72h	- (10000)	- (-)	- (10000)	++++ (0.8)	Anticholinergic SE, delirium
Diphenhydramine	25-50 mg PO/IV/SC q 6h	- (10000)	- (-)	+++ (17)	++ (120)	Anticholinergic SE, delirium
Steroids						
Dexamethasone	2-4 mg PO/IV QAM-BID (↑ if ↑ ICP or brain mets)	- (-)	- (-)	- (-)	- (-)	Insomnia, anxiety, dyspepsia, ↑BG/BP, edema, appetite
Cannabinoids						
Dronabinol	2.5 mg PO BID (max 20 mg/d)	- (-)	- (-)	- (-)	- (-)	Dysphoria, hallucinations, delirium drowsiness

JAMA.2007;298(10):1196-1207
Palliative Care. NCCN.org
https://kidbdev.med.unc.edu/databases/pdsp.php
Tucker et al. *Managing Nonpain Symptoms*. AAHPM: Glenview, IL; 2012
Lancet 1982; 1 (8273): 658-659
Drugs 1992; 43 (3):295-315

Antiemetic Selection for OINV: Mechanistic Based Approach

"Clues" from Assessment	*Possible Source of OINV*	*Drug Action Needed*	*Antiemetic Selection*
OINV stimulated by motion or rapid head movement, or dehydration May complain of poor balance, vertigo/dizziness, or ear ringing *(Acute OINV when opioids initiated or when patients are ambulating)*	Direct stimulation of the vestibular apparatus (vestibular source)	H1 blockade in the vestibular apparatus or vomiting center	*1st generation antihistamines* (Diphenhydramine, Meclizine, Hydroxyzine) *Antiemetics with activity vs* H1 (Promethazine, Olanzapine)
		Ach-M blockade in the vestibular apparatus or vomiting center	*Anticholinergics* (Scopolamine, Meclizine)

Pain Medicine 2009; 10(4): 654-662 *J Pain Symptom Manage* 1991; 6: 389-393 *Clin Geriatr Med* 1996; 12: 313-327
Hallenbeck, JL. *Palliative Care Perspectives. NY, NY:* Oxford Press, 2003. *Pharmacotherapy* 2002; 22(2):240-250 *Current Pharmaceutical Design* 2012; 18: 6043-6052

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Butyrophenones						
Haloperidol	0.5-2 mg TID SC/IV = ½ PO	**++++ (4.2)**	- (-)	- (1600)	- (10000)	EPS, ↑QTc, ↑ death in dementia patients

NCCN Guideline Version 2.2021. Palliative Care. NCCN.org
Lancet 1982; 1 (8273): 658-659 *JAMA*.2007;298(10):1202 https://kidbdev.med.unc.edu/databases/pdsp.php
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Agents for Vestibular Source						
Scopolamine	1.5 mg TD q 72h	- (10000)	- (-)	- (10000)	++++ (0.8)	Anticholinergic SE, delirium, constipation
Diphenhydramine	25-50 mg PO/IV/SC q 6h	- (10000)	- (-)	+++ (17)	++ (120)	Anticholinergic SE, delirium, constipation
Steroids						
Dexamethasone	2-4 mg PO/IV QAM-BID (↑ if ↑ ICP or brain mets)	- (-)	- (-)	- (-)	- (-)	Insomnia, anxiety, dyspepsia, ↑BG/BP, edema, appetite
Cannabinoids						
Dronabinol	2.5 mg PO BID (max 20 mg/d)	- (-)	- (-)	- (-)	- (-)	Dysphoria, hallucinations, delirium drowsiness

Non-sedating antihistamines = not effective

JAMA.2007;298(10):1196-1207
Palliative Care. NCCN.org
https://kidbdev.med.unc.edu/databases/pdsp.php
Tucker et al. *Managing Nonpain Symptoms*. AAHPM: Glenview, IL; 2012
Lancet 1982; 1 (8273): 658-659
Drugs 1992; 43 (3):295-315

Antiemetic Selection for OINV: Mechanistic Based Approach

"Clues" from Assessment	Possible Source of OINV (gastrointestinal source)	Drug Action Needed	Antiemetic Selection
Chronic nausea ~ 2 weeks or more of stable opioid doses	Opioid-induced gastroparesis and small bowel dysmotility	Regulation of upper bowel dysmotility; 5HT4 stimulation of GI tract	*Prokinetic Agent* (Metoclopramide)
Post-prandial bloating, early satiety, or small volume emesis 45 min-1 hour after a meal (suggestive of gastric stasis/delayed gastric emptying)	Gut distention with luminal contents leading to release of serotonin from mucosal enterochromaffin cells	5HT3 blockade in GI tract	*Serotonin antagonists* (ondansetron, *metoclopramide)*
	Opioid related effects on the colon, small bowel, and internal anal sphincter	Peristalsis-induction	*Stimulant Laxatives* (Senna, Bisacodyl) *Osmotic Laxatives* (polyethylene glycol)
Constipation, hard or dry stools		Peripheral mu opioid receptor antagonism	PAMORAs

Pain Medicine 2009; 10(4): 654-662 *J Pain Symptom Manage* 1991; 6: 389-393 *Clin Geriatr Med* 1996; 12: 313-327
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Antiemetic	Dose (lower end for older adults)	Receptor Affinities (lower number= tighter binding)				Side effects
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5-HT3 Antagonists						
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Agents for Vestibular Source						
Scopolamine	1.5 mg TD q 72h	- (10000)	- (-)	- (10000)	++++ (0.8)	Anticholinergic SE, delirium, constipation
Diphenhydramine	25-50 mg PO/IV/SC q 6h	- (10000)	- (-)	+++ (17)	++ (120)	Anticholinergic SE, delirium, constipation
Steroids						
Dexamethasone	2-4 mg PO/IV QAM-BID (↑ if ↑ ICP or brain mets)	- (-)	- (-)	- (-)	- (-)	Insomnia, anxiety, dyspepsia, ↑BG/BP, edema, appetite
Cannabinoids						
Dronabinol	2.5 mg PO BID (max 20 mg/d)	- (-)	- (-)	- (-)	- (-)	Dysphoria, hallucinations, delirium drowsiness

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Drugs 1992; 43 (3):295-315

Advanced Cancer Patients with No Definite Etiology

- Systematic review of 93 studies of cancer patients with nausea unrelated to chemotherapy, radiation
  - Author's conclusion: "the best evidence for an antiemetic drug exists for metoclopramide"
  - **"very limited literature"**

- **NCCN Palliative care guideline, 2021 for non-specific N/V:**
  - Dopamine receptor antagonist:
    - Prochlorperazine, haloperidol, metoclopramide, olanzapine
  - (or 5-HT3 receptor antagonist)
  - Titrate dopamine antagonist to maximum effect or tolerance
  - For continued N/V, add additional agents

NCCN Guideline Version 2.2021. Palliative Care. NCCN.org

J Pain Symptom Manage 2010;39:756-767.

Annals of Oncology 2016; 27 (Supplement 5): v119-v133

Clinical Interventions in Aging 2011: 6: 243-259

PAINWEEK

What do you think about multimodal therapy with Scopolamine and Metoclopramide?

Metoclopramide binds to 5HT4 receptors which releases **acetylcholine** from enteric neurons in the gut to stimulate motility.

So… **anticholinergics** reduce the prokinetic effect of metoclopramide

Let's test out our skills…

Back to Mr. E

What changes should we make to Mr. E's medication regimen to reduce OINV?

A. Restart oxycodone, but at a lower dose
B. Rotate oxycodone to an alternative opioid (i.e. transdermal opioid or methadone)
C. Initiate dopamine antagonist for 2-3 days scheduled and then prn
D. Initiate metoclopramide
E. Start stimulant laxative regimen
F. Assess for vestibular symptoms
G. Any combination of the above?

Patient Case: Mr. E

- At 1/26/2021 clinic visit:
  - Oxycodone was discontinued
  - Ibuprofen was discontinued
  - Transdermal Fentanyl 12.5 mcg/hr q 72 h was initiated
  - Senna 1 tab BID was initiated
  - Haloperidol 1 mg po QID prn nausea/vomiting was initiated (as first line)
  - Ondansetron 8 mg po TID continued as prn (as second line)
  - Prochlorperazine suppositories were discontinued
  - Pantoprazole 40 mg po BID continued
  - Decision to discontinue Radium

Patient Case: Mr. E

- On 2/5/21:
  - Admitted to the hospital with lethargy, worsening nausea, and suspected to have aspiration pneumonia
  - Until this time, the patient was able to manage his nausea with small meals, small sips of fluids throughout the day and antiemetic therapy (haloperidol, ondansetron, and addition of prn lorazepam)
  - During the hospitalization, scopolamine patch was started with some improvement suggested. However, patient had decrease in alertness and scopolamine was discontinued.
  - Patient went home with hospice

Antiemetics for Refractory OINV?

Clinical Note

Transdermal Scopolamine Use in the Control of Narcotic-Induced Nausea

Frank D. Ferris, MD, Ian G. Kerr, MD, Marcia Sone, RN, and Mary Marcuzzi, BScPhm

Toronto-Bayview Regional Cancer Centre, Sunnybrook Medical Centre, and the University of Toronto, Ontario, Canada

J Pain Symptom Manage 1991; 6: 389-393

Conclusion…

- OINV can have detrimental consequences, including suboptimal pain management, functional decline, and reduced quality of life
- Little guidance is available for the management of acute and chronic N/V outside of CINV, radiation-induced nausea, PONV, and malignant bowel obstruction
- The best practice for opioid switching, changing route of administration, and optimal antiemetic are not well defined, and clinicians should select the strategy most appropriate for the individual patient
- Etiology-based (or mechanistic) approach may be the most reasonable management strategy for antiemetic selection:
  - Underlying causes, including drug-related etiologies, are investigated and in some cases, may be resolved without drug therapy
  - Antiemetic therapies used are the most potent antagonist vs suspected receptors in an individual patient's OINV.