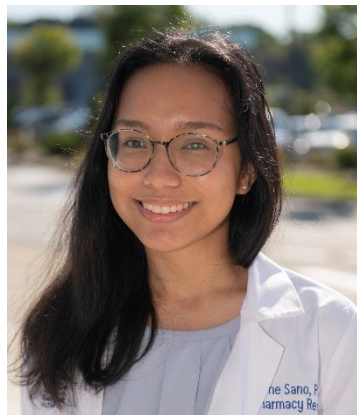


Management of Post-operative Nausea & Vomiting in Adults Using ERAS Protocols

A presentation for HealthTrust Members
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Speaker Disclosures

- There are no financial interests to disclose for myself or the preceptor in the last 24 months.
- This presentation may include the mention of brand products or drugs. All content is for educational purposes only.
- Certain medications may not have an FDA-approved indication for their use in post-operative nausea & vomiting. These medications will be labeled with “off-label” under indications.

Objectives

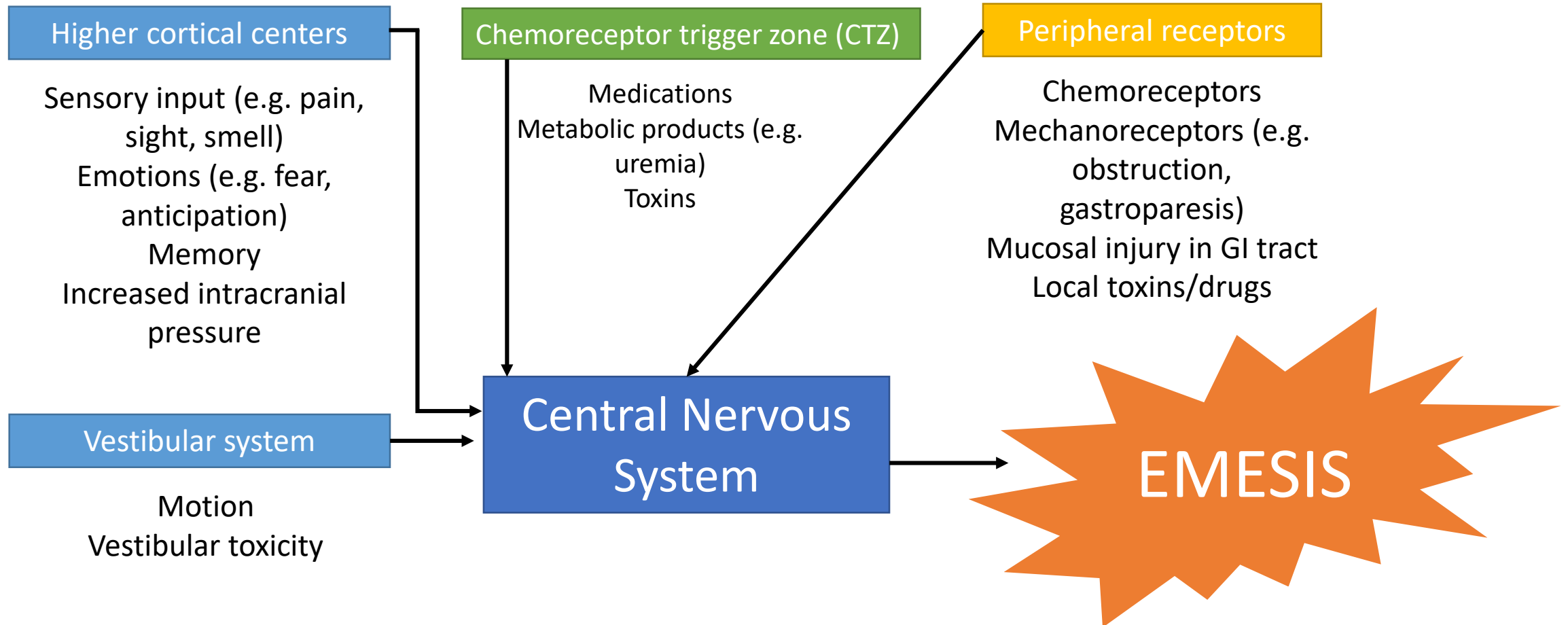
For Pharmacists & Pharmacy Technicians

- Recall the definition of enhanced recovery after surgery (ERAS)
- Recognize medications used in the pharmacologic management of post-operative nausea and vomiting (PONV) and indications for use
- Identify evidence-based practice guidelines for the management of PONV

Post-operative nausea & vomiting (PONV)

- ~30% of all surgical patients experience PONV
 - ~80% of high-risk surgical patients
- Associated with poor patient outcomes
 - Longer stay in Post-Anesthesia Care Unit (PACU)
 - Higher incidence of hospital admission
 - Increased healthcare costs
 - Patient dissatisfaction
- Pathophysiology = multifactorial

Pathophysiology of nausea & vomiting



Major receptors of nausea & vomiting

Serotonin
(5-HT₃)
receptors

Substance P NK-
1 receptors

Dopamine D_{2/3}
receptors

Acetylcholine
receptors

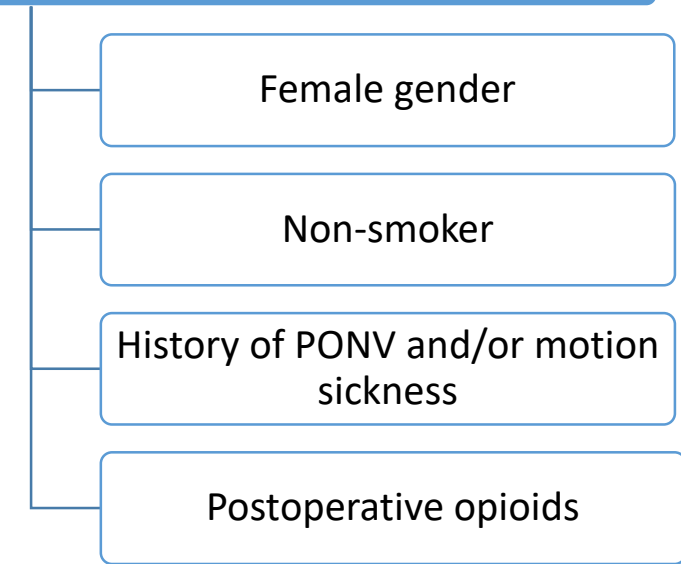
Histamine-1
receptors

Opiate mu,
kappa, and
delta receptors

Risk factor stratification

- Risk scores intended to predict incidence of PONV and guide choice in prophylactic management
- Each risk factor = 1 point
 - Risk factor corresponds to percentage risk of PONV
 - Score of 0 = 10%
 - 1 = 20%
 - 2 = 40%
 - 3 = 60%
 - 4 = 80%
- Additional risk factors: younger age, surgery type, opioid analgesia

Simplified Apfel Score



Apfel Scoring

Points	Scoring
0 – 1	Low
2	Moderate
3 +	High

Guidance for choice of anti-emetic prophylaxis

Risk stratification	Management
Low-moderate risk (0-2 risk factors)	2 antiemetics
High risk (3+ factors)	3-4 antiemetics

- Additional strategies for risk mitigation
 - Minimize use of nitrous oxide, volatile anesthetics, high-dose neostigmine
 - Opioid sparing & multimodal approaches to analgesia
 - Regional anesthesia

Sources: Smith CA, et al. *J Perianesth Nurs*. 2016;31(2):158-71.

Gan TJ, et al. *Anesth Analg*. 2020;131(3):411-48.

Pt case: Nida Santiago

- Nida is a 29-year-old female that is scheduled for a bariatric surgical procedure.
- Past medical history: Exercise-induced asthma
- Surgical history: None
- Social history: 1-2 glasses of wine on weekends, denies tobacco use or recreational substances
- Medications: Albuterol inhaler as needed, multivitamin

Assessment question: Based on this patient's Apfel score, how many prophylactic anti-emetics should be prescribed to Nida?

- A. 1
- B. 2
- C. 3
- D. 4
- E. 0

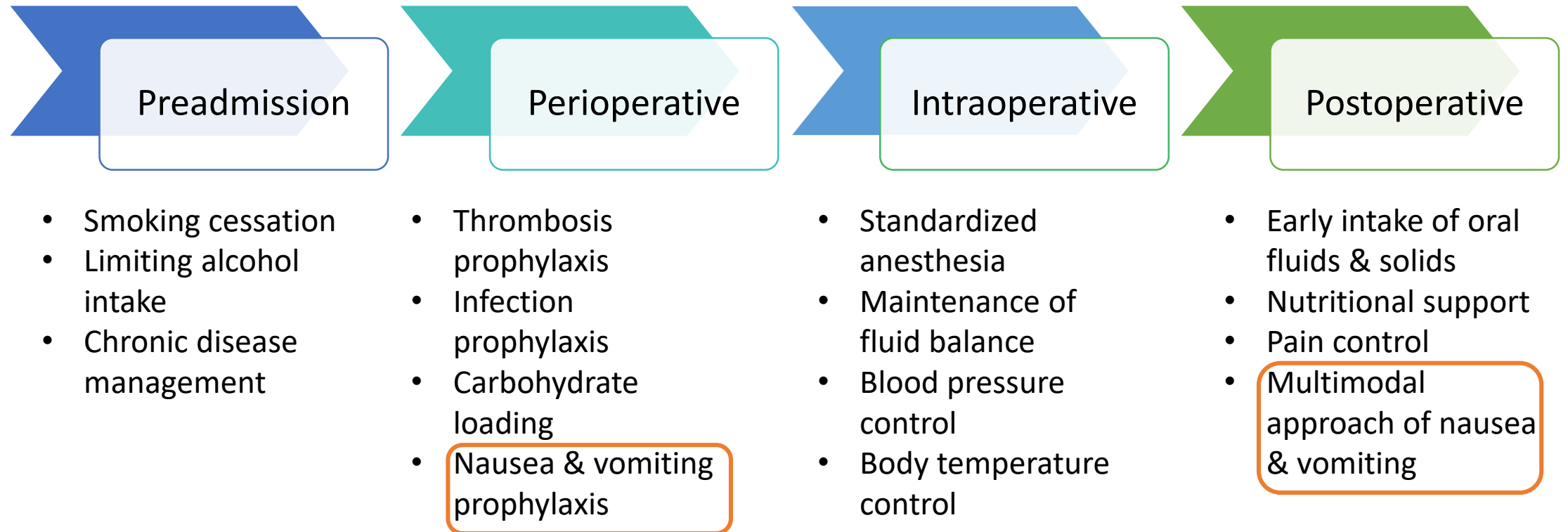
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- A. 1
- **B. 2**
- C. 3
- D. 4
- E. 0

Enhanced Recovery After Surgery (ERAS)

- Set of interventions designed to help body mitigate and cope with stress of surgery
 - Accelerates recovery
 - Multi-modal & multi-disciplinary
- Benefits:
 - Reduces risk of postoperative complications
 - Reduces hospital length of stay & rates of readmissions
 - Reduces costs
 - Improves patient satisfaction

ERAS Elements



Benefits of ERAS

Study	Study findings
Das-Neves-Pereira JC, et al. “Fast-track rehabilitation for lung cancer lobectomy: a five-year experience”	Reduction in post-operative complications (e.g. constipation after opioids use) Reduced hospital stay
Muehling BM, et al. “Reduction of postoperative pulmonary complications after lung surgery using a fast track clinical pathway”	Reduction in postoperative pulmonary complications

Assessment question: Which of the following is false regarding the definition of ERAS?

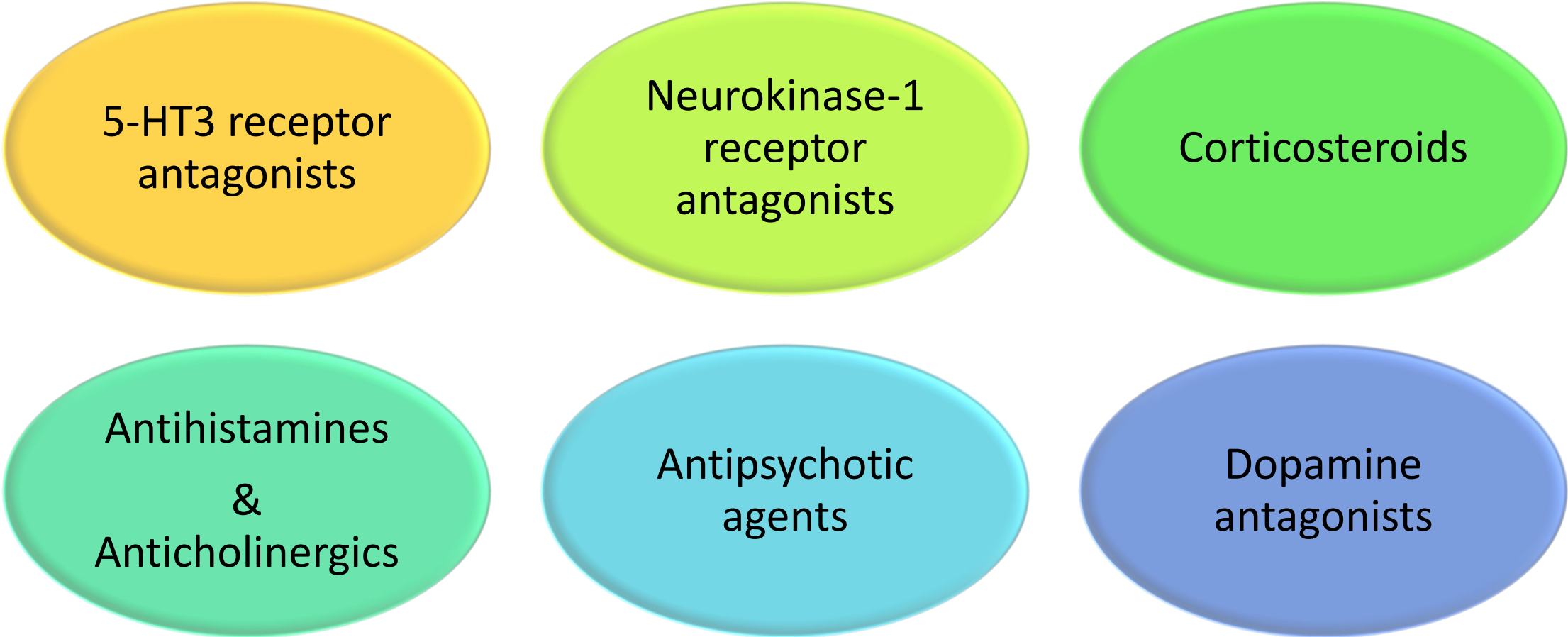
- A. A set of interventions designed to help body mitigate and cope with stress of surgery
- B. It provides the benefits of reduced length of hospital stay and reduction of post-operative complications
- C. It is a multi-modal, multi-disciplinary approach
- D. A set of interventions performed by nurses to only improve cost savings for surgical patients

Assessment question: Which of the following is false regarding the definition of ERAS?

- A. A set of interventions designed to help body mitigate and cope with stress of surgery
- B. It provides the benefits of reduced length of hospital stay and reduction of post-operative complications
- C. It is a multi-modal, multi-disciplinary approach
- **D. A set of interventions performed by nurses to only improve cost savings for surgical patients**

Anti-emetics by Pharmacologic Class

Overview of pharmacologic classes



5-HT₃ receptor
antagonists

Neurokinase-1
receptor
antagonists

Corticosteroids

Antihistamines
&
Anticholinergics

Antipsychotic
agents

Dopamine
antagonists

5-HT₃ Receptor antagonists

- **Mechanism of action:** Selectively blocks serotonin 3 (5-HT₃) peripherally in the vagal nerve terminals and centrally in the chemoreceptor trigger zone
- **Medications:** **Ondansetron**, dolasetron, **granisetron**, **palonosetron**, ramosetron, tropisetron
- **Adverse effects:** QTc prolongation, risk of serotonin syndrome

Ondansetron

- **Indications:** PONV treatment & prevention
- **Dosing:**
 - **Prevention:**
 - Moderate-high risk: IV 4 mg once at end of surgery
 - Low-risk: May be considered, 4 mg
 - **Treatment:**
 - 4 mg once
- **Half-life:** 3-6 hours
- **Onset of action:** ~30 minutes
- **Formulations:** oral tablet, oral disintegrating tablet, IV
- **Additional considerations:**
 - No renal dose adjustments
 - QTc prolongation associated with doses of >16 mg/24 hours

Palonosetron

- **Indications:** PONV prevention
- **Dosing:** 0.075 mg IV once immediately prior to anesthesia induction
- **Half-life:** ~40 hrs
- **Additional considerations:**
 - No renal or hepatic dose adjustments

Granisetron

- **Indications:** Off-label for PONV treatment & prevention
- **Dosing:** 5 – 20 mcg/kg at end of surgery
 - 0.35 to 3 mg
- **Formulations:** IV, subcutaneous, oral
- **Half-life:**
 - IV: 5 – 9 hrs
- **Onset of action:** ~1-3 minutes
- **Additional considerations:**
 - Side effect: Constipation
 - CYP3A4 substrate
 - No renal adjustment for IV, PO

NK-1 Receptor antagonists

- **Mechanism of action:** Inhibits the substance P/neurokinin 1 (NK-1) receptor to prevent acute and delayed vomiting
- **Medications:** aprepitant, fosaprepitant, rolapitant
- **Adverse effects:** Hypersensitivity reactions

Aprepitant

- **Indications:** PONV prevention
- **Dosing :** 40 mg PO once within 3 hours prior to anesthesia induction
- **Side effects:** fatigue, hypotension
- **Half-life:** ~ 9-13 hours
- **Additional considerations:**
 - CYP3A4 inhibitor
 - No renal dose adjustment
 - Caution in severe hepatic impairment

*****NOTE: Reduces efficacy of hormonal contraception**

during treatment and for 1 month following last aprepitant dose

- Alternative/backup contraception should be taken during and after 1 month of treatment

Fosaprepitant

- **Indications:** Off-label use for PONV prevention
- **Dosing:** 150 mg IV once prior to anesthesia induction
- **Side effects:** fatigue, diarrhea, infusion site reaction
- **Half-life:** Once converted to aprepitant → ~9-13 hours
- **Additional considerations:**
 - Prodrug of aprepitant
 - No specified renal or hepatic adjustments
 - CYP3A4 substrate → caution with concomitant use of inhibitors/inducers

Rolapitant

- **Indications:** Off-label use for PONV prevention
- **Dosing :** 70 – 200 mg PO preoperatively
- **Side effects:** Neutropenia, dizziness, hiccups, dyspepsia
- **Half-life:** ~ 7 days
- **Additional considerations:**
 - Contraindicated with concomitant use of CYP2D6 substrates with a narrow therapeutic index
 - No renal dose adjustment indicated – not studied
 - Avoid use in patients with Child-Pugh class C

Glucocorticoids

- **Mechanism of action**: not well-established for antiemetic properties
- **Medications**: **dexamethasone**, methylprednisolone
- **Adverse effects**: psychiatric disturbances (e.g. confusion), hyperglycemia, immunosuppression, adrenal suppression

Dexamethasone

- **Indications:** Off-label for prevention of PONV
- **Dosing:** 4-10 mg IV once before or after induction of anesthesia
- **Half-life:** IV: ~1-5 hours
- **Onset of action:** IV – rapid.
- **Additional considerations:**
 - Dose depends on risk and type of surgery
 - No renal or hepatic adjustment

Antihistamines

- **Mechanism of action**: Muscarinic-blocking effect for antiemetic effect
- **Medications**: Dimenhydrinate, promethazine, diphenhydramine
- **Adverse effects**: tachycardia, **sedation**, urinary retention, constipation, flushing, confusion, blurred vision, dry mouth
- **Warning**: Avoid use in older adults – Beer's criteria medications.

Dimenhydrinate

- **Indications:** Off-label use for prevention of PONV
- **Dosage:** 50 mg once prior to procedure, then 50 mg post-procedure
- **Formulations:** PO, IV, IM
- **Half-life:**
 - IV: unknown
 - PO: ~5-8 hours
- **Onset of action:** immediate
- **Additional considerations:**
 - Avoid use in older adults.

Promethazine

- **Indications:** Off-label use for prevention & treatment of PONV
- **Dosage:**
 - **Prevention:** 6.25 mg PO/IV/IM once
 - **Treatment:** 12.5 – 25 mg PO or PR as needed every 4-6 hours
- **Half-life:** IV ~9-16 hours
- **Onset of action:** ~5 minutes
- **Additional considerations:**
 - To avoid intolerable adverse effects, recommended max dose of 50 mg/day
 - IV & IM are generally avoided due to risk of severe tissue injury
 - Avoid use in older adults.

Diphenhydramine

- **Indications:** Off-label use for treatment of PONV
- **Dosage:**
 - **PO:** 25 – 50 mg every 4-6 hours as needed
 - **IV, IM:** 10 – 50 mg every 6 hours as needed
- **Formulations:** PO, IV, IM
- **Half-life:** 7 – 12 hours
- **Additional considerations:**
 - Avoid use in older adults

Anticholinergics

- **Mechanism of action:** Inhibits anticholinergic receptors
- **Medicines:** scopolamine
- **Adverse effects:** tachycardia, sedation, urinary retention, constipation, flushing, confusion, blurred vision, dry mouth
- **Warning:** Avoid use in older adults – Beer's criteria medications

Scopolamine

- **Indications:** Prevention of PONV
- **Dosing:** 1 transdermal patch (1 mg/3 days) behind ear the night before surgical procedure
 - Remove 24 hours after procedure
 - May also be applied at least 1-2 hours prior to surgical procedure
- **Half-life:** 9.5 hours
- **Onset of action:** 4-8 hours
- **Additional considerations:**
 - Contraindicated in patients with narrow angle closure glaucoma
 - No renal or hepatic impairment adjustments

Dopamine antagonists/Antipsychotic agents

- **Mechanism of Action:** Antagonizes the dopamine 2 receptors in the chemoreceptor trigger zone, which results in inhibitory signaling
- **Antipsychotic medications:** droperidol, haloperidol, perphenazine
- **General antidopaminergic medications:** haloperidol, amisulpride
- **Adverse effects:** QTc prolongation, somnolence
- **Contraindications:** Parkinson's disease, dementia of Lewy bodies

Sources: Droperidol injection, solution. Package insert. 2019.

Haldol® (haloperidol injection). Package insert. 2013.

Droperidol

- **Indications:** Prevention of PONV
- **Dosing:** 0.625-1.25 mg IV given at end of procedure
- **Onset of action:** 3-10 minutes
- **Half-life:** ~2 hours
- **Additional considerations:**
 - **Black box warning:** QTc prolongation and development of arrhythmias
 - **Additional side effects:** hypotension, tachycardia

Haloperidol

- **Indications:** Off-label use for PONV prevention for moderate to high-risk patients
- **Dosing:** 0.5 – 2 mg IV once after induction of anesthesia or at end of surgery
- **Half-life:** IV 14-26 hours
- **Additional considerations:**
 - **Black box warning:** Increased mortality in elderly patients with dementia-related psychosis
 - **Additional side effects:** extrapyramidal reactions, parkinsonism

Perphenazine

- **Indication:** Off-label prevention of PONV
- **Dosing:** 5 mg IV
- **Half-life:** ~9-12 hours
- **Additional considerations:**
 - **Black box warning:** Increased mortality in elderly patients with dementia-related psychosis
 - No renal dose adjustments specified – use with caution
 - Contraindicated in patients with liver damage

Metoclopramide

- **Indications:** Off-label treatment of PONV
- **Dosing:** 10 mg once
- **Formulations:** PO, IV, IM
- **Half-life:**
 - **IV:** 1-3 minutes
 - **IM:** 10-15 minutes
 - **PO:** 30-60 minutes
- **Additional considerations:**
 - Caution for CNS depression, extrapyramidal symptoms, hyperprolactinemia

Literature analysis of Amisulpride: Kranke P, et al.

Title	Amisulpride prevents post-operative nausea and vomiting in patients at high risk: a randomized, double-blinded, placebo-controlled trial
Objective	To assess the efficacy of amisulpride 5 mg IV in combination with standard of antiemetic to prevent PONV in adult surgical patients
Design	Double-blind, randomized, placebo-controlled, international, multi-center trial Included patients with Apfel scores of 3-4 N=1,147 → 572 participants with intervention, 575 participants with placebo
Intervention	Amisulpride 5 mg IV once vs. placebo In combination with 1 non-dopaminergic antiemetic (ondansetron, dexamethasone)
Primary endpoint	Incidence of PONV prevented in 24 hours post-surgical procedure
Results	Complete response occurred in 57.7% of intervention group vs. 46.6% in placebo group (95% CI 5.3-16.8%, $p<0.001$).
Conclusion	Amisulpride IV was safe and effective for PONV prophylaxis when given in combination with another antiemetic from another class.

Assessment question: Which of the following anti-emetics has actions by inhibiting serotonin?

- A. Rolapitant
- B. Perphenazine
- C. Palonosetron
- D. Dexamethasone

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- A. Rolapitant
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- **C. Palonosetron**
- D. Dexamethasone

Assessment Question: Which of the following medication classes would not be appropriate to provide to Nida as part of her PONV regimen?

- A. Anticholinergics
- B. Dopamine agonists
- C. Serotonin 3 inhibitors
- D. Corticosteroids

Assessment Question: Which of the following medication classes would not be appropriate to provide to Nida as part of her PONV regimen?

- A. Anticholinergics
- B. **Dopamine agonists**
- C. Serotonin 3 inhibitors
- D. Corticosteroids

Summary of anti-emetics

Pharmacologic class	Medications
5-HT3 Antagonists	Ondansetron Granisetron Palonosetron
NK-1 Receptor Antagonists	Aprepitant Fosaprepitant Rolaprepitant
Corticosteroids	Dexamethasone
Anticholinergics	Scopalamine
Antihistamines	Dimenhydrinate Diphenhydramine Promethazine
Antipsychotics	Droperidol Haloperidol Perphenazine
Dopamine antagonists	Amisulpride Metoclopramide

Combination therapy

- 2020 PONV guidelines in multimodal prophylaxis in patients with 1+ risk factors
- Examples of pharmacologic therapy combinations:
 - 5HT3 antagonists + dexamethasone
 - 5HT3 antagonists + aprepitant
 - Dexamethasone + aprepitant
 - 5HT3 antagonist + droperidol
 - Haloperidol + dexamethasone
 - Metoclopramide + dimenhydrinate
 - Aprepitant + dexamethasone + ondansetron

Pt case: Nida Santiago

- Nida is a 29-year-old female that is scheduled for a bariatric surgical procedure.
- Past medical history: Exercise-induced asthma
- Surgical history: None
- Social history: 1-2 glasses of wine on weekends, denies tobacco use or recreational substances
- Medications: Albuterol inhaler as needed, multivitamin

Assessment question: Based on the patient's Apfel score, which of the following would be appropriate for Nida as PONV prophylaxis?

- A. Metoclopramide + amisulpride
- B. Ondansetron
- C. Scopolamine + dimenhydramine
- D. Aprepitant + dexamethasone

Assessment question: Based on the patient's Apfel score, which of the following would be appropriate for Nida as PONV prophylaxis?

- A. Metoclopramide + amisulpride
- B. Ondansetron
- C. Scopolamine + dimenhydramine
- **D. Aprepitant + dexamethasone**

Assessment question: If Nida were to experience vomiting despite appropriate PONV prophylaxis, which of the following pharmacologic options would *not* be appropriate for treatment?

- A. Scopolamine
- B. Metoclopramide
- C. Ondansetron
- D. Haloperidol

Assessment question: If Nida were to experience vomiting despite appropriate PONV prophylaxis, which of the following pharmacologic options would *not* be appropriate for treatment?

- **A. Scopolamine**
- B. Metoclopramide
- C. Ondansetron
- D. Haloperidol

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Thank you!

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