Newer Antiemetics

Washington Drug Archive Report

Washington P&T Committee

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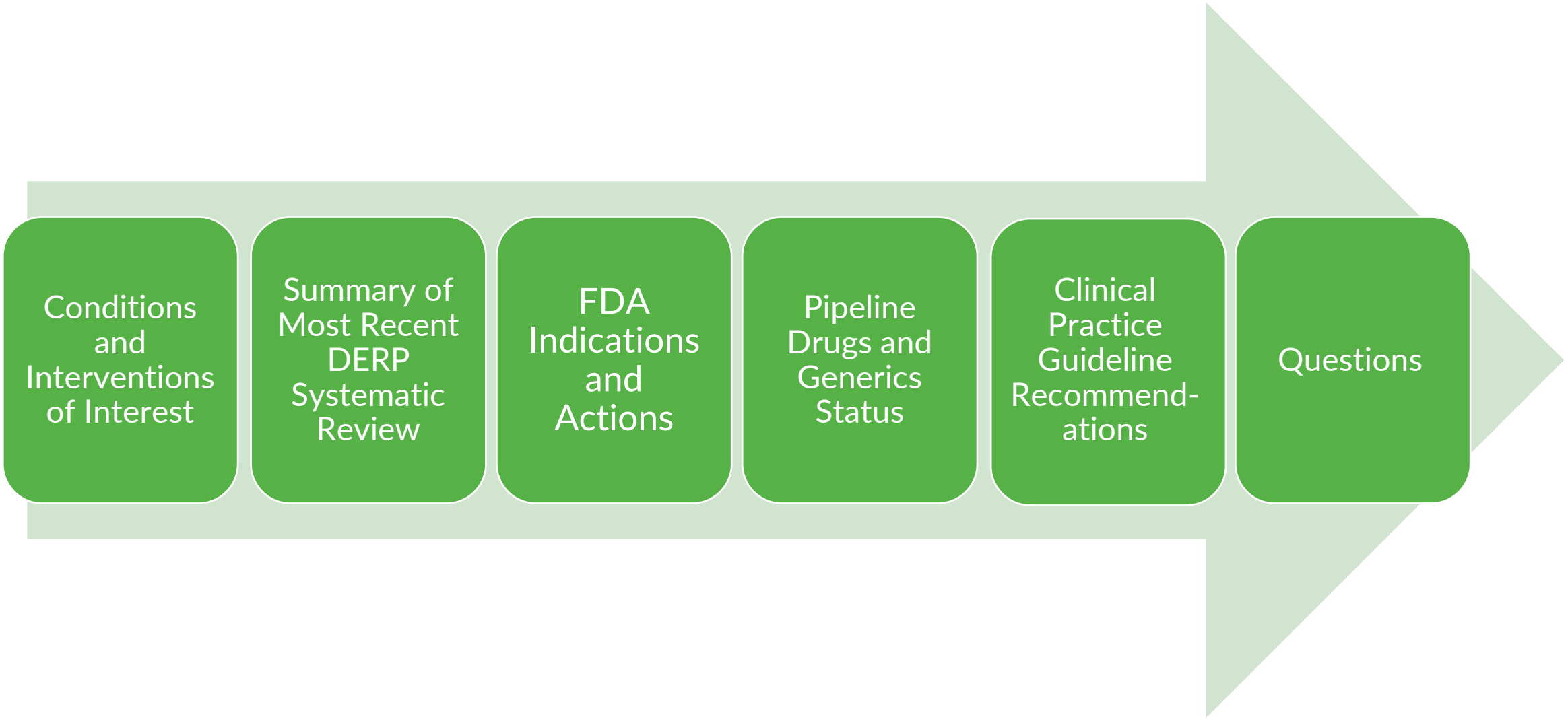
OHSU

Aim of Project

- The Drug Effectiveness Review Project (DERP) aims to present information to the Washington State Pharmacy and Therapeutics (P&T) Committee with topic reports on 9 drug classes that are candidates to be archived from active review by the Committee
- The 9 drug classes identified by the Washington Health Care Authority (HCA) as archive candidates are:
    - Anticoagulants
    - **Antiemetics**
    - Antiplatelets
    - Asthma controllers
    - Asthma quick relief drugs
    - Long-acting opioids
    - Overactive bladder drugs
    - PCSK9 inhibitors
    - Statins

*Drug class in **green** is presented in this report*

Overview


Conditions and Interventions of Interest
Summary of Most Recent DERP Systematic Review
FDA Indications and Actions
Pipeline Drugs and Generics Status
Clinical Practice Guideline Recommend-ations
Questions

Nausea and Vomiting: Condition & Epidemiology (slide 1 of 2)

- Symptoms of nausea and vomiting (N&V) associated with chemotherapy, radiation therapy, anesthesia, and surgery are thought to present via common neurophysiological pathways
- Chemotherapy-induced N&V
  - Very common, with up to 80% of patients experiencing N&V
  - Complications include metabolic imbalances, nutritional depletion/anorexia, deterioration of physical and mental status, esophageal tears, wound withdrawal from potentially curative treatments
  - Risk factors include type of cancer and treatment (i.e., emetogenicity), advanced age, nonsmokers, females, history of N&V due to other causes
- Postoperative N&V
  - Incidence is common at about 25% to 30%
  - Vomiting postoperation increases risk for wound dehiscence, esophageal rupture, aspiration, dehydration, increased intracranial pressure, pneumothorax
  - Risk factors include type of surgical procedure, type of anesthesia used

Nausea and Vomiting: Condition & Epidemiology (slide 2 of 2)

Etiology of pregnancy-induced N&V unclear; may follow similar neurophysiological pathway

- A common condition that affects up to 85% of pregnant individuals
  - Typically begins within first 9 weeks and subsides before 20 weeks
  - More severe forms (e.g., hyperemesis gravidarum) affect 0.3% to 3% of pregnant individuals, and is characterized by intractable vomiting, dehydration, electrolyte imbalance, ketosis, nutritional deficiencies and weight loss
    - Some evidence for association with preterm delivery and small-for-gestational-age infants
- Risk factors: family history, history of N&V with prior pregnancy and other causes, multiple gestation, some genetic fetal disorders

Treatments for Prevention of Nausea and Vomiting (slide 1 of 3)

- Earlier pharmacologic agents to treat chemotherapy-induced N&V
  - Histamine-1 blockers (e.g., diphenhydramine, anticholinergics)
  - Dopamine antagonists (e.g., chlorpromazine, perphenazine)
  - Metoclopramide
  - Droperidol
- Prevention of chemotherapy-induced N&V
  - Pre-chemotherapy management depends on the emetogenic potential of treatment agents, as well as expected subtypes (acute, delayed, anticipatory, breakthrough/refractory)
    - Low to moderate potential: serotonin antagonist and/or dexamethasone (single vs. multiple doses)
    - High potential: combination of drugs (usually more than 1 day of serotonin antagonists, dexamethasone, neurokinin [NK]-1 antagonists)
    - Ginger and acupressure are other nonpharmacologic agents sometimes used

Treatments for Prevention of Nausea and Vomiting (slide 2 of 3)

- Prevention of postoperative N&V
  - Regional anesthesia is recommended over general anesthesia if possible, with provision of adequate oxygen and hydration
  - Most common pharmacological agents include the following:
    - Serotonin antagonists
    - Dopamine antagonist (e.g., droperidol)
    - Corticosteroids (e.g., dexamethasone)
    - Antihistamines (e.g., diphenhydramine)
    - Anticholinergics (e.g., scopolamine)

Treatments for Prevention of Nausea and Vomiting (slide 3 of 3)

- Treatments for pregnancy-induced N&V
  - For mild symptoms
    - Lifestyle behaviors (dietary patterns, fluids/electrolytes, adequate sleep, stress reduction)
    - Ginger, vitamin B6 (pyridoxine), antihistamines
  - For moderate to severe symptoms
    - Pyridoxine-doxylamine combination
    - Dopamine agonists
    - Serotonin agonists
    - Corticosteroids may be third-line treatments for more severe symptoms

Summary of Most Recent DERP Products

Last Report	2009
Date Presented	January 2009
Report Title	*Newer Antiemetics*
Search Dates	From inception (most databases) through April 2008
Authors	Oregon Evidence-based Practice Center researchers
Scans/Surveillance Since Last Report	
August 2018 (last scan)	*Newer Antiemetics* • Search Dates: January 2017 through May 2018
7 additional scans since 2010	*Newer Antiemetics*

PICOS of Most Recent DERP Report

- *Population*
  - Adults and children at risk for, or with, nausea, vomiting (including retching), or both related to the following therapies and conditions:
    - Chemotherapy of various emetogenicity
    - Radiation therapy
    - Surgical procedure
    - Pregnancy
- *Comparators*
  - Another listed intervention (head-to-head)
  - Another FDA-approved medication (active comparator) used to treat N&V
  - Placebo if limited or no other evidence
- *Study Designs*
  - Randomized controlled trials, systematic reviews (including meta-analyses), and observational studies for safety outcomes only

PICOS of Most Recent DERP Report

- *Interventions (antiemetics)*

Name	Brand	Mechanism	Formulation	FDA Approval Date
Aprepitant	Emend	NK1 receptor agonist	Oral capsule	March 3, 2003
Fosaprepitant (analog of aprepitant)			Injection	January 25, 2008
Dolasetron	Anzemet	5-HT3 serotonin receptor antagonist	Oral tablet, injection	September 11, 1997
Granisetron	Kytril	5-HT3 serotonin receptor antagonist	Oral tablet, injection	December 29, 1993
	Sancuso	5-HT3 serotonin receptor antagonist	ER transdermal film	September 12, 2008
Ondansetron	Zofran	5-HT3 serotonin receptor antagonist	Oral tablet, oral solution, injection	January 4, 1991
Palonosetron	Aloxi	5-HT3 serotonin receptor antagonist	Oral capsule, injection	July 25, 2003

Abbreviations. ER: extended release; FDA: US Food and Drug Administration; NK1: neurokinen-1.

PICOS of Most Recent DERP Report

- *Outcomes*
  - Success (absence of nausea or vomiting) at different times
  - Number of episodes of emetic events
  - Degree of nausea
  - Number of emesis-free days
  - Delay until first emetic event
  - Need for rescue medications
  - Satisfaction and quality of life
  - Duration of hospitalization
  - Adverse events (AEs), including specific AEs, withdrawals due to AEs, and serious AEs

Key Questions in Most Recent DERP Report

1. What is the comparative effectiveness of newer antiemetics in treating or preventing nausea and/or vomiting?
2. What are the comparative tolerability and safety of newer antiemetics when used to treat or prevent nausea and/or vomiting?
3. Are there subgroups of patients based on demographics (age, race, gender), pregnancy, other medications, or comorbidities for which one newer antiemetic is more effective or associated with fewer AEs?

Summary of Findings in Most Recent DERP Report (slide 1 of 2)

- 2009 report
  - Included 185 studies, cumulative since original report
    - 81 head-to-head trials, 77 placebo- or active-controlled trials, 14 systematic reviews, 12 observational studies, 1 pooled analysis
- Summary of key findings
  - No differences in effectiveness for dolasetron, granisetron, and ondansetron in adults for prevention of chemotherapy-induced or postoperative N&V; no differences between dolasetron and ondansetron for prevention of postoperative N&V in children
  - Some evidence that ondansetron was less likely to reduce need for rescue therapy than dolasetron, but no difference in response compared with granisetron
  - Ondansetron may be associated with higher specific AEs than granisetron, but mixed results compared with dolasetron in adults treated with chemotherapy; inconsistent results in studies of postoperative N&V

Summary of Findings in Most Recent DERP Report (slide 2 of 2)

- Summary of key findings (cont.)
  - Aprepitant was more effective than dexamethasone in adults for chemotherapy-induced N&V, and noninferior with ondansetron with postoperative N&V; no differences in AEs between treatments
  - Palonosetron was more effective or noninferior compared with dolasetron and ondansetron in adults with chemotherapy-induced N&V; may be more effective in children than ondansetron; no differences in AEs between treatments
  - A lack of evidence for
    - Children undergoing chemotherapy or who are postoperative
    - Individuals undergoing radiation therapy
    - Quality of life and patient satisfaction outcomes
    - Pregnancy-induced N&V
    - Serious AEs for antiemetics

Summary of Findings in Most Recent Surveillance

- Cumulative from most recent report through 2018 surveillance
  - 3 new drugs
    - Doxylamine succinate/pyridoxine hydrochloride (brands Diclegis and Bonjesta as delayed-release [DR] oral tablets [2 different dose products] approved April 2013 and November 2016)
    - Netupitant/palonosetron (brand Akynzeo, oral capsule and intravenous [IV] infusion; approved October 2014 and April 2018)
    - Rolapitant (brand Varubi, oral tablet and IV infusion; approved September 2015 and October 2017)
  - 8 new formulations or generic approvals
  - No new boxed warnings
  - 76 new studies
    - 34 head-to-head trials, 22 trials comparing the addition of an NK1 agonist with standard therapy, 20 placebo-controlled trials

New FDA Drugs Since Most Recent DERP Report

- **New drugs**
  - Amisulpride (Barhemsys)
    - Dopamine receptor agonist (intravenous) approved February 2020 for prevention of postoperative N&V in adults
  - Doxylamine succinate/pyridoxine hydrochloride (Diclegis, Bonjesta)
    - NK1 receptor antagonist/5-HT3 serotonin receptor antagonist approved April 2013 for pregnancy-associated N&V
  - Netupitant or fosnetupitant/palonosetron (Akynzeo)
    - NK1 receptor antagonist/5-HT3 serotonin receptor antagonist approved October 2014 for prevention of chemotherapy-induced N&V in adults, in combination with dexamethasone
  - Rolapitant (Varubi)
    - NK1 receptor antagonist approved September 2015 for prevention of chemotherapy-induced N&V in adults, in combination with other antiemetics

New FDA Indications Since Most Recent DERP Report

- **New indications**
  - Aprepitant (Emend, oral capsule)
    - Expanded to include pediatric patients at least 12 years (August 2015)
    - REMOVED indication: postoperative N&V in adults (September 2019)
  - Fosaprepitant (Emend, injection)
    - Expanded to include pediatric patients ≥ 6 months (December 2015)
  - Palonosetron (generic Aloxi)
    - REMOVED indication: pediatric populations removed from most indications due to lack of evidence (April 2020)

FDA-Approved Indications

- Indications as of January 23, 2024

Generic Name (Brand Name)	Prevention of Postoperative N&V in Adults	Prevention of N&V Associated with General, Moderately, or Highly Emetogenic Cancer Chemotherapy	N&V of Pregnancy	Prevention of N&V Associated with Radiotherapy
Amisulpride[a]	√			
Aprepitant or fosaprepitant		√[b] • ≥ 6 months for oral solutions or injections, ≥ 12 years for all formulations		
Dolasetron	Brand discontinued; generic equivalent not available			
Doxylamine succinate/ pyridoxine HCl[a]			√	
Granisetron	√ (generic Kytril)	√ (generic Kytril[c]; adults only for Sancuso and Sustol)		
Netupitant or fosnetupitant/ palonosetron[a,b]		√[a]		
Ondansetron	√	√[c]		√[c]
Palonosetron		√ (adults)		
Rolapitant[a]		√[b] (adults)		

Note. [a] Newly approved drug since last report; [b] In combination with other antiemetic agents; [c] Age of population indicated not clear and/or reported as not studied in younger populations (some formulations preferred over others for younger age groups).
Abbreviations. HCl: hydrochloride; N&V: nausea and vomiting.

New FDA Warnings Since Most Recent DERP Report

- **New boxed warnings**
  - No new boxed warnings
- **New warnings or precautions**
  - Fosaprepitant (Emend, injection)
    - Hypersensitivity reactions including anaphylaxis and shock (August 2017)
    - Infusion site reactions (March 2018)
  - Granisetron (Sancuso transdermal system)
    - Avoid exposing patch to direct external heat source (September 2015)
  - Ondansetron (generic Zofran)
    - Generic Zofran (oral/IV): Risk of myocardial ischemia (October 2021)
  - With all 5-HT3 serotonin receptor agonists
    - Serotonin syndrome can occur, particularly with concomitant use of serotonergic drugs (most around 2014)

Generic Drug Status & Brand Discontinuation (slide 1 of 2)

Name	Generic Availability	Status
Amisulpride	No	Estimated loss of exclusivity February 2024; no applications for generic manufacturing have been submitted at this time
Aprepitant or fosaprepitant	Yes	***Newly available as generic since last report for oral capsules and injection formulations*** • Generic status unclear for oral suspension, and for new IV emulsion brands
Dolasetron	No	Potential for future generic availability unclear • Anzemet brand discontinued
Doxylamine succinate/ pyridoxine HCl	Yes	***Delayed release tablet newly available as generic since last report*** • Extended release tablet generic status unclear (appears to be in litigation)
Granisetron	Yes	• Kytril oral tablets, injection formulations already available as generic with last report • Transdermal system (Sancuso) earliest possible generic launch, January 2025 • ER subcutaneous (Sustol) formula loss of exclusivity, September 2024

Abbreviations. ER: extended release; HCl: hydrochloride; IV: intravenous.

Generic Drug Status & Brand Discontinuation (slide 2 of 2)

Name	Generic Availability	Status
Netupitant or fosnetupitant/ palonosetron	No	Estimated loss of exclusivity September 2031; no applications for generic manufacturing have been submitted at this time
Ondansetron	Yes	Already available as generic with last report • Zofran and Zuplenz brands discontinued
Palonosetron	Yes	***Likely newly available as generic since last report*** • Aloxi brand discontinued
Rolapitant	No	Estimated loss of exclusivity August 2028; no applications for generic manufacturing have been submitted at this time

Pipeline Therapies

- No new pipeline therapies identified

Of note:

- Cannabinoid (dronabinol) agents (brand names Marinol [available as generic], Syndros) are indicated for chemotherapy-induced N&V
- Scopolamine (brand name Transderm Scop, also available as generic) is indicated for postoperative N&V in addition to motion sickness

Clinical Practice Guidelines (1 of 4)

- Chemotherapy-induced N&V
  - Treatment for prevention is based on emetogenicity of agent
    - Pharmacotherapy agents considered effective alone, or in combinations
      - Serotonin (5-HT3) receptor agonists (as single agent, evidence for palonosetron as more effective; some guidelines don't specify preferred 5-HT3 agent)
        - Avoid use in patients with congenital long QT syndrome; assess and correct potassium and magnesium levels (injected dolasetron is contraindicated in both children and adults)
      - NK1 receptor agonists (evidence suggests similar efficacy across approved agents)
      - Glucocorticoids (dexamethasone often mentioned)
      - Olanzapine when used in combination with other antiemetics

Note. Primary source UpToDate; recommendations cross-referenced and verified against key clinical practice guidelines (slide 27).

Clinical Practice Guidelines (2 of 4)

- Radiotherapy-induced N&V
  - Risk classification based on location and surface volume of radiation therapy
  - Less evidence for this condition; prophylaxis is similar to chemotherapy-induced recommendations
- Postoperative N&V
  - Prophylaxis for all patients (opioid-sparing postoperative plan)
  - Treatment plan based on risk score and can include:
    - 1 to 3 antiemetics from different drug classes
    - Emphasis on regional anesthesia rather than general if possible
    - Acupuncture (not common in children)

Note. Primary source UpToDate; recommendations cross-referenced and verified against key clinical practice guidelines (slide 27).

Clinical Practice Guidelines (3 of 4)

- Pregnancy-induced N&V (including hyperemesis gravidarum)
  - Treatment goals
    - Reduce severity, improve quality of life
    - Correct hypovolemia, ketonuria, electrolyte imbalances
    - Prevent serious complications of persistent vomiting (e.g., weight loss)
    - Minimize potential fetal effects of maternal pharmacotherapy
  - First-line treatments (nonpharmacologic): dietary changes, ginger/ginger supplements, prenatal vitamin changes (take with food, chewable formulation, temporary formulation without iron), acupressure wristbands

Note. Primary source UpToDate; recommendations cross-referenced and verified against key clinical practice guidelines (slide 27).

Clinical Practice Guidelines (4 of 4)

- Pregnancy-induced N&V (including hyperemesis gravidarum; cont.)
  - With persistent N&V
    - Vitamin B6 (pyridoxine) alone or in combination with antihistamine doxylamine (fixed dose doxylamine-pyridoxine product)
      - Without hypovolemia, consider diphenhydramine or dimenhydrinate
    - As needed, other drug classes considered in this order: dopamine antagonist (prokinetic), serotonin antagonist (ondansetron, granisetron)

Note. Primary source UpToDate; recommendations cross-referenced and verified against key clinical practice guidelines (slide 27).

Key Clinical Practice Guidelines

Focus	Date	Title of Guideline
American College of Obstetricians and Gynecologists (ACOG)		
Pregnancy	2018	Nausea and Vomiting of Pregnancy
American Society of Clinical Oncology (ASCO)		
Cancer treatments	2020	Antiemetics: Update
American Society of Enhanced Recovery (ASER) and Society for Ambulatory Anesthesia (SAMBA)		
Postoperative	2020	Consensus Guidelines for the Management of Postoperative Nausea and Vomiting

Questions?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