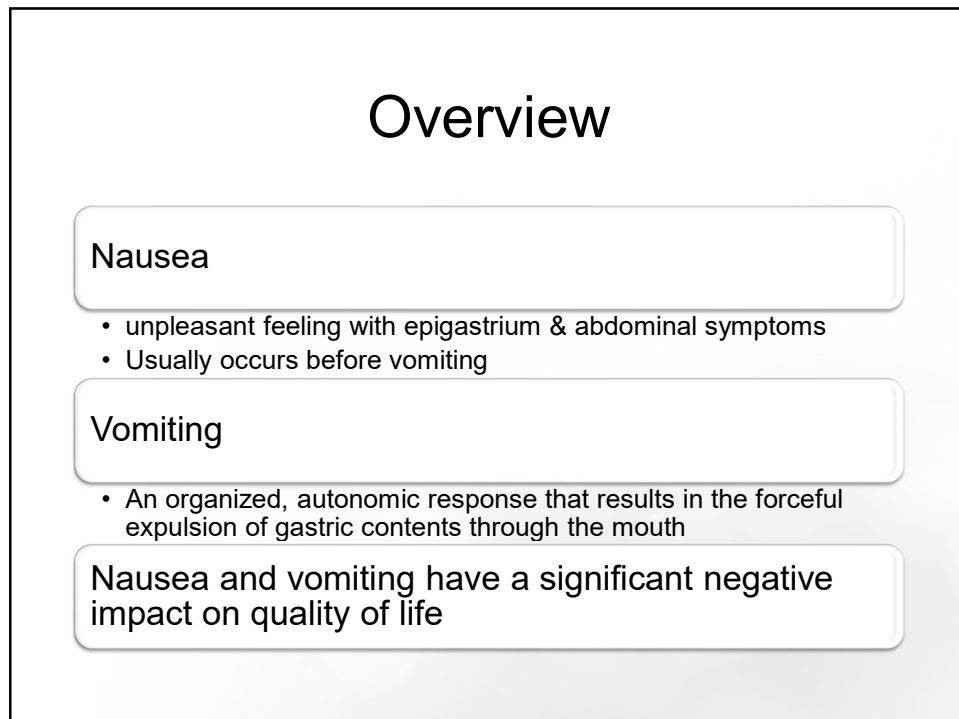


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Etiology

Nausea and/or vomiting may be associated with a number of conditions including gastrointestinal (Pancreatitis Hepatitis), cardiovascular, infectious, neurologic, metabolic, psychogenic processes, or pregnancy

Nausea and/or vomiting is also associated with numerous medications and noxious agents

3

Iatrogenic, Toxic, and Infectious Causes

Almost any medication can cause N/V with chemotherapeutic agents being the most well known

Overdoses of alcohol, illicit drugs, and other toxins may cause acute N/V

Infectious causes usually result in acute onset N/V

- Viral gastroenteritis is very common
- Bacteria and their toxins may also be the cause

4

Gastrointestinal Disorders

Acute N/V typically the result of an inflammatory process

- Appendicitis, cholecystitis, pancreatitis

Obstructions can cause acute or chronic symptoms

- Gastric outlet obstructions tend to cause intermittent N/V
- Intestinal obstructions tend to acute N/V and severe pain

5

Gastrointestinal Disorders

Motility disorders

- Gastroparesis produces N/V from the inability to move food through the GI tract

The following GI disorders may have N/V associated with them, but these are not the primary symptoms

- Dyspepsia, GERD, PUD, and IBS

6

CNS and Psychiatric Conditions

Conditions that increase intracranial pressure can cause N/V

- Tumor, infarct, infection

Migraine headaches often cause N/V

Patients may also experience N/V from emotional or physical stressors

N/V can also be associated with anorexia nervosa,, depression, and anxiety

7

Other Conditions

Pregnancy is the most common endocrinologic cause of N/V

Metabolic causes of N/V include the following:

- Acidosis, uremia, hyperthyroidism, adrenal disorders, parathyroid disorders

8

Pathophysiology

3 phases of emesis include:

Nausea

- The need to vomit

Retching

- Labored movement of the abdominal and thoracic muscles before vomiting

Vomiting

- Forceful expulsion of gastric contents through the mouth caused by GI retroperistalsis

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Pathophysiology

Areas involved in nausea and vomiting

Vomiting center

- Integrates afferent impulses from sensory centers to efferent impulses to different areas including the salivation and respiratory centers and to pharyngeal, GI, and abdominal muscles leading to vomiting

Chemoreceptor trigger zone (CTZ)

- Located in the brain and is the major chemosensory organ for emesis
- Associated with chemically-induced vomiting

GI tract

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Pathophysiology

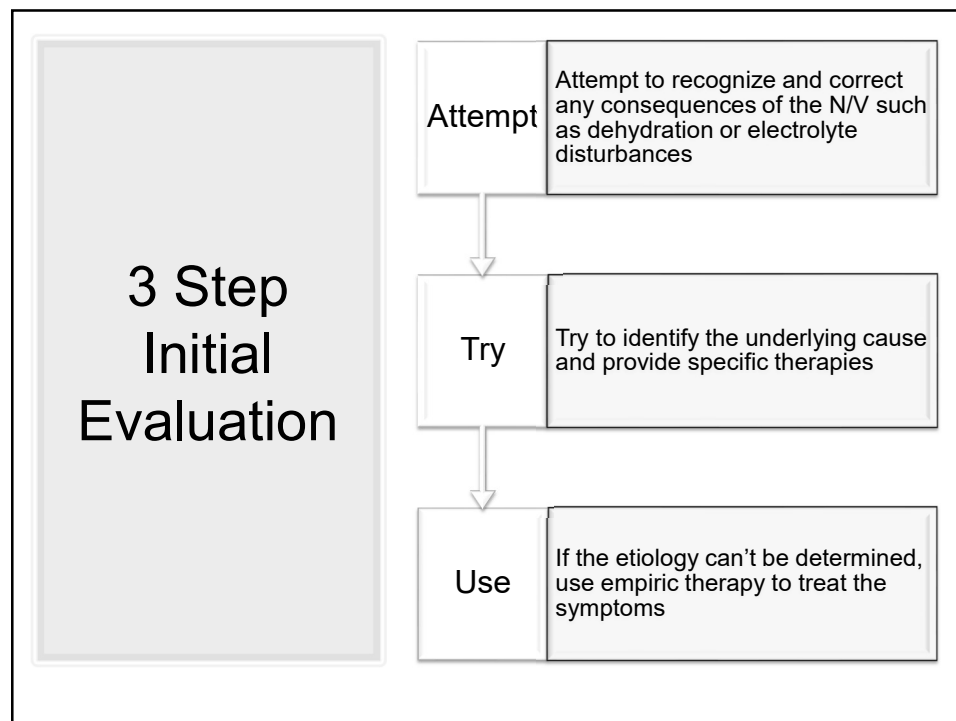
Neurotransmitter receptors are in the vomiting center, CTZ, and GI tract

- These include cholinergic, histaminic, dopaminergic, opiate serotonergic, neurokinin, and benzodiazepine receptors

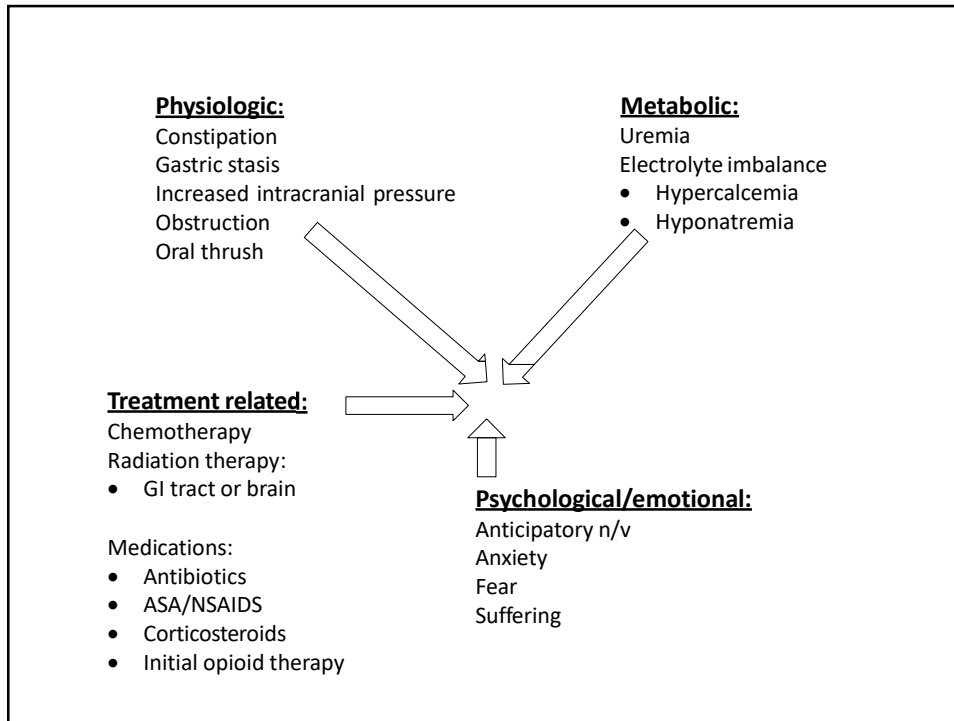
Medications, disease states, and various circumstances can cause stimulation of these receptors to cause N/V

There are antiemetic drugs that block these receptors

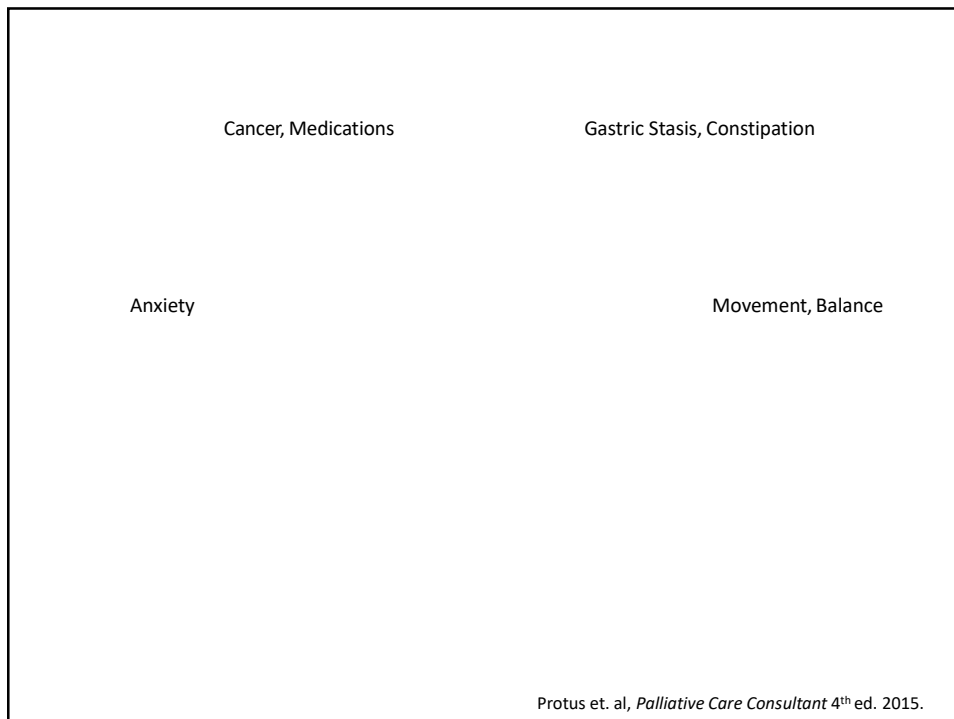
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14

Clinical Presentation

Simple

- Self limiting, may resolve spontaneously
- Queasiness and/or discomfort
- Only symptomatic therapy required
- May self treat

Complex

- Not relieved with antiemetics
- Fluid-electrolyte imbalance
- Persistent vomiting when pregnant
- Weight loss/fever/abdominal pain
- Usually associated with noxious agents (e.g. oncology/chemotherapy agents) or psychogenic events
- Requires work up with clinician

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Complications of Nausea and Vomiting

Dehydration

Electrolyte imbalances (hypokalemia)

Esophageal tear

Malnutrition long term

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Simple and Complex Nausea and Vomiting

Other information to consider when evaluating simple or complex nausea and vomiting include:

Fluid input and output

Medication history

Recent history of behavioral or visual changes, headache, pain, or stress

Family history positive for psychogenic vomiting

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Nonpharmacologic Therapy

Modalities utilized depends on the etiology of the nausea/vomiting

Avoid food/beverages that may be problematic and avoid overindulgence

If the N/V is part of the symptomatology of an illness, the N/V will subside as the illness resolves

If the N/V are related to changes produced by motion, the N/V will improve by adapting a stable physical position

Behavioral Intervention

- Relaxation
- Hypnosis
- Distraction
- Acupuncture

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Pharmacologic Therapy

Based on targeting the various chemoreceptors (5-HT₃, D₂, NK₁, H₁, muscarinic)

Factors to consider:

- success of previous therapy
- route (IV/rectal/PO/transdermal)
- etiology
- frequency and severity of episodes

Simple N/V:

- self-care
- restricting oral intake
- eating smaller meals
- avoiding spicy or fried foods

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Pharmacologic Therapy

Nonprescription and prescription categories

Simple N/V is often managed by the patient using nonprescription agents (self-care)

- If the patient's condition does not improve or gets worse, prescription medication(s) are usually warranted

Complex N/V requires prescription medications and often in combination therapy

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Pharmacologic Therapy

Antiemetic medications have different mechanisms of action and are also available in different dosage forms

Choosing a medication

- Etiology of the N/V
- Frequency, duration, and severity of the N/V
- Ability of the patient to use oral, rectal, injectable, or transdermal products
- Success of previously used antiemetic therapies

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Antiemetic Medication Classes

Antacids

Antihistamines-Anticholinergics

Butyrophenones

H₂-receptor antagonists

5-hydroxytryptamine-3 receptor antagonists (5-HT₃ RA)


Phenothiazines

Corticosteroids

Neurokinin 1 receptor antagonists

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OTC Medications



- First step for simple N/V
- Antacids
- Antihistamines
- H₂ Antagonists
- Emetrol
- Cola Syrup

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Antacids



Can be used to help relieve simple nausea and vomiting

- Work primarily through gastric acid neutralization
- Useful in simple N/V caused by overeating or secondary to heartburn/GERD

MOA

- Neutralize hydrochloric acid in the stomach, which results in an increase in gastric pH

Agents

- Magnesium hydroxide
- Aluminum hydroxide
- Calcium carbonate

Adverse effects

- Diarrhea (magnesium hydroxide)
- Constipation (aluminum hydroxide and calcium carbonate)
- Alterations in mineral metabolism
- Acid-base disturbances

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Antacids

Monitoring

- Periodic calcium and phosphate levels if on chronic antacid therapy

Patient counseling

- Antacids can decrease the levels of numerous other drugs including tetracyclines, digoxin, iron supplements, fluoroquinolones, and ketoconazole.
- Patients should separate antacids and other medications by at least 2 hours
- Patients with renal impairment should not use aluminum or magnesium containing antacids unless directed by their physician

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Antihistamine- Anticholinergic Drugs



Used for simple N/V associate with motion sickness

MOA

- Interrupt visceral afferent pathways that stimulate N/V
- Suppresses vestibular end-organ receptors and inhibits activation of central cholinergic pathways

Agents

- Dimenhydrinate (Dramamine)
- Diphenhydramine (Benadryl)
- Hydroxyzine (Vistaril, Atarax)
- Meclizine (Bonine, Antivert)
- Scopolamine (Transderm Scop)
- Trimethobenzamide (Tigan)

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Antihistamine- Anticholinergic Drugs



Adverse effects

- Drowsiness, confusion, blurred vision, dry mouth, urinary retention

Monitoring

- Improvement in N/V

Patient counseling

- Especially problematic in the elderly
- Increased risk of complications in those with BPH, narrow angle glaucoma, or asthma
- Avoid activities that require mental alertness until the the effects of the medication is realized
- Avoid alcohol and other CNS depressants as an additive effect may occur

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Butyrophenones

Used in palliative care and postoperative nausea and vomiting (PONV)

Not recommended as first-line therapy

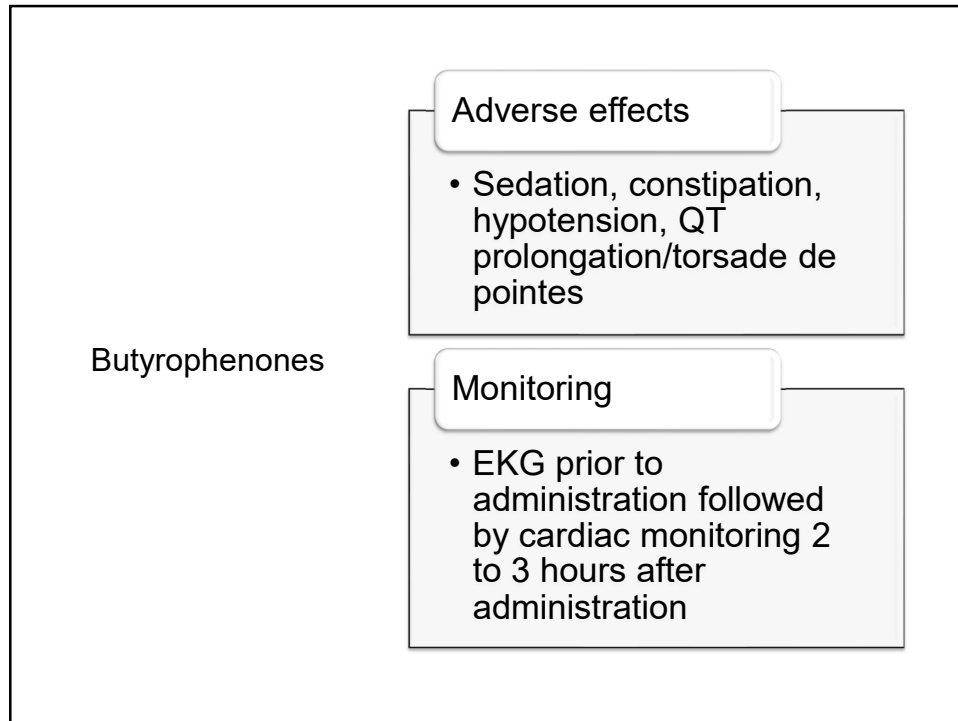
MOA

- Block dopaminergic stimulation of the CTZ

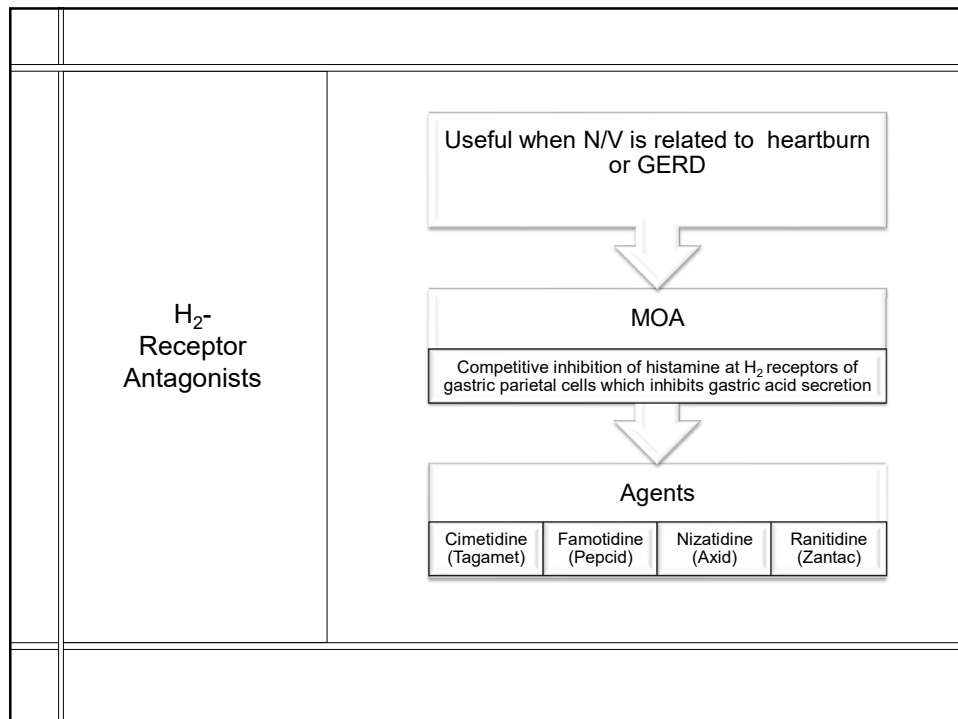
Agents

- Haloperidol (Haldol)
- Droperidol (Inapsine)

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H₂- Receptor Antagonists

Adverse effects

- Headache, somnolence, fatigue, dizziness, constipation, diarrhea

Monitoring

- Monitor for CNS effects (rare) in those over 50 years old or in those with renal or hepatic impairment

Patient counseling

- Onset of relief is 30 to 45 minutes and duration of relief is 4 to 10 hours

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Dopamine Antagonists

Metoclopramide

Central blockage of CTZ

Cholinergic prokinetic activity, promotes gastric motility

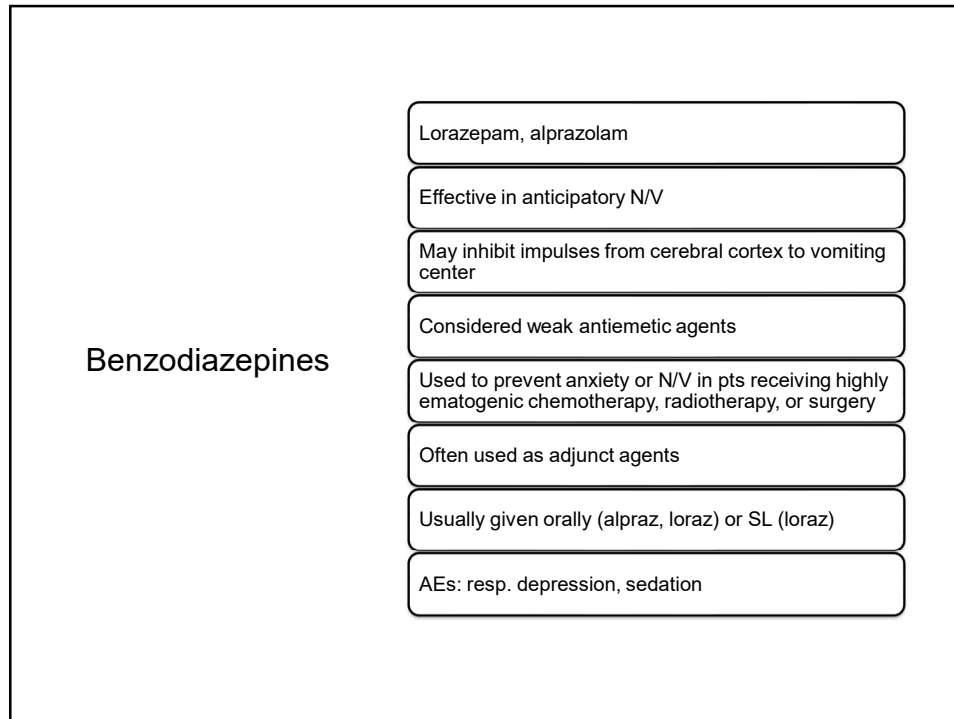
Useful in N/V in patients with diabetic gastroparesis

Aids in gastric emptying

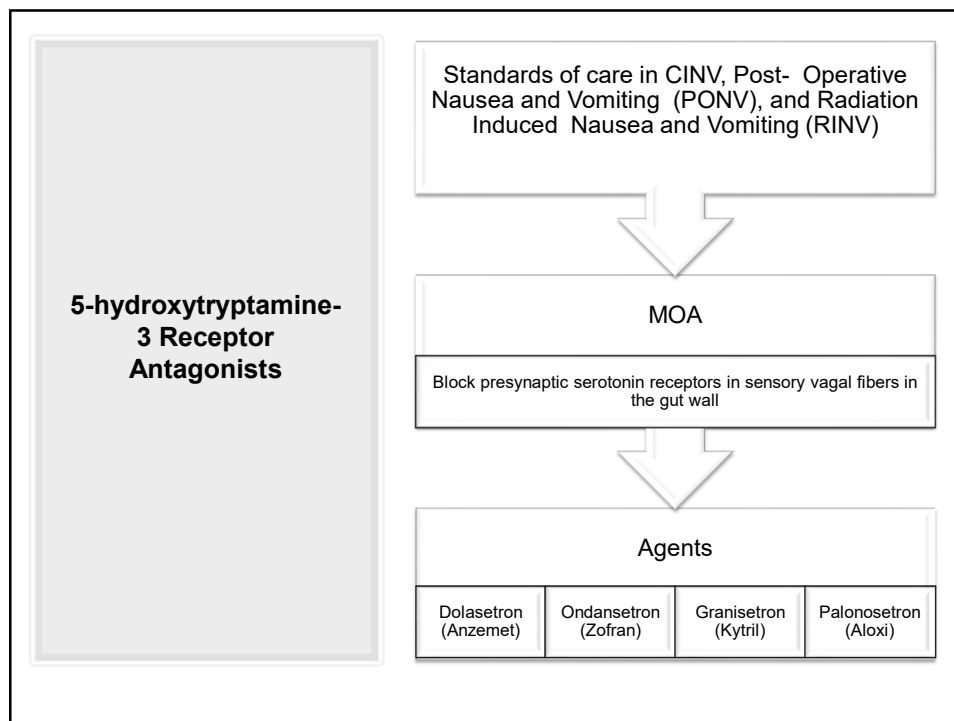
AEs: EPS, hyperprolactinemia, gynecomastia

Use declining

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**5-hydroxytryptamine-
3 Receptor
Antagonists**

Adverse effects

- Asthenia, constipation, headache

Oral or IV formulation

Monitoring

- Effectiveness in preventing N/V/hydration status
- QT prolongation with Dolasetron and Ondansetron

Patient counseling

- Counsel patients regarding adverse effects and to report any signs/symptoms of cardiac arrhythmias

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Phenothiazines

Useful in simple N/V and for breakthrough CINV

MOA

- Block dopamine receptors in the CTZ (chlorpromazine and prochlorperazine)
- Competitively blocks histamine-1 receptors (promethazine)

Agents

- Chlorpromazine (Thorazine)
- Prochlorperazine (Compazine)
- Promethazine (Phenergan)

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Phenothiazines	Adverse effects
	<ul style="list-style-type: none"> • Constipation, dizziness, sedation, tachycardia, tardive dyskinesia, prolonged QT interval
	Multiple dosage forms available
	<ul style="list-style-type: none"> • Rectal useful in vomiting patients • IV formulation is quick and effective in emergency setting
	Inexpensive
Monitoring	
<ul style="list-style-type: none"> • Improvement of N/V 	
Patient counseling	
<ul style="list-style-type: none"> • May cause photosensitivity (use sunblock and avoid prolonged exposure to sunlight) • Avoid activities that require mental alertness until the the effects of the medication is realized • Avoid alcohol 	

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Corticosteroids	Used as monotherapy or in combination therapy for prophylaxis of CINV and PONV
	MOA
	<ul style="list-style-type: none"> • Exact mechanism of action for nausea/vomiting prophylaxis is unknown
Agents	
<ul style="list-style-type: none"> • Dexamethasone • Most commonly used corticosteroid for N/V • Methylprednisolone (Medrol) 	

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Corticosteroids	Adverse effects
	<ul style="list-style-type: none"> • Insomnia, GI symptoms, agitation, appetite stimulation
	Monitoring
	<ul style="list-style-type: none"> • Effectiveness in preventing N/V
	Patient Counseling
	<ul style="list-style-type: none"> • If on long-term therapy advise to avoid live or live, attenuated vaccines • Report signs/symptoms of infection or hyperglycemia • Diabetic patients may need to closely monitor their blood glucose

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NK-1 Receptor Antagonists	Efficacious in delayed phase of CINV and PONV
	Can be used alone or in combination (particularly with 5-HT ₃ receptor antagonists and corticosteroids)
	MOA
	<ul style="list-style-type: none"> • Prevents acute and delayed vomiting by inhibiting substance P/neurokinin 1 (NK₁) receptor
	Agents
	<ul style="list-style-type: none"> • Aprepitant (Emend)

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NK-1 Receptor Antagonists

Adverse effects

- Constipation, diarrhea, headache, hiccups, alopecia
- Post marketing effects of rash and rarely Stevens-Johnson Syndrome

Significant Drug interactions (CYP3A4)

- Oral contraceptives
- Warfarin (decreased INR)
- Dexamethasone (decrease dose)

Monitoring

- Improvement in N/V

Patient counseling

- Educate on adverse effects

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Simple Nausea and Vomiting

Treatment often involves self-care with nonprescription (OTC) agents

If OTC medications do not help or if the patient's symptoms worsen, prescription agents are often employed

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Nausea and Vomiting

For both simple and complex nausea and vomiting, an attempt should be made to identify the etiology so that targeted therapy can be utilized

If the etiology is unknown and OTC medications are not working:

- It is reasonable to begin prescription therapy with a trial of a phenothiazine, such as prochlorperazine
- 5-HT₃RA's like ondansetron are also effective and may be better tolerated than phenothiazines, but their high cost is a concern particularly if being used long-term

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CINV

CINV: Acute (< 24h), delayed (> 24h), anticipatory, breakthrough, refractory

General Principles

- Primary goal is no N/V during emetic risk period (2 days moderate and 3 day high)
- Choice of drug based on Chemotherapy agent with highest risk, prior emetic experience, and patient specific factors
- When given in equipotent doses, oral and IV 5-HT₃-RAs are equally effective
- Consider and manage toxicities of antiemetics

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CINV

Anticipatory

- Triggers: tastes, odors, sights, thoughts associated with chemo

Goals of therapy: prevention N/V

- Prevention of acute N/V important

Ematogenic potential of chemo agents:

Minimal (< 10% risk), low (10-30%), moderate (30-90%), high (>90%)

Duration of emetic risk: 2-3d (peak), up to 7d

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Emetic Risk Antineoplastic Agents Administered Intravenously				
High	Moderate	Low		Minimal
Carmustine	Azacitidine	5-FU	Panitumumab	Bevacizumab
Cisplatin	Alemtuzumab	Bortezomi	Pemetrexed	Bleomycin
Cyclophosphamide	Bendamustine	b	Temsirolimus	Busulfan
>1500	Carboplatin	Cabazitax	Topotecan	Cetuximab
mg/m2	Cyclophosphamide	el	Trastuzumab	Fludarabine
Dacarbazine	<1500	Cytarabine		Pralatrexate
Dactinomycin	mg/m2	<1000 mg/m2		Rituximab
Mechlorethamine	Cytarabine	Docetaxel		Vinblastine
Streptozotocin	>1000	Doxorubicin		Vincristine
	mg/m2	(liposoma		Vinorelbine
	Daunorubicin	l) Etoposide		
	Doxorubicin	Gemcitabine		
	Epirubicin	Ixabepilone		
	Idarubicin	Methotrexate		
	Ifosfamide	Mitomycin		
	Irinotecan	Mitoxantrone		
	Oxaliplatin	Paclitaxel		

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Table 3. Antiemetic Dosing by Chemotherapy Risk Category

Risk Category	Dosing on Day of Chemotherapy	Dosing on Subsequent Days
High emetic risk*		
NK ₁ antagonist Aprepitant	125 mg oral	80 mg oral; days 2 and 3
Fosaprepitant	150 mg IV	
5-HT ₃ antagonist Granisetron	2 mg oral; 1 mg or 0.01 mg/kg IV	
Ondansetron	8 mg oral twice daily; 8 mg or 0.15 mg/kg IV	
Palonosetron	0.50 mg oral; 0.25 mg IV	
Dolasetron	100 mg oral ONLY	
Tropisetron	5 mg oral; 5 mg IV	
Ramosectron	0.3 mg IV	
Corticosteroid† Dexamethasone	12 mg oral or IV	8 mg oral or IV; days 2-3 or days 2-4
Moderate emetic risk‡		
5-HT ₃ antagonist Palonosetron	0.50 mg oral; 0.25 mg IV	
Corticosteroid Dexamethasone	8 mg oral or IV	8 mg; days 2 and 3
Low emetic risk		
Corticosteroid Dexamethasone	8 mg oral or IV	

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Acute CINV Prophylaxis

Low ematogenic potential: single agent is effective (dexamethasone, metoclopramide, or 5HT3-RA, prochlorperazine, lorazepam) on day of chemo

Moderate ematogenic potential: two antiemetic drug combination (5-HT₃ RAs on day 1, dexamethsone on day 1-3) for most regimens

High ematogenic potential: 3 antiemetic drug combination given on day 1 of chemo (5-HT₃ RAs, dexamethsone, NK₁ RA,)

Other option (olanzapine + 5-HT3+DEX)

IV 5-HT₃ RAs equivalent in efficacy/Oral

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Delayed CINV Prophylaxis

Most common with cisplatin- and cyclophosphamide-based regimens

Best to control acute CINV and provide adequate prophylaxis for delayed CINV

Monotherapy or dual therapy for days 2-4 for high ematogenic regimen

Monotherapy for days 2-3 for moderate ematogenic regimen

No prophylaxis necessary for low ematogenic regimen

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Delayed CINV Prophylaxis

Aprepitant, dexamethasone, metoclopramide are effective in delayed CINV

2-drug regimens superior to 1-drug

Examples:

- High ematogenic potential
 - Dexamethasone (2-4) + aprepitant (2-4)
 - OR
 - Dexamethasone (2-4) alone
- Moderate ematogenic potential
 - Ondansetron (2-3) OR
 - Dexamethasone (2-3)

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Anticipatory CINV Prophylaxis	Anticipatory
	Due to inadequate control of N/V in the past
	Use of BDZ combined with standard antiemetic may be considered in high risk pts
	Lorazepam given night before and morning of chemotherapy 1 to 2 hours before chemo

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Breakthrough CINV Treatment	Agents with different MOA preferred
	E.g., prochlorperazine, promethazine, lorazepam, metoclopramide, haloperidol, 5- HT ₃ -RAs, dexamethasone, cannabinoids, etc.

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Radiation-Induced N/V (RINV)

Incidence: 50-80%

Risk factors: combination chemotherapy, prior CINV, upper abdomen RT, radiation field size

Risk:

- Minimal: 5-HT₃ RAs, metoclopramide, or prochlorperazine may be offered as rescue
- Low: 5-HT₃ RAs either throughout RT or as needed
- Moderate: 5-HT₃ RAs prior to each fraction and dexamethasone on fractions 1-5
- High: 5-HT₃ RAs throughout RT and dexamethasone on fractions 1-5 in pts who are receiving total body irradiation

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Overview of Postoperative Nausea and Vomiting (PONV)

PONV is common and distressing to patients

General incidence of vomiting is 30%

General incidence of nausea is 50%

High-risk patients can have a PONV rate of 80%

General approach taken is to assess a patient's PONV risk, reduce baseline risks, and provide appropriate PONV prophylaxis

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Risk Factors for PONV

- Female sex
- History of PONV or motion sickness
- Nonsmoking
- Younger age (< 50 years old)
- General vs. regional anesthesia
- Use of volatile anesthetics and nitrous oxide
- Postoperative opioids
- Duration of anesthesia
- Type of surgery
 - Higher incidence with cholecystectomy, laparoscopic, gynecological)

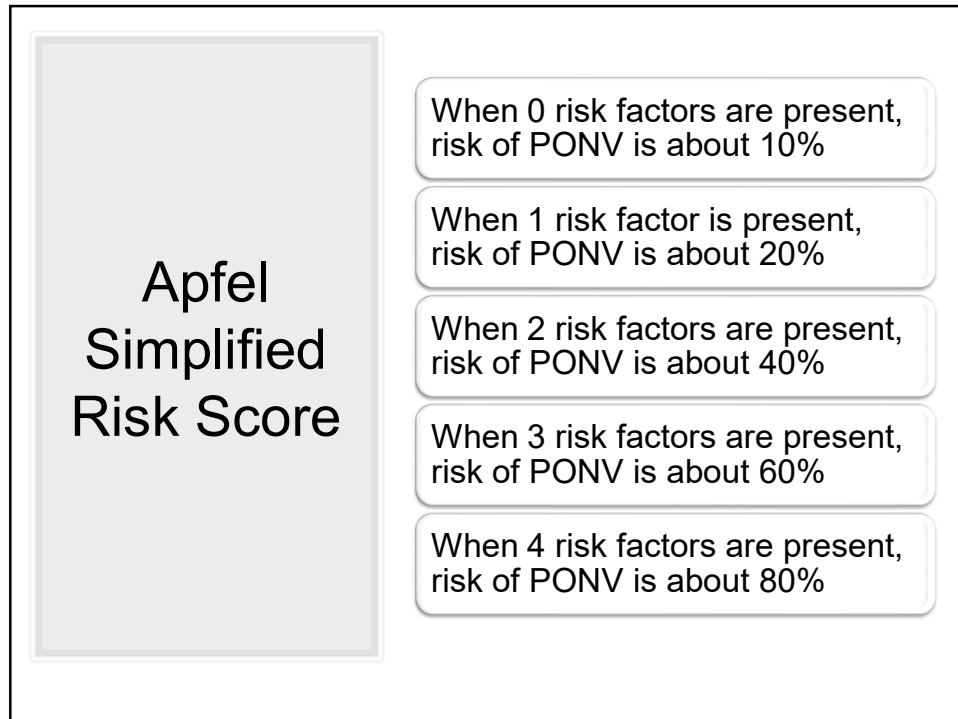
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Apfel Simplified Risk Score

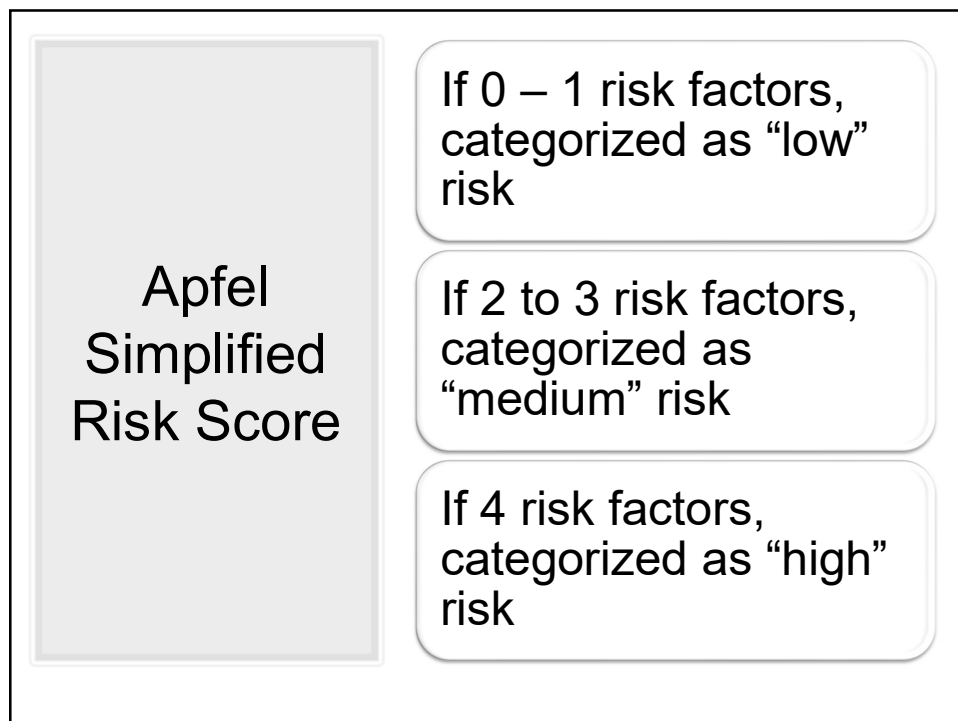
Predicts a patient's risk of PONV based on presence of 4 risk factors

Risk Factors	Points
Female Gender	1
Non-smoker	1
History of PONV	1
Postoperative Opioids	1
Sum	0 to 4

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Strategies to Reduce Baseline Risk

Reducing baseline risk factors can significantly decrease the incidence of PONV

Strategies recommended to reduce baseline risk include:

- Avoidance of general anesthesia by the use of regional anesthesia
- Preferential use of propofol infusions
- Avoidance of nitrous oxide
- Avoidance of volatile anesthetics
- Minimization of peri-operative opioids
- Adequate hydration

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PONV Prophylaxis

Who should receive PONV prophylaxis and the number of interventions used depends on risk

Low risk

- Prophylaxis not recommended
- Use a wait and see approach

Medium risk

- Use 1 or 2 interventions

High risk

- Use more than 2 interventions (a multimodal approach)

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Monotherapy

5-HT₃ receptor antagonists

- Ondansetron is the “gold standard” antiemetic
- Granisetron
- Ramosetron
- The 5HT₃ receptor antagonists are most effective for prophylaxis when given at the end of surgery

NK-1 receptor antagonists

- Aprepitant
- Similar to ondansetron in achieving complete response 24 hours after surgery
- Significantly more effective than ondansetron for preventing vomiting at 24 and 48 hours after surgery and reducing nausea 48 hours after surgery
- Given within 3 hours of the induction of anesthesia

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Monotherapy

Corticosteroids

- Dexamethasone
- Similar efficacy to ondansetron and droperidol
- Given at induction of anesthesia

Butyrophenones

- Droperidol
- Similar efficacy to ondansetron
- Given at the end of surgery
- Low doses used for PONV and hence unlikely to be associated with significant cardiovascular events

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Two Drug Combination Therapy

Combination therapy for PONV is preferable to using a single drug alone

Adults at moderate or high risk for PONV should receive combination therapy with drugs from different classes

The following combinations are frequently used

- 5-HT₃ RA plus droperidol
- 5-HT₃ RA plus dexamethasone
- Droperidol plus dexamethasone

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Treatment of PONV

When N/V occur postoperatively, treatment should be administered with an antiemetic from a pharmacologic class that is different from the prophylactic drug(s) given

If no prophylactic drug(s) were given, the recommended treatment is a low-dose 5-HT₃ receptor antagonist

- Doses of 5-HT₃ RA are lower for treatment than for prophylaxis
- Ondansetron 1mg, Granisetron 0.1mg

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Treatment of N/V in Disorders of Balance

Disorders of balance include vertigo, dizziness, and motion sickness

Antihistaminergic-Anticholinergic agents work best

Give medication prior to motion

- They are thought to act as vestibular depressants and hence can help decrease vertigo in addition to nausea and vomiting

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H₁ antagonist

meclizine (Antivert®) OTC

- 25 mg Given 1 hour prior to travel or every 12-24 hours as needed

diphenhydramine (Benadryl®) OTC

- 25-50 mg po q6h prn (max 400mg)
- Liquid available

hydroxyzine (Atarax®) RX

- 25-50 mg po q6h prn

dimenhydrinate (Dramamine®) OTC

- 50-100 mg po, IV/IM q4h prn (max 400mg)

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Anticholinergic agent

Transdermal scopolamine patch

No better than antihistamines

Apply 1 patch to hairless area behind ear at least 4 hours prior to exposure and q3 days prn

Effective if applied as soon as 2-3 hours before need, best if 12 hours before

ADR: Anticholinergic (esp confusion, visual changes)

DI: CNS depressants, anticholinergic agents

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Overview: Antiemetic Use During pregnancy

Up to 75% of pregnant woman nausea and vomiting to some degree during the first trimester

Symptoms are self-limiting for most women but 1% to 3% develop hyperemesis gravidarum

Hyperemesis gravidarum is marked by severe N/V and complications requiring hospitalization

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Prevention and Treatment (Mild N/V in Pregnancy)

Taking prenatal vitamins for 3 months prior to conception may reduce the incidence and severity of N/V in pregnancy

First-line therapy for treatment

- Pyridoxine (10-25 mg 1-4 times daily) with or without doxylamine (12.5-20 mg 1-4 times daily)
- Diclegis® - cost - \$627 for 100 tablets
- Can acquire each separately OTC or the combination by prescription

Treatment with ginger has shown benefit in reducing nausea and can be considered a nonpharmacologic option

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Treatment of Severe N/V in Pregnancy or Hyperemesis Gravidarum

If dehydrated, the patient should receive IV fluid replacement with thiamine

Ondansetron

- 2-8 mg orally/IV every 8 mg daily
- Avoid in first trimester if possible (Cat B)
- Increased risk for cleft palate
- QT prolongation

For refractory cases, can treat with methylprednisolone

- 16 mg orally/IV every 8 hours for 3 days then taper for two weeks
- No more than 6 weeks therapy
- Cat C (D in first trimester)
- Increased risk of still birth and other forms of teratogenicity

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Take Home Points

Differentiate between patient self treatment and when they should seek additional care and which OTC drug should be recommended

The overall goal of treatment should be to prevent or eliminate nausea and vomiting regardless of etiology.

Treatment options for nausea and vomiting include drug and non-drug modalities such as relaxation, biofeedback, and self-hypnosis.

The primary goal with chemotherapy-induced nausea and vomiting (CINV) is to prevent nausea and/or vomiting and the emetic risk of the chemotherapeutic regimen is a major factor to consider when selecting a prophylactic regimen.

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Take home Points

Patients at high risk of vomiting should receive prophylactic antiemetics for postoperative nausea and vomiting (PONV)

Patients undergoing radiation therapy (RT) to the upper abdomen or receiving total or hemibody irradiation should receive prophylactic antiemetics for radiation-induced nausea and vomiting (RINV)

Beneficial therapy for patients with balance disorders can most reliably be found among the antihistaminic-anticholinergic agents.

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