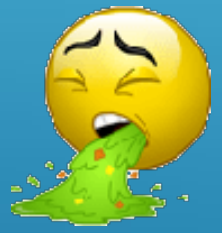
Antiemetics:

Revisiting an Old Topic ad Nauseam



Bernard Lee, Pharm.D., BCPS, BCPPS
Clinical Pharmacist
Johns Hopkins All Children's Hospital
St. Petersburg, FL

DISCLOSURES

- None

OBJECTIVES - TECHNICIANS

- Discuss the pathophysiologic mechanisms of nausea and vomiting
- Differentiate the between common and uncommon pharmacologic drug combinations aimed to remedy nausea and vomiting
- Explore novel drug classes and new agents aimed to treat nausea and vomiting

OBJECTIVES - PHARMACISTS

- Establish the etiology and pathophysiology of nausea and vomiting
- Differentiate the between established pathologic and iatrogenic management strategies aimed to remedy nausea and vomiting
- Explore novel drug classes and new agents strategies aimed to treat nausea and vomiting

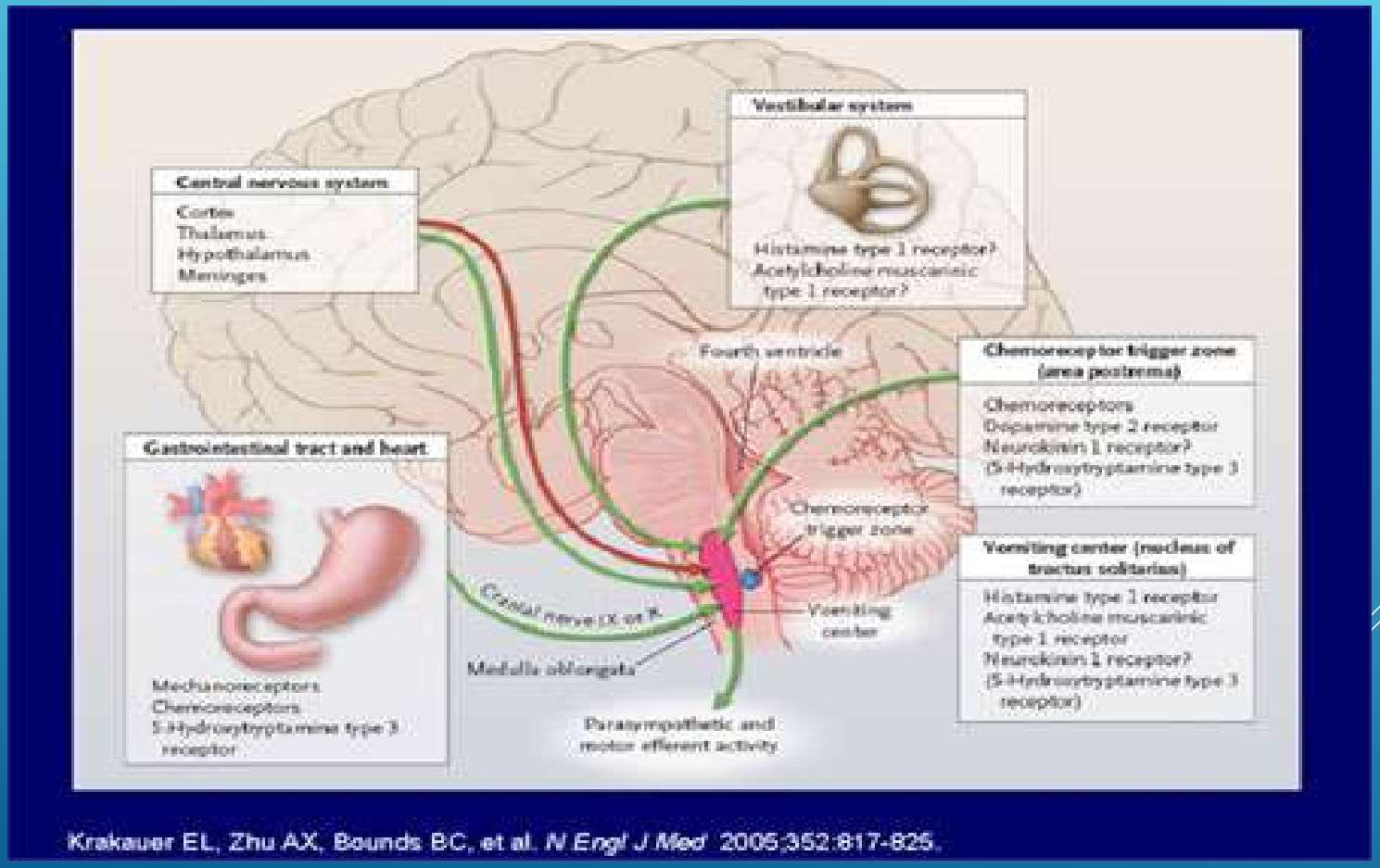
NAUSEA AND VOMITING (N/V) DEFINITION

- Nausea
  - Inclination to vomit, a feeling in the throat or epigastric region alerting that vomiting is imminent
- Vomiting
  - Ejection or expulsion of gastric contents through the mouth

ETIOLOGY AND RISK FACTORS

- Mechanical obstruction
- Acute gastroenteritis
- Cardiovascular diseases
- Migraine headache
- Diabetic ketoacidosis
- Elevated ICP
- Radiation Therapy
- Drugs and withdrawal
- Conditioning/ Psychologic
- Anxiety
- Pregnancy
- Uremia

THE CHEMORECEPTOR TRIGGER ZONE ("IT'S ALL IN YOUR HEAD")



Krakauer EL, Zhu AX, Bounds BC, et al. *N Engl J Med* 2005;352:817-825.

GOALS OF THERAPY

- Prevent or eliminate nausea and vomiting
  - Minimize adverse effects
- Manage costs
  - Particularly important for management of chemotherapy-induced and postoperative nausea and vomiting

NON-PHARMACOLOGIC THERAPY

- Dietary
  - Avoidance/moderation of irritating foods in dietary intake
- Physical
  - If due to motion sickness, maintain stable position
- Psychological
  - Relaxation, biofeedback, aroma therapy, self-hypnosis, cognitive distraction, guided imagery, systematic desensitization
- Treat underlying/contributing illness(es)

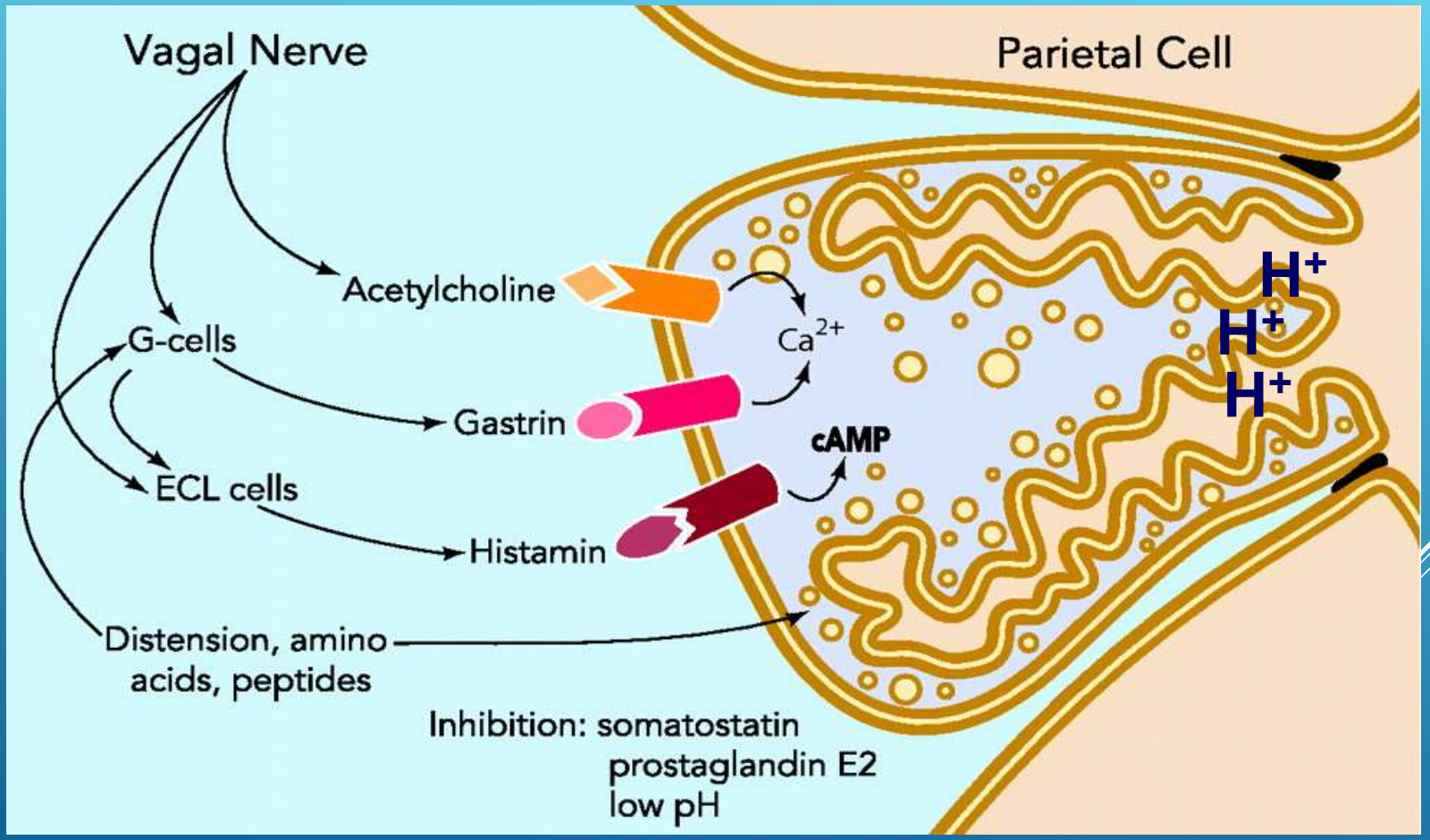
NON-ANTIEMETIC PHARMACOLOGIC THERAPY

- Acid suppression
  - Similar efficacy (e.g. ulcer-healing rates, maintenance effect, GERD relief, etc.) among all PPIs when used in recommended dosages
    - Degree of acid suppression increases over first 3-4 days
  - Comparable efficacy among equipotent multiple daily doses or single full dose of H2RAs after dinner or QHS
    - Tachyphylaxis to anti-secretory effect occurs

NON-ANTIEMETIC PHARMACOLOGIC THERAPY

- Adjunctive therapy
  - Sucralfate
  - Bismuth preparations
- High Risk patients
  - Ulcer Complications
  - Failed *H. pylori* Eradication
  - *H. pylori*-negative ulcers

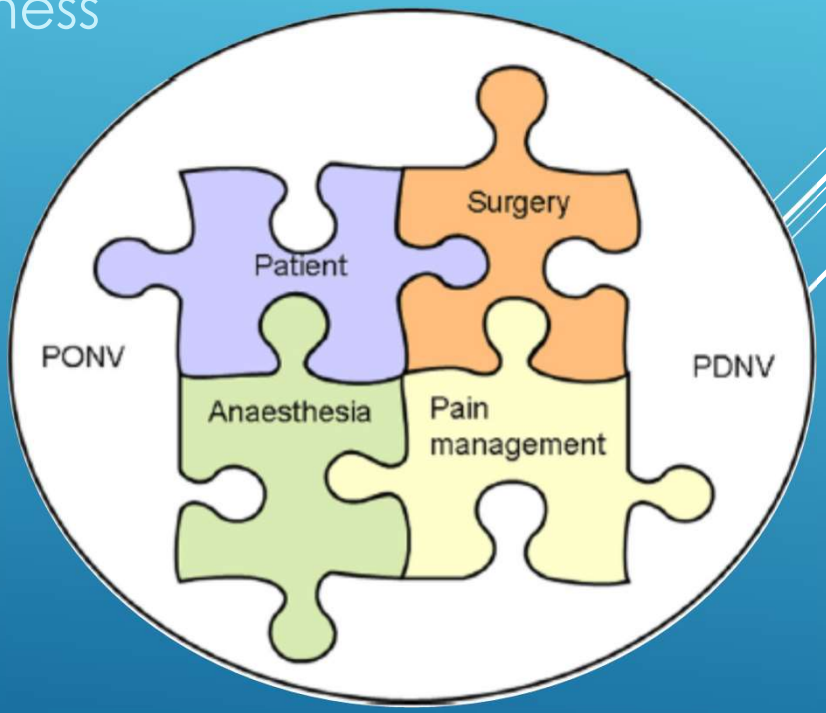
ACID SUPPRESSION PHARMACOLOGY



Heitzmann D, Warth R. Physiology (Bethesda). 2007 Oct;22:335-41.

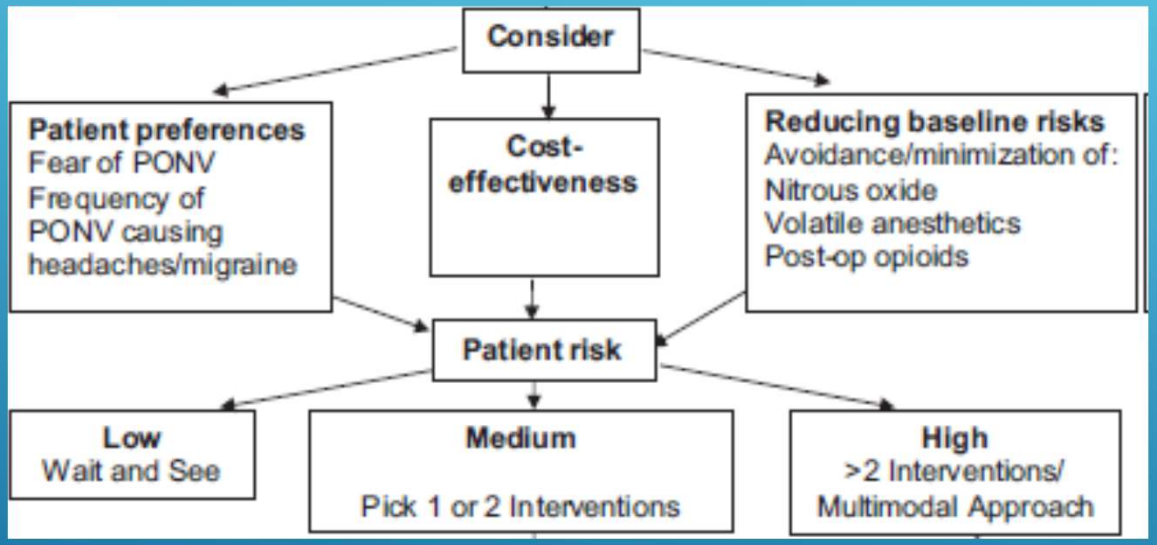
POSTOPERATIVE N&V (PONV)

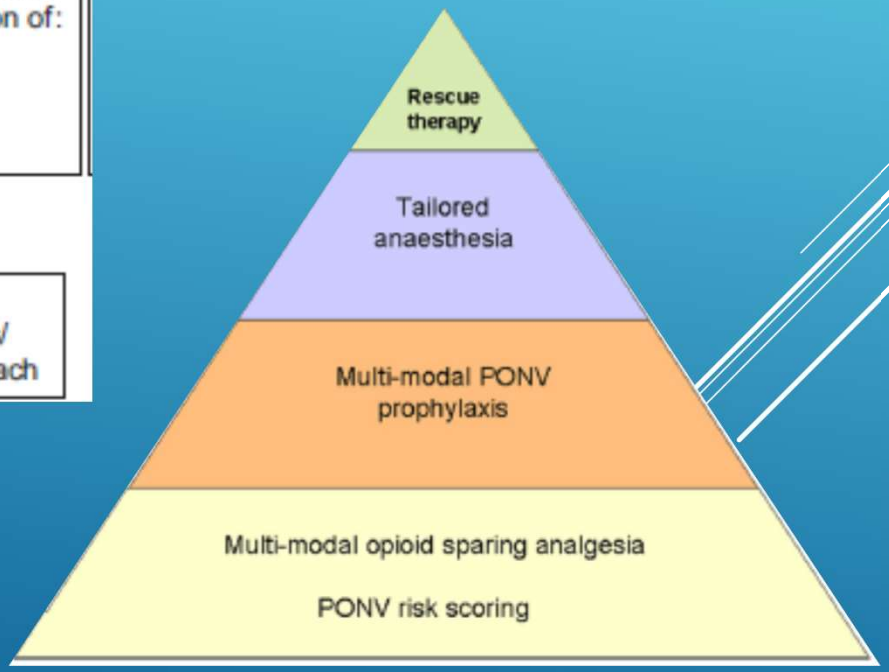
- Adult Risk Factors
  - History of previous PONV/motion sickness
  - Female gender
  - Non-smoker
  - Postoperative opioids
  - Emetogenic Surgery
- Pediatric Risk Factors
  - Surgery > 30 min
  - Stabismus surgery
  - History or +family history of PONV



Int J Surg. 2015 Mar;15:100-6.
Anesth Analg. 2014 Jan;118(1):85-113

POSTOPERATIVE N&V (PONV) APPROACHES





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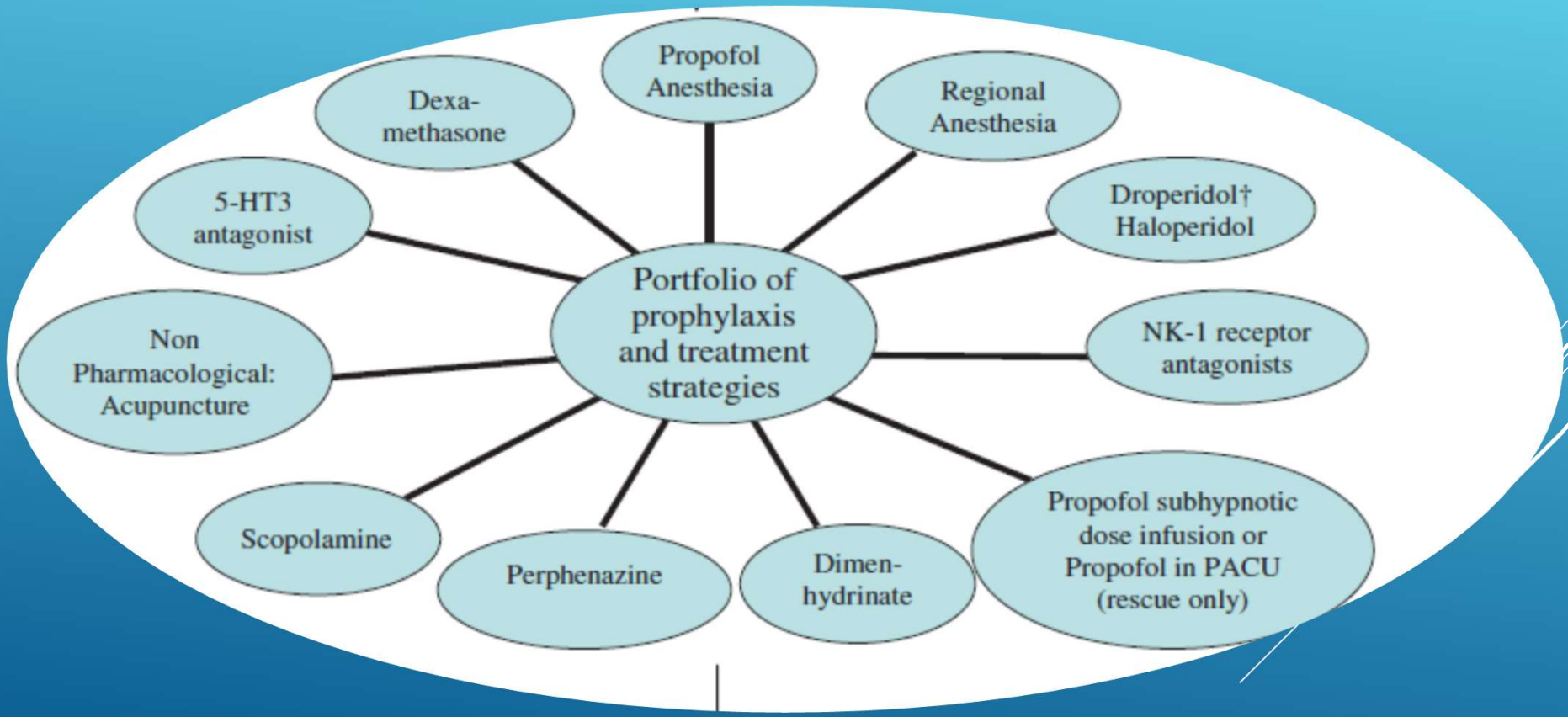
POSTOPERATIVE N&V (PONV) AGENTS



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POSTOPERATIVE N&V (PONV) AGENTS

Table 3. Antiemetic Doses and Timing for Prevention of PONV in Adults

Drugs	Dose	Evidence	Timing	Evidence
Aprepitant	40 mg per os	A2[113,115]	At induction	A2[113]
Casopitant	150 mg per os	A3[117,118]	At induction	
Dexamethasone	4–5 mg IV	A1[121]	At induction	A1[326]
Dimenhydrinate	1 mg/kg IV	A1[152–154]		
Dolasetron	12.5 mg IV	A2[84,85]	End of surgery; timing may not affect efficacy	A2[85]
Droperidol[a]	0.625–1.25 mg IV	A1[138,139]	End of surgery	A1[140]
Ephedrine	0.5 mg/kg IM	A2[223,224]		
Granisetron	0.35–3 mg IV	A1[91–93]	End of surgery	A1[108–110]
Haloperidol	0.5–<2 mg IM/IV	A1[146]		
Methylprednisolone	40 mg IV	A2[137]		
Ondansetron	4 mg IV, 8 mg ODT	A1[74,75]	End of surgery	A1[107]
Palonosetron	0.075 mg IV	A2[105,106]	At induction	A2[105,106]
Perphenazine	5 mg IV	A1[162]		
Promethazine	6.25 - 12.5 mg IV	A2[222,295]		
Ramosetron ★	0.3 mg IV	A2[102]	End of surgery	A2[102]
Rolapitant	70–200 mg per os	A3[119]	At induction	
Scopolamine	Transdermal patch	A1[157,158]	Prior evening or 2 h before surgery	A1[157]
Tropisetron ★	2 mg IV	A1[97]	End of surgery	Expert opinion

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CHEMOTHERAPY INDUCED N&V (CINV)

- **Cytotoxic chemotherapy**
- **Radiation**
- Anticonvulsants
- Digoxin
- Opiates
- Antibiotics

PHARMACOLOGIC THERAPY

- Antihistamine/Anticholinergic Drugs
- 5-HT3 Receptor Antagonists
- Corticosteroids
- Metoclopramide
- Phenothiazines
- Butyrophenones
- Atypical antipsychotics
- Substance P/Neurokinin 1 Receptor Antagonists
- Cannabinoids

ANTIHISTAMINE/ANTICHOLINERGICS EFFICACY & SAFETY

- **Agents:** dimenhydrinate (Dramamine®), diphenhydramine (Benadryl®), hydroxyzine (Atarax®), meclizine (Antivert®), scopolamine (Transderm Scop®)
- **MOA:** Histamine and acetylcholine receptor inhibition effect in CNS chemoreceptor trigger zone
- **Role:** Simple nausea and vomiting
- **ADRs:** drowsiness, confusion, blurred vision, dry mouth, urinary retention, tachycardia (elderly)
  - Caution for more pronounced effects in elderly

5-HT_3 RECEPTOR ANTAGONISTS EFFICACY & SAFETY

- **Agents:** ondansetron (Zofran®), dolasetron (Anzemet®), granisetron (Kytril®), palonosetron (Aloxi®)
- **MOA:** Serotonin ($5HT_3$) receptor blockade in CNS chemoreceptor trigger zone and presynaptic on sensory vagal fibers in gut wall
- **Role:** Acute phase CINV, PONV, radiation-induced N/V (RINV)
- **ADRs**: constipation, headache, asthenia, QT prolongation
- **Drug Interactions:** Other QT-prolonging agents

CORTICOSTEROIDS EFFICACY & SAFETY

- **Agents:** dexamethasone (Decadron®), prednisone (Deltasone®), prednisolone (Orapred®), methylprednisolone (Medrol®, Solumedrol®)
- **MOA:** Not well understood
  - May antagonize prostaglandin or release endorphins
- **Role:** CINV and PONV
  - Not indicated for simple nausea and vomiting or prolonged use
- **ADRs:** hyperglycemia, flushing (single doses well tolerated)

Am J Health-Syst Pharm 2005;62:1247-1262

METOCLOPRAMIDE EFFICACY & SAFETY

- **MOA:** Dopamine blockade in chemoreceptor trigger zone, increases lower esophageal sphincter tone, prokinetic aids in gastric emptying, accelerates small bowel transit
- **Role:** Useful as antiemetic in patients with diabetic gastroparesis
- **ADRs:** tardive dyskinesia, fluid retention, acute dystonic reactions, hallucinations (rare), akathisia, parkinsonian-like symptoms
  - Risks usually outweigh benefits

PHENOTHIAZINES
EFFICACY & SAFETY

- **Agents:** promethazine (Phenergan®), prochlorperazine (Compazine®), chlorpromazine (Thorazine®)
- **MOA:** Dopamine receptor inhibition in CNS chemoreceptor trigger zone
- **Role:** Simple nausea and vomiting
  - Reasonable long-term treatment option
- **ADRs:** extrapyramidal reactions, hypersensitivity reactions, excessive sedation
- **Drug Interactions:** Other QT-prolonging agents

BUTYROPHENONES EFFICACY & SAFETY

- **Agents:** haloperidol (Haldol®), droperidol (Inapsine®)
- **MOA:** Dopamine receptor inhibition in CNS chemoreceptor trigger zone
- **Role:** PONV
  - Haloperidol NOT considered first-line for uncomplicated N/V
- **ADRs:** somnolence, dysphoric mood, hypotension, tachycardia, dystonic reactions, EPS
- **Drug Interactions:** Other QTc-prolonging agents

ATYPICAL ANTIPSYCHOTICS EFFICACY & SAFETY

- **Agents:** olanzapine (Zyprexa®, Zydis®)
- **MOA:** Dopamine receptor inhibition in CNS chemoreceptor trigger zone
- **Role:** CINV
  - NOT considered first-line for uncomplicated N/V
- **ADRs:** somnolence, dysphoric mood, dystonic reactions, EPS, tachycardia (typically < butyrophenones)
- **Drug Interactions:** Other QTc-prolonging agents

SUBSTANCE P/NEUROKININ 1 RECEPTOR ANTAGONISTS EFFICACY

- **Agent**: aprepitant (Emend®), fosaprepitant (Emend® IV), rolapitant (Varubi®), netupitant/palonosetron (Akynzeo®)
- **MOA:** Selective substance P/neurokinin 1 receptor antagonist in CNS chemoreceptor trigger zone
  - *Acute* N&V mediated by serotonin and substance P
  - Substance P primary mediator of *delayed* N&V
- **Role:** CINV, in multi-antiemtic drug combinations for highly emetogenic chemotherapy regimens

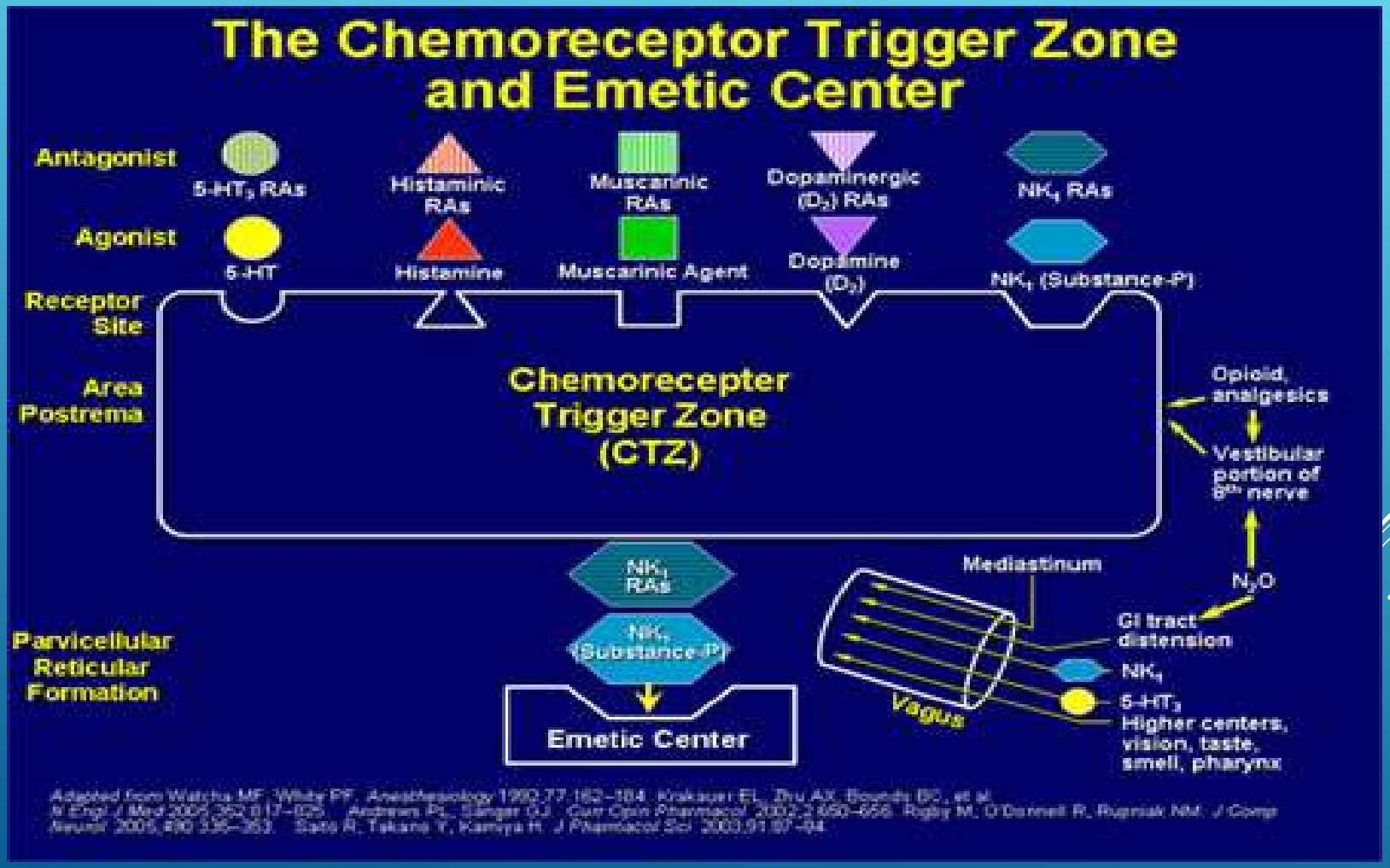
SUBSTANCE P/NEUROKININ 1 RECEPTOR ANTAGONISTS SAFETY

- **ADRs**: constipation, diarrhea, headache, hiccoughs, fatigue
- **Drug Interactions:** oral contraceptives (decreased efficacy), warfarin (decreased INR), dexamethasone (increased concentrations)
  - Substrate, moderate inhibitor, and inducer of CYP3A4 and inducer of CYP2C9

CANNABINOIDS
EFFICACY & SAFETY

- **Agents:** dronabinol (Marinol®)
- **MOA:** Not completely understood, potentially cannabinoid receptors in neural tissues
- **Role:** CINV
  - NOT considered first-line for uncomplicated N/V
- **ADRs:** somnolence, dysphoric/euphoric moods
- **Drug Interactions:** other CNS depressive agents

ANTIEMETIC PHARMACOLOGY ALL TOGETHER



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