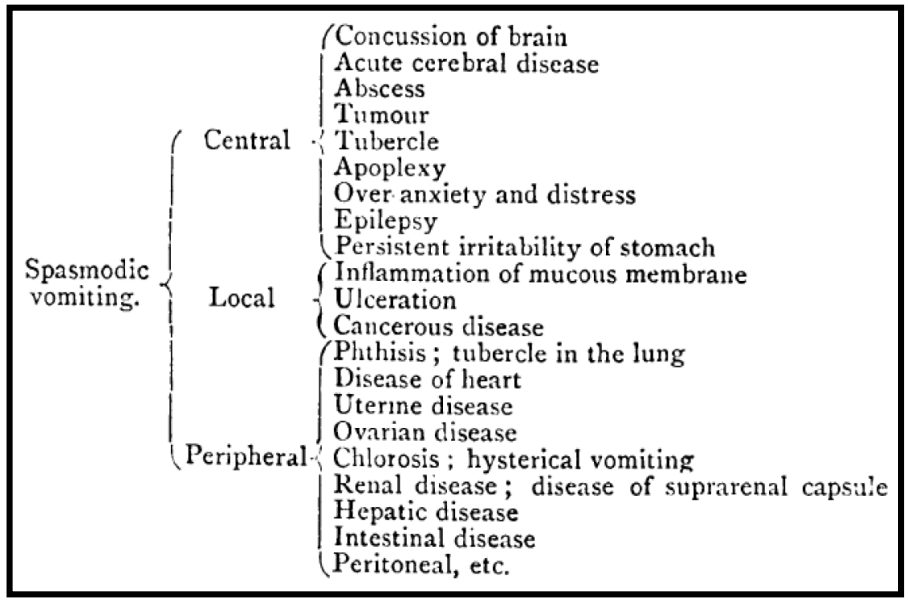
NAUSEA AND VOMITING

Prof. G. Zuliani



Spasmodic vomiting.	Central	Concussion of brain
		Acute cerebral disease
		Abscess
		Tumour
		Tubercle
		Apoplexy
		Over-anxiety and distress
		Epilepsy
		Persistent irritability of stomach
	Local	Inflammation of mucous membrane
		Ulceration
		Cancerous disease
	Peripheral	Phthisis; tubercle in the lung
		Disease of heart
		Uterine disease
		Ovarian disease
		Chlorosis; hysterical vomiting
		Renal disease; disease of suprarenal capsule
		Hepatic disease
		Intestinal disease
		Peritoneal, etc.

Habershon S.O., 'Lumleian Lectures on the Pathology of the Pneumogastric Nerve', *BMJ* (27th May 1876), p. 651.

Background

Emesis:

- Is a protective mechanism
- It rids the body of ingested toxins and poisons before dangerous amounts can be absorbed

- ***However, sometimes it is inappropriate response or not desirable (e.g. surgical procedures, chemotherapy, motion sickness)***
- Protracted emesis can cause: dehydration, malnutrition, and metabolic disturbances

Terminology

- Nausea: from the Latin *naus* (ship); very unpleasant sensation that one may soon vomit
- Retching: muscular activity of the abdomen and thorax, leading to forced inspiration against a closed mouth and glottis without oral discharge of gastric content (“dry heaves”)
- Vomiting: involuntary contractions of the abdominal, thoracic, and GI (smooth) muscles leading to forceful expulsion of stomach contents from the mouth

Terminology

Table 1. Some Definitions of Terminology

Vomiting	Forceful oral expulsion of gastric contents associated with contraction of the abdominal and chest wall musculature
Nausea	The unpleasant sensation of the imminent need to vomit, usually referred to the throat or epigastrium; a sensation that may or may not ultimately lead to the act of vomiting
Regurgitation	The act by which food is brought back into the mouth without the abdominal and diaphragmatic muscular activity that characterizes vomiting
Anorexia	Loss of desire to eat, that is, a true loss of appetite
Sitophobia	Fear of eating because of subsequent or associated discomfort
Early satiety	The feeling of being full after eating an unusually small quantity of food
Retching	Spasmodic respiratory movements against a closed glottis with contractions of the abdominal musculature without expulsion of any gastric contents, referred to as "dry heaves"
Rumination	Chewing and swallowing of regurgitated food that has come back into the mouth through a voluntary increase in abdominal pressure within minutes of eating or during eating

Pathophysiology

Vomiting occurs after stimulation of either:

- 1. **vomiting center (VC)** or
- 2. **chemo receptor trigger zone (CTZ)**

Pathways to stimulation:

- Psychological stress
- The labyrinth of the inner ear
- Chemical signals from bloodstream and CSF
- The vagal and visceral nerves by GI irritation,distension, and delayed gastric emptying

Pathophysiology

A. Vomiting Center (VC): is located in the dorsal portion of the lateral reticular formation in the medulla

- coordinates the respiratory, GI, and abdominal muscles
- vomiting can be induced by electrical stimulus of VC
- it is the final common pathway that mediates vomiting from all causes

Pathophysiology

B. Chemoreceptor Trigger Zone CTZ:

is located in area postrema on the floor of the 4° ventricle

- accessible to blood and cerebrospinal fluid (CSF)
- (may not be as important to vomiting induction as previously felt)

C. Vomiting can also be induced by direct the stimulation of the **GI tract**, and **vestibular apparatus**

Pathophysiology

- **CTZ:** is important, however:
  - when CTZ is surgically ablated can still have vomiting in response to certain toxins
- **GI tract** may be important initiator of emesis as well
- Multiple **neurotransmitters** involved in N&V:
  - *Dopamine, serotonin, acetylcholine, and histamine* found in CTZ
  - *Dopamine and serotonin* found in GI tract

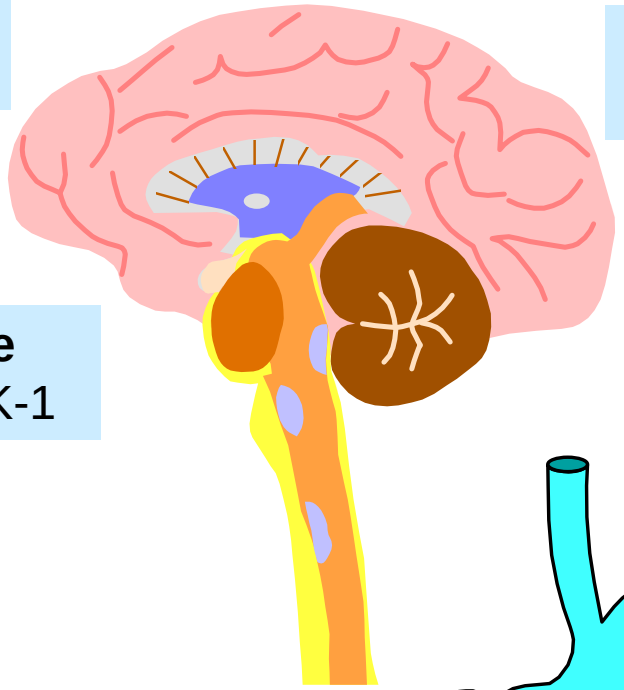
Pathophysiology

- Input to **VC** also occurs from **higher Cortical Centers**
  - e.g. patient experiences N&V in response to **terror**; also, in some cancer patients who have conditioned response and have emesis even at sight of hospital
- **Disturbance in vestibular function** -> stimulate cranial nerve VIII -> stimulates the VC.
  - **motion sickness:** main neurotransmitters involved are *acetylcholine and histamine*

Pathophysiology

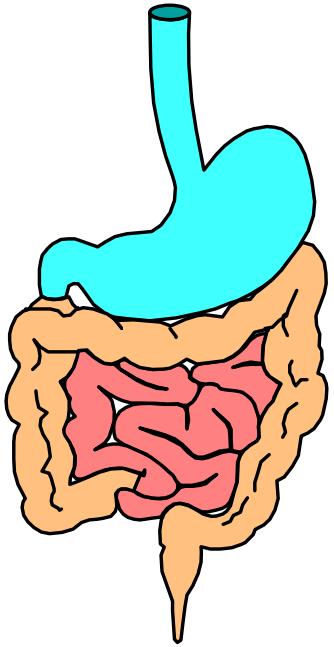
Cerebral Cortex
GABA, CB1

Chemoreceptor Trigger Zone
D2, 5HT3, NK-1



Vomiting Centre
H1, M1, 5HT2, NK-1

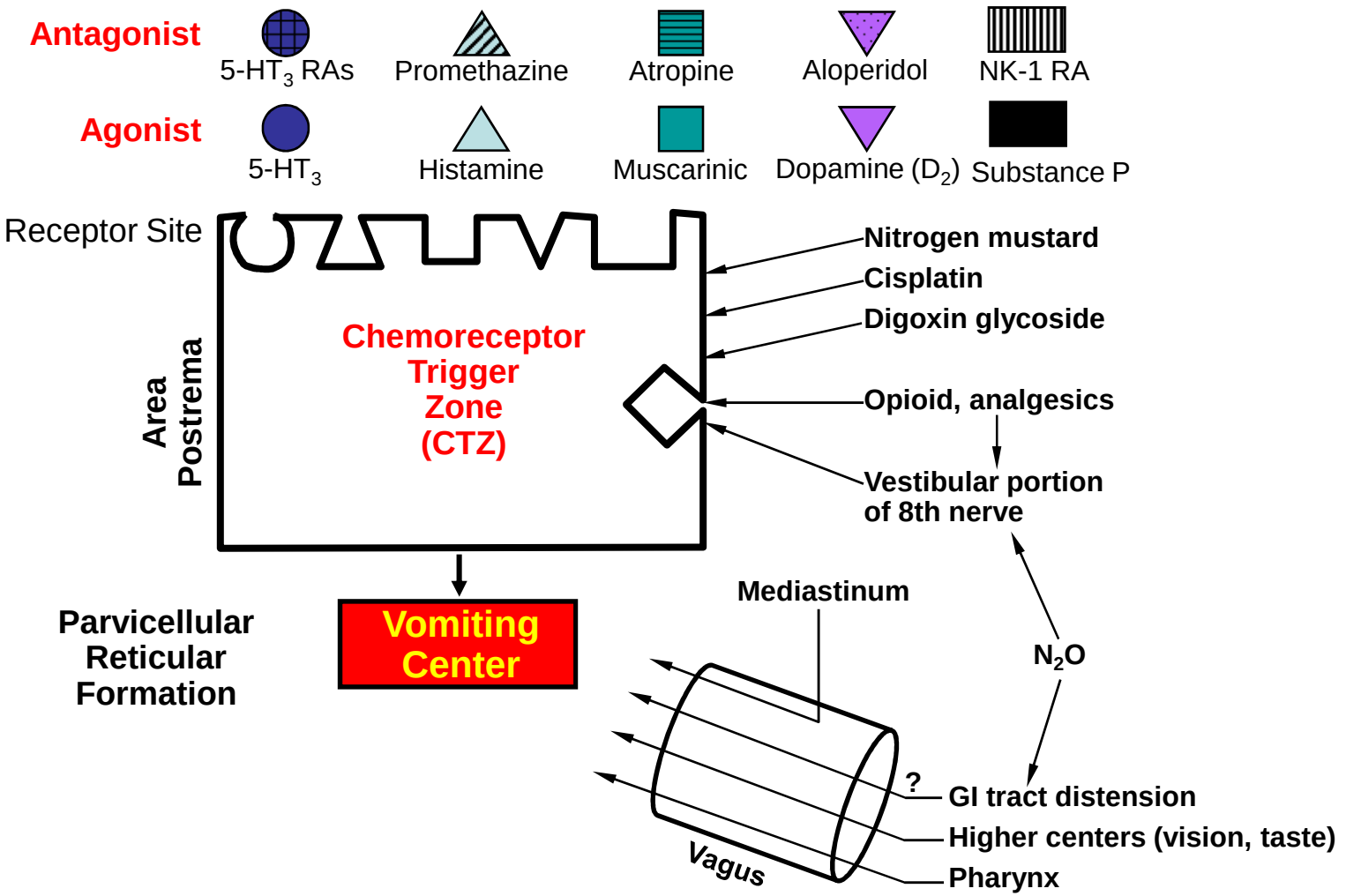
Vestibular Apparatus
H1, M1



Gastrointestinal Tract
D2, 5HT3, 5HT4

Adapted from G Fyles, 2008

Chemoreceptor Trigger Zone and Emetic Center



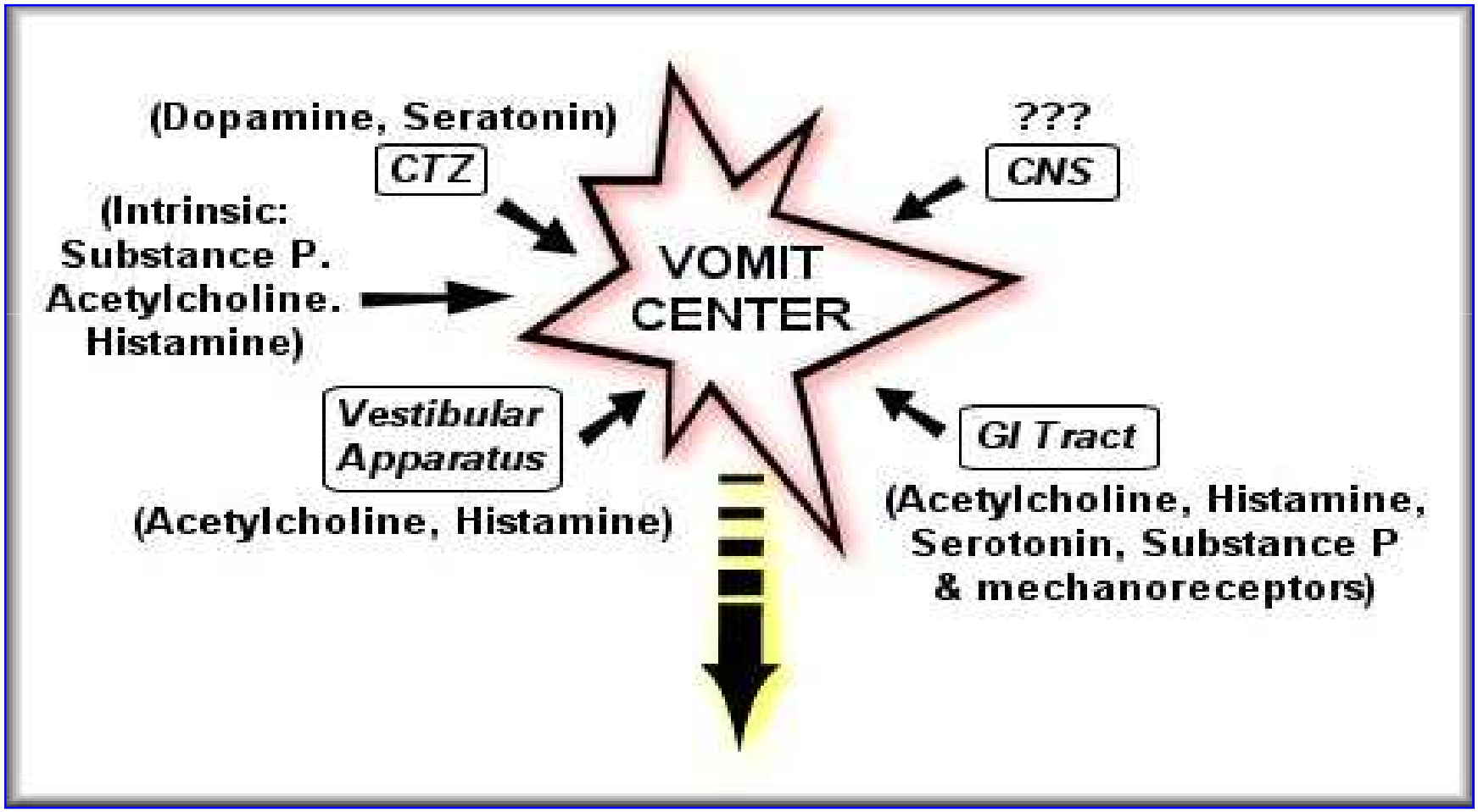
Watcha MF, White PF. *Anesthesiology*

Post Operative Nausea & Vomiting: The Role of Antiemetics - Cedric Dupont-Eisner M.D.

Stimuli of vomiting pathways

Chemoreceptor Trigger Zone	Vestibular	Cortical	Peripheral
Drugs • opioids • chemoTx Biochemical • ↑ Ca^{++} • renal failure • liver failure Sepsis Radiotherapy	Tumors Opioids	Anxiety ↑ Cranial Pressure	Radiotherapy Chemotherapy GI irritation • inflammation • obstruction • paresis • compression

A final pathway for nausea



Large inter-subject variability in emesis threshold

- 18 healthy volunteers received the same dose of the opiate/dopamine agonist ***Apomorphine***
- Dose adjusted for weight (0.03 mg/kg)
- Responses among volunteers were heterogeneous:
  - 16 reported *nausea* within 6±2 minutes after injection
  - 14 developed *vomiting* 8±2 minutes after injection while the other 2 did not vomit
  - **2 neither reported nausea nor experienced vomiting**

Cannon et al. Behavior Research & Therapy

Table 1. Differential Diagnosis of Nausea and Vomiting

Central nervous system
- Closed head injury[4]
- Increased intracranial pressure
  - Cerebrovascular accident (infarction/hemorrhage)
  - Hydrocephalus
  - Mass lesion
  - Meningitis/encephalitis/abscess
  - Pseudotumor cerebri
- Migraine
- Seizure disorders[2]
- Vestibular
  - Labyrinthitis
  - Ménière's disease
  - Motion sickness

Gastrointestinal
- Functional disorders
  - Chronic intestinal pseudo-obstruction
  - Gastroparesis
  - Irritable bowel syndrome
  - Nonulcer dyspepsia
- Obstruction
  - Adhesions
  - Esophageal disorders/achalasia
  - Intussusception
  - Malignancy
  - Pyloric stenosis
  - Strangulated hernia
  - Volvulus
- Organic disorders
  - Appendicitis
  - Cholecystitis/cholangitis
  - Hepatitis
  - Inflammatory bowel disease
  - Mesenteric ischemia
  - Pancreatitis
  - Peptic ulcer disease
  - Peritonitis

Infectious
- Acute otitis media
- Bacteria
- Bacterial toxins
- Food-borne toxins
- Pneumonia[5]
- Spontaneous bacterial peritonitis
- Urinary tract infection/pyelonephritis
- Viruses
  - Adenovirus
  - Norwalk
  - Rotavirus

Medications/Toxins
- Medications
  - Antiarrhythmics
  - Antibiotics
  - Anticonvulsants
  - Chemotherapeutics
  - Digoxin
  - Ethanol overdose
  - Hormonal preparations
  - Illicit substances
  - Nonsteroidal anti-inflammatory drugs
  - Opiates
  - Overdoses/withdrawal[6]
  - Radiation therapy
- Toxins
  - Arsenic[7]
  - Organophosphates/pesticides[8]
  - Ricin[9]

Metabolic
- Adrenal disorders
- Diabetic ketoacidosis
- Paraneoplastic syndromes
- Parathyroid disorders
- Pregnancy
- Thyroid disorders
- Uremia

Miscellaneous
- Acute glaucoma[5]
- Acute myocardial infarction
- Nephrolithiasis[10]
- Pain
- Psychiatric disorders
  - Anorexia nervosa
  - Anxiety
  - Bulimia nervosa
  - Conversion disorder
  - Depression
- Psychogenic/emotional

Common causes of nausea and vomiting

- **GI tract disorders**
  - Infections, toxins, GI obstruction, inflammation, motility disorders
- **Non-GI infections**
  - liver, CNS, renal, pneumonia, others
- **Pregnancy**
- **Visceral inflammation**
  - pancreas, GB, peritoneum
- **Myocardial ischemia or infarction !**

- **Other CNS disorders**
  - migraine, neoplasm, bleed
- **Vestibular disorders**
- **Metabolic/endocrine**
  - DKA, uremia, adrenal insufficiency, hyper-or hypothyroidism, hyper- or hypoparathyroidism
- **Alcohol intoxication**
- **Psychogenic**
- **Radiation exposure**
- **Medications**

Major causes of nausea and vomiting

Drug/treatment - induced	**Cancer chemotherapy** **Opiates** **Nicotine** **Antibiotics** **Radiotherapy**
Labyrinth disorders	**Motion** **Meniere's disease**
Endocrine causes	**Pregnancy**
Infectious causes	**Gastroenteritis** **Viral labyrinthitis**
Increased intracranial pressure	**Haemorrhage** **Meningitis**
Post-operative	**Anaesthetics** **Analgesics** **Procedural**
CNS causes	**Anticipatory** **Migraine** **Anoressia/Bulimia nervosa**

Medications that often cause nausea and vomiting

- Cancer chemotherapy
  - e.g. cisplatin
- Analgesics
  - e.g. opiates, NSAIDs
- Anti-arrhythmic
  - e.g., digoxin, quinidine
- Antibiotics
  - e.g., erythromycin
- Oral contraceptives

- Metformin
- Anti-parkinson
  - e.g., bromcryptine, **L-DOPA**
- Anti-convulsants
  - e.g., phenytoin, carbamazepine
- Theophylline
- Anesthetic agents
- Anti-hypertensives

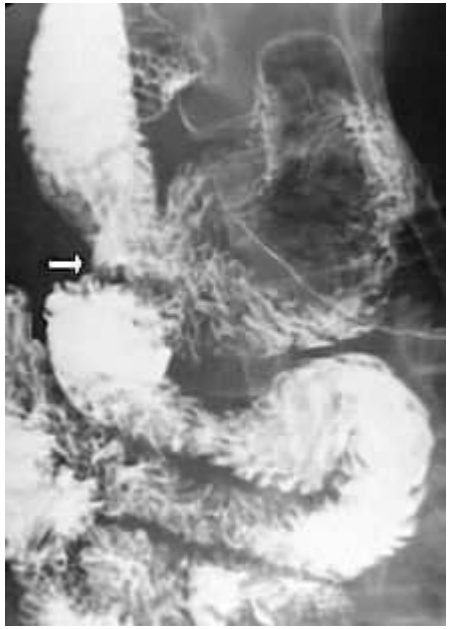
Less commonly recognized causes of nausea and vomiting

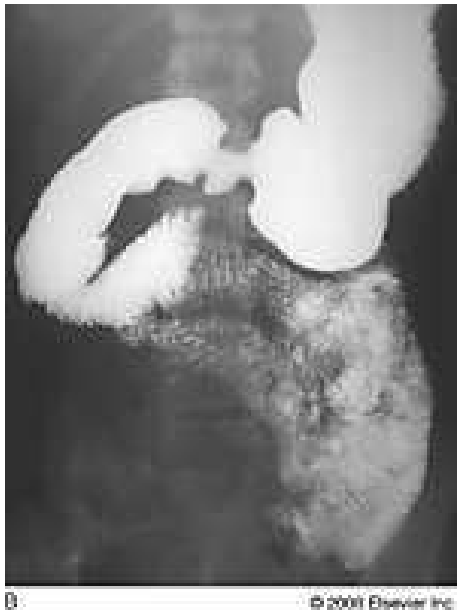
- Rapid weight loss/body casts (SMA syndrome)
- Infectious esophagitis
  - especially in immunocompromised subjects
- Opiate withdrawal
- Herbal preparations
- Pregnancy
  - nausea of early pregnancy
  - hyperemesis gravidarum
  - AFLP/ HELLP syndrome

SMA syndrome (rare)

Superior mesenteric artery syndrome is a rare cause of proximal intestinal obstruction. It has been referred to by a variety of other names including Cast syndrome, Wilkie syndrome, arteriomesenteric duodenal obstruction, and chronic duodenal ileus.

The syndrome is characterized by **compression of the 3° portion of the duodenum due to narrowing of the space between the superior mesenteric artery and aorta** with vomiting and weight loss.





AFLP/ HELLP syndrome

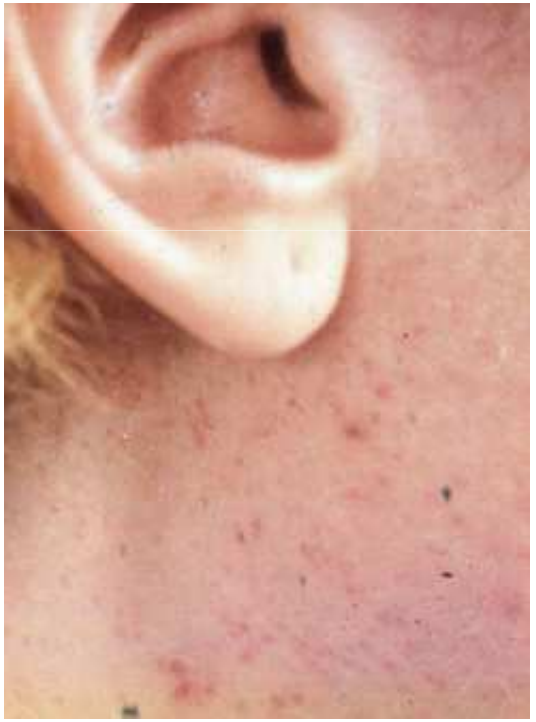
- **Acute fatty liver of pregnancy (AFLP)**
- **Pre-eclampsia, and**
- **HELLP** (haemolysis, elevated liver enzymes, and low blood platelet count) syndrome have been demonstrated as being ***the main causes of severe hepatic failure in pregnancy.*** They are thought to represent a spectrum of the same pathological process.

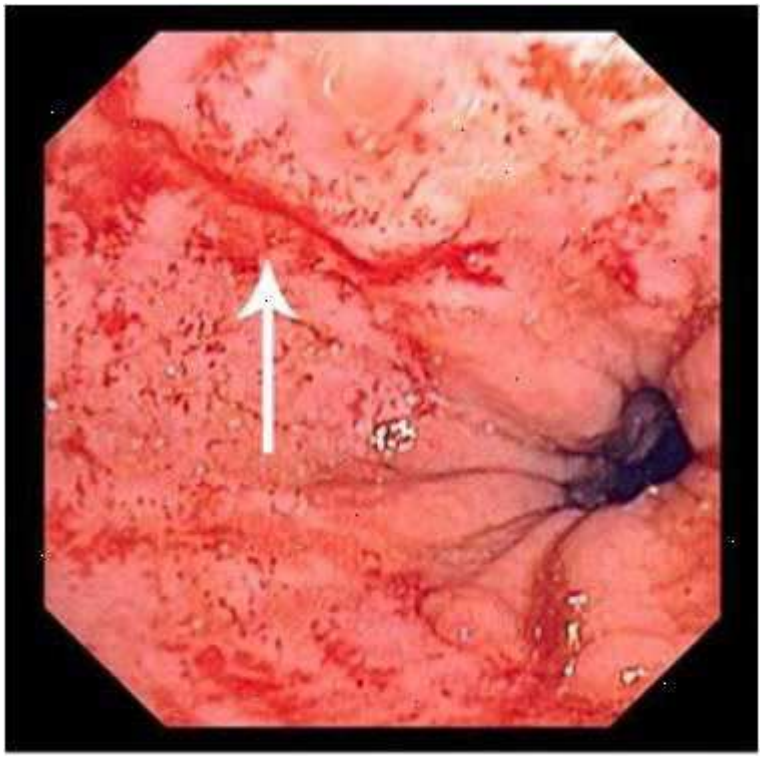
The diagnosis of liver disease in pregnancy is challenging and relies on laboratory investigations.
Signs and symptoms are often not specific and consist of **jaundice, nausea, vomiting, and abdominal pain**.
The underlying disorder can have a significant effect on morbidity and mortality in both mother and fetus, and a diagnostic workup should be initiated promptly.

Complications of Vomiting

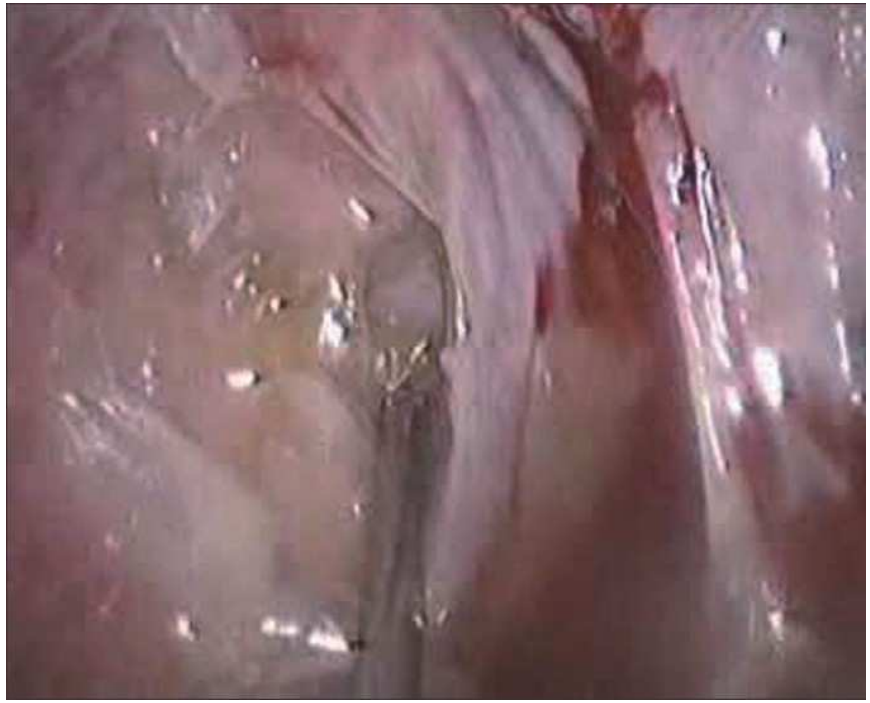
- Nutritional:
  - adults: weight loss; kids: failure to gain
- Cutaneous: petechiae, purpura
- Orophayngeal: dental, sore throat
- Esophagitis/esophageal hematoma
- GE Junctional: M-W tears; rupture: Boorhaave's)
- Metabolic: electrolyte, alkalosis, loose water
- Renal: pre-renal azotemia; acutetubular necrosis; hypokalemic nephropathy

Post-emetic purpura
(“mask phenomenom)





M-W tears



Boorhaave’s

Electrolyte and acid-base disorders due to vomiting

Metabolic alkalosis

loss H+, retention of HCO_3^- ; volume-contraction

Hypokaliemia

GI K^+ + renal K^+ losses
↓ oral K^+ intake

Hypochloremia

gastric chloride losses

Hyponatremia

free water retention due to volume contraction

Note: Patients with uremia or Addison's disease may have normal or even high serum K^+ despite vomiting !

Nausea and Vomiting: Key Questions

- How long ?
- Relationship to meals ?
- Contents of vomits ?
- Associated symptoms
  - pain in chest or abdomen, fever, myalgias, diarrhea, vertigo, dizziness, headache, focal neurological symptoms, jaundice, weight loss
- Diabetes ?
- **When was last menstrual period ?**

Table 2. Possible Diagnoses Based on the History in Patients with Nausea and Vomiting

History	*Possible diagnoses*
Onset of symptoms	
Abrupt	Cholecystitis, food poisoning, gastroenteritis, illicit drugs, medications, pancreatitis
Insidious	Gastroesophageal reflux disease, gastroparesis, medications, metabolic disorders, pregnancy
Timing of symptoms	
Before breakfast	Ethyl alcohol, increased intracranial pressure, pregnancy, uremia
During or directly after eating	Psychiatric causes
	Less likely: peptic ulcer disease or pyloric stenosis
One to four hours after a meal	Gastric outlet obstructions (e.g., from peptic ulcer disease, neoplasms), gastroparesis
Continuous	Conversion disorder, depression
Irregular	Major depression
Nature of vomited matter	
Undigested food	Achalasia, esophageal disorders (e.g., diverticulum, strictures)
Partially digested food	Gastric outlet obstruction, gastroparesis
Bile	Proximal small bowel obstruction
Feculent or odorous	Fistula, obstruction with bacterial degradation of contents
Large volume (> 1,500 mL per 24 hours)	Suggests organic rather than psychiatric causes
Abdominal pain	
Right upper quadrant	Biliary tract disease, cholecystitis
Epigastric	Pancreatic disease, peptic ulcer disease
Severe pain	Biliary disease, pancreatic disease, peritoneal irritation, small bowel obstruction
Severe pain that precedes vomiting	Small bowel obstruction
Associated symptoms/findings	
Weight loss	Malignancy (significant weight loss may also occur secondary to sitophobia in gastric outlet obstructions and peptic ulcer disease)
Diarrhea, myalgias, malaise, headache, contact with ill persons	Viral etiologies
Headache, stiff neck, vertigo, focal neurologic deficits	Central neurologic causes (e.g., encephalitis/meningitis, head injury, mass lesion or other cause of increased intracranial pressure, migraine)
Early satiety, postprandial bloating, abdominal discomfort	Gastroparesis
Repetitive migraine headaches or symptoms of irritable bowel syndrome	Cyclic vomiting syndrome

Laboratory studies: guided by history and physical

- Electrolytes, glucose, BUN/creatinine
- Calcium, albumin, total serum proteins
- CBC
- Liver
- Urinalysis
- Serum lipase ± amylase
- Pregnancy test

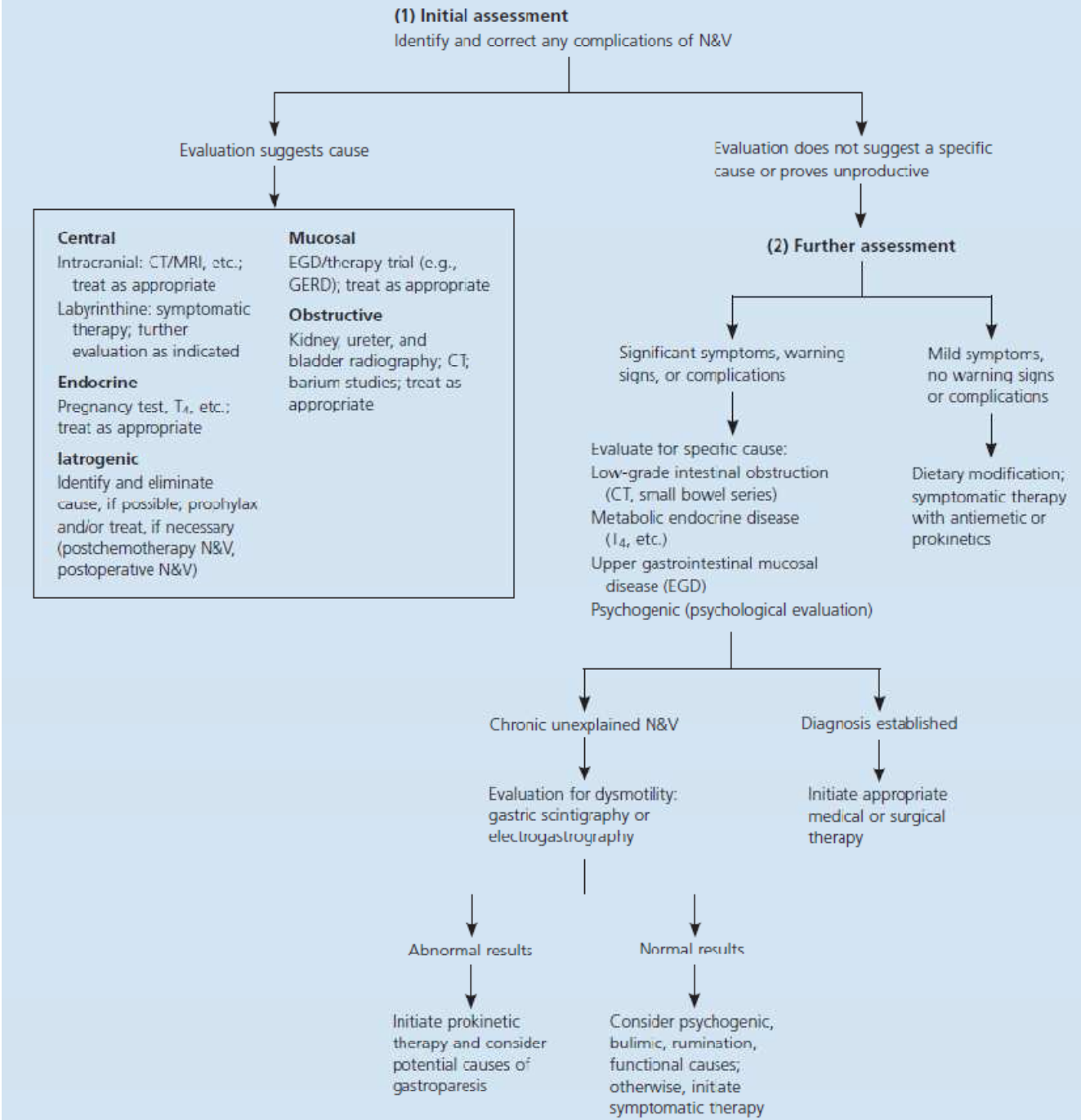
Table 3. Diagnostic Tests and Clinical Suspicion for Patients with Nausea and Vomiting

Test	*Clinical suspicion*
Laboratory tests	
Complete blood count	Leukocytosis in an inflammatory process, microcytic anemia from a mucosal process
Electrolytes	Consequences of nausea and vomiting (e.g., acidosis, alkalosis, azotemia, hypokalemia)
Erythrocyte sedimentation rate	Inflammatory process
Pancreatic/liver enzymes	For patients with upper abdominal pain or jaundice
Pregnancy test	For any female of childbearing age
Protein/albumin	Chronic organic illness or malnutrition
Specific toxins	Ingestion or use of potentially toxic medications
Thyroid-stimulating hormone	For patients with signs of thyroid toxicity or unexplained nausea and vomiting
Radiographic testing	
Supine and upright abdominal radiography	Mechanical obstruction
Further testing	
Esophagogastroduodenoscopy	Mucosal lesions (ulcers), proximal mechanical obstruction
Upper gastrointestinal radiography with barium contrast media	Mucosal lesions and higher-grade obstructions; evaluates for proximal lesions
Small bowel follow-through	Mucosal lesions and higher-grade obstructions; evaluates the small bowel to the terminal ileum
Enteroclysis	Small mucosal lesions, small bowel obstructions, small bowel cancer
Computed tomography with oral and intravenous contrast media	Obstruction, optimal technique to localize other abdominal pathology
Gastric emptying scintigraphy	Gastroparesis (suggestive)
Cutaneous electrogastrography	Gastric dysrhythmias
Antroduodenal manometry	Primary or diffuse motor disorders
Abdominal ultrasonography	Right upper quadrant pain associated with gallbladder, hepatic, or pancreatic dysfunction
Magnetic resonance imaging of the brain	Intracranial mass or lesion

Radiology studies: guided by history and physical

- **Plain abdominal films**
- **Abdominal Echo or CT if pain is key feature**
- Head CT or MRI if severe headache, papill-edema, marked hypertension, altered mental status, or focal neurological findings
- **EGDS** or upper GI to separate pylorus or high duodenal obstruction from gastroparesis
- Radiopaque marker emptying studies or radionuclide scintigraphy, esp. if diabetic

Evaluation of Nausea and Vomiting



Post Operative Nausea and Vomiting (PONV)

• Incidence of PONV: varies with age, surgical procedure, anesthetic technique

• **Vomiting unpleasant and medical risks**:

- *aspiration* of gastric content

- jeopardizes *abdominal or inguinal closures*

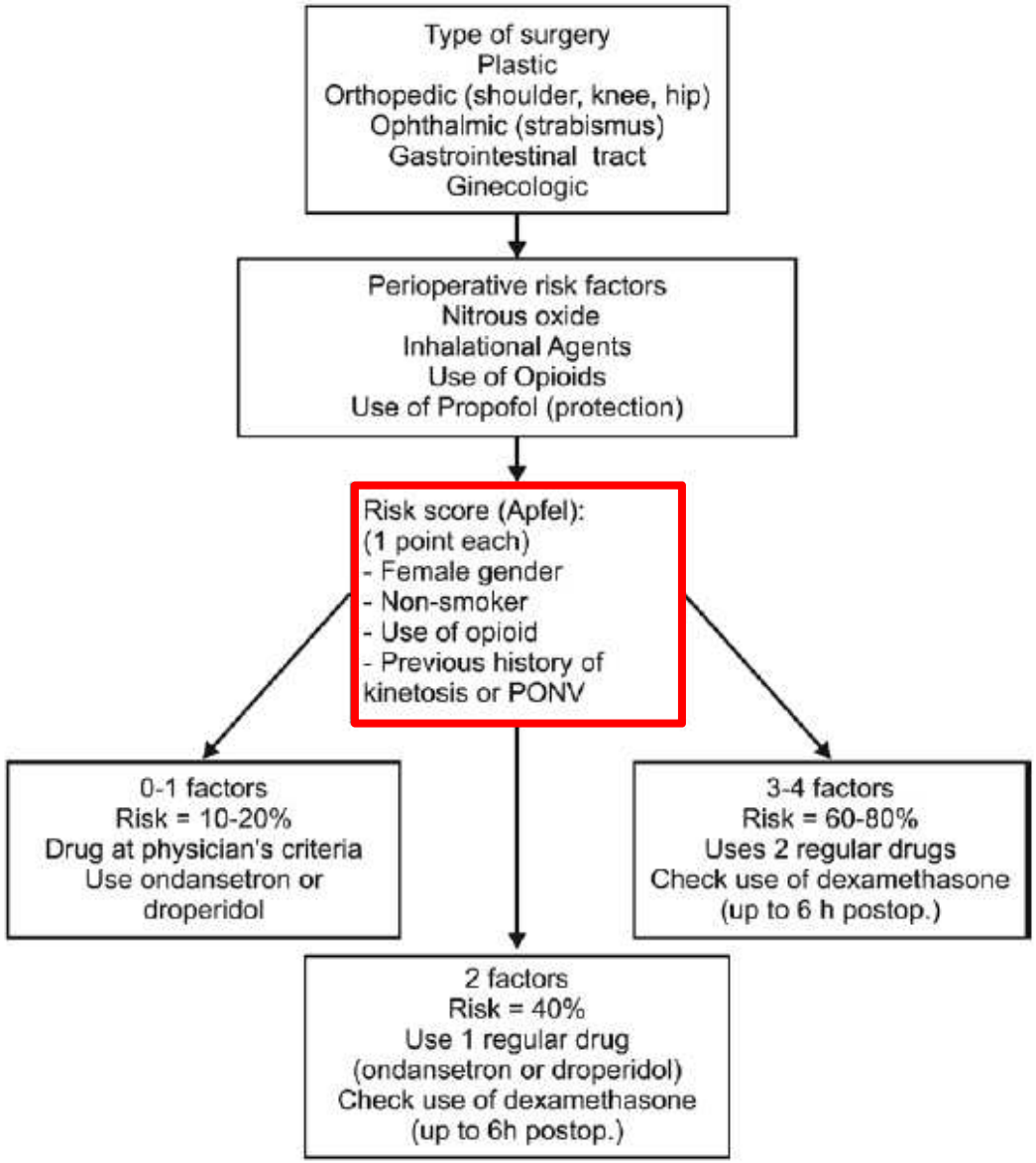
- increased IV pressure: increase morbidity after *ocular*, *tympanic*, *intracranial procedures*

- elevate HR and BP: risk for *MI and arrhythmias*

- gagging and retching: *parasympathetic* response: *bradycardia* and *hypotension*.

Major Risk Factors for PONV in Adults

- **Patient-specific Risk Factors**
  - **- Age (adult)**
  - **- Non-smoking status**
  - History of PONV / motion sickness
  - Predisposing gastric disorders
  - **- Low threshold for nausea**
  - **- Preoperative anxiety**
  - Obesity (disputed in recent studies)
  - Gastric distension (disputed in recent studies)
- **Anesthetic Risk Factors**
  - **- Pre-anesthetic medications (opioids, atropine)**
  - **- Volatile anesthetics**
  - **- Nitrous Oxide**
  - **- Intraoperative or postoperative use of opioids**
  - **- Duration of anesthesia (> 120 min**)
- **Surgical Risk Factors**
  - **- Duration of surgery (each 30 min increases PONV risk by 60%)**
  - **- Type of surgery** (craniotomy; ear, nose, throat procedures; major breast procedures; strabismus surgery; laparoscopy; laparotomy).
  - Intubation (disputed in recent studies)
  - Early oral intake



PONV – postoperative nausea and vomiting

Figure 1 - Algorithm proposed for management of postoperative nausea and vomiting.

Prophylaxis of PONV

Chart 1 – Drugs for prevention and treatment of postoperative nausea and vomiting

Drugs	Class	Dose for prophylaxis	Time of prophylaxis	Dose for treatment	Comments
Scopolamine	Anticolinergic	Transdermal patch	Up to 4 hours before end of surgery	Not indicated	Wash hands after handling patch
Dimnenhydrinate	Antihistamine	1-2 mg/kg or50-100 mg IV or IM	Before induction of anesthesia	50-100 mg IV	-
Promethazine	Phenothiazine	12.5-25mg IV. IM or trans-rectal	At end of surgery	12.5-25 mg	The 6.25 mg dose is advised for patients at risk due to sedation
Droperidol	Butyrophenones	0.625-1.25 mg IV	At end of surgery	1.25-2.5 mg IV	Electrocardiographic monitoring is needed due to risk of prolongation of QT and of *torsades de pointes*
Ondansetron	Antagonist of 5-HT3 receptors	4 mg IV	At end of surgery	4 mg IV	Risk of dose-dependent alterations
Dolasetron	Antagonist of 5-HT3 receptors	12.5 mg	At end of surgery	25-50 mg IV	Risk of dose-dependent alterations
Granisetron	Antagonist of 5-HT3 receptors	5 ug/kg or 1mg	At end of surgery	0.1 – 1 mg IV	Risk of dose-dependent alterations
Dexametasona	Corticosteroids	4-10 mg IV	Before induction of anesthesia	Not indicated	Well tolerated in single dose
Metoclopramide	Benzamides	10-20 mg IV	At end of surgery	10-20 mg IV	Indicated in case of NV induced by opioid , its use is not considered in PONV prophylaxis

IV - intravenous; IM - intramuscular; NV – nausea and vomiting; PONV – postoperative nausea and vomiting.

Treatment of nausea and vomiting

1. Treat complications regardless of cause:

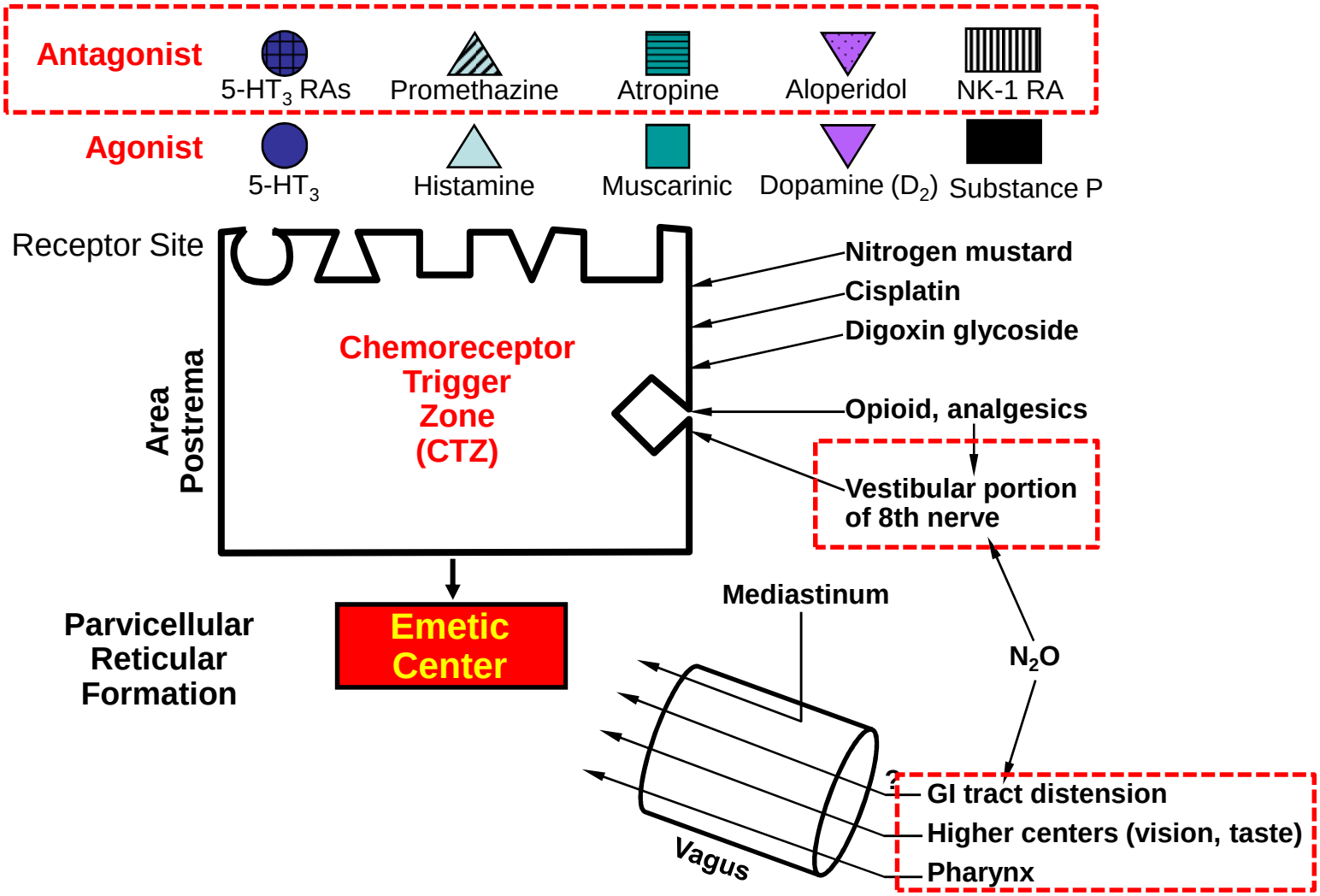
   replace salt, water, potassium losses

2. Identify and treat underlying cause, whenever possible
3. Provide temporary **symptomatic relief** of the symptoms
4. Use preventive measures when vomiting is likely to occur (e.g. cancer chemotherapy, parenteral opiate administration)

Main classes of anti-emetic drugs

Class	Drug
Anti-cholinergic	scopolamine (L-hyoscine)
Anti-histamine	cinnarizine cyclizine promethazine (?)
Dopamine antagonists	metoclopramide domperidone haloperidol (droperidol : withdrawn 2001)
Cannabinoid	nabilone
Corticosteroid	dexamethasone
Histamine analogue	betahistine
$5HT_3$-receptor antagonist	granisetron ondansetron tropisetron

Chemoreceptor Trigger Zone and Emetic Center



Watcha MF, White PF. *Anesthesiology*

Post Operative Nausea & Vomiting: The Role of Antiemetics - Cedric Dupont-Eisner M.D.

Receptor Affinities of Selected Anti-emetics

	Dopamine D2 antagonist	Histamine H1 antagonist	Acetylcholine (muscarinic) antagonist	5HT2 antagonist	5HT3 antagonist	5HT4 agonist
Metoclopramide (Maxeran®)	++	0	0	0	(+)	++
Domperidone (Motilium®)	++	0	0	0	0	0
Ondansetron (Zofran®)	0	0	0	0	+++	0
Hyoscine HydroBr (Scopolamine®)	0	0	+++	0	0	0
Haloperidol (Haldol®)	+++	0	0	0	0	0
Prochlorperazine (Stemetil®)	++	+	0	0	0	0
Chlorpromazine (Largactil®)	++	++	+	0	0	0
Methotrimeprazine (Nozinan®)	++	+++	++	+++	0	0

(Modified from Twycross & Back, European Journal of Palliative Care

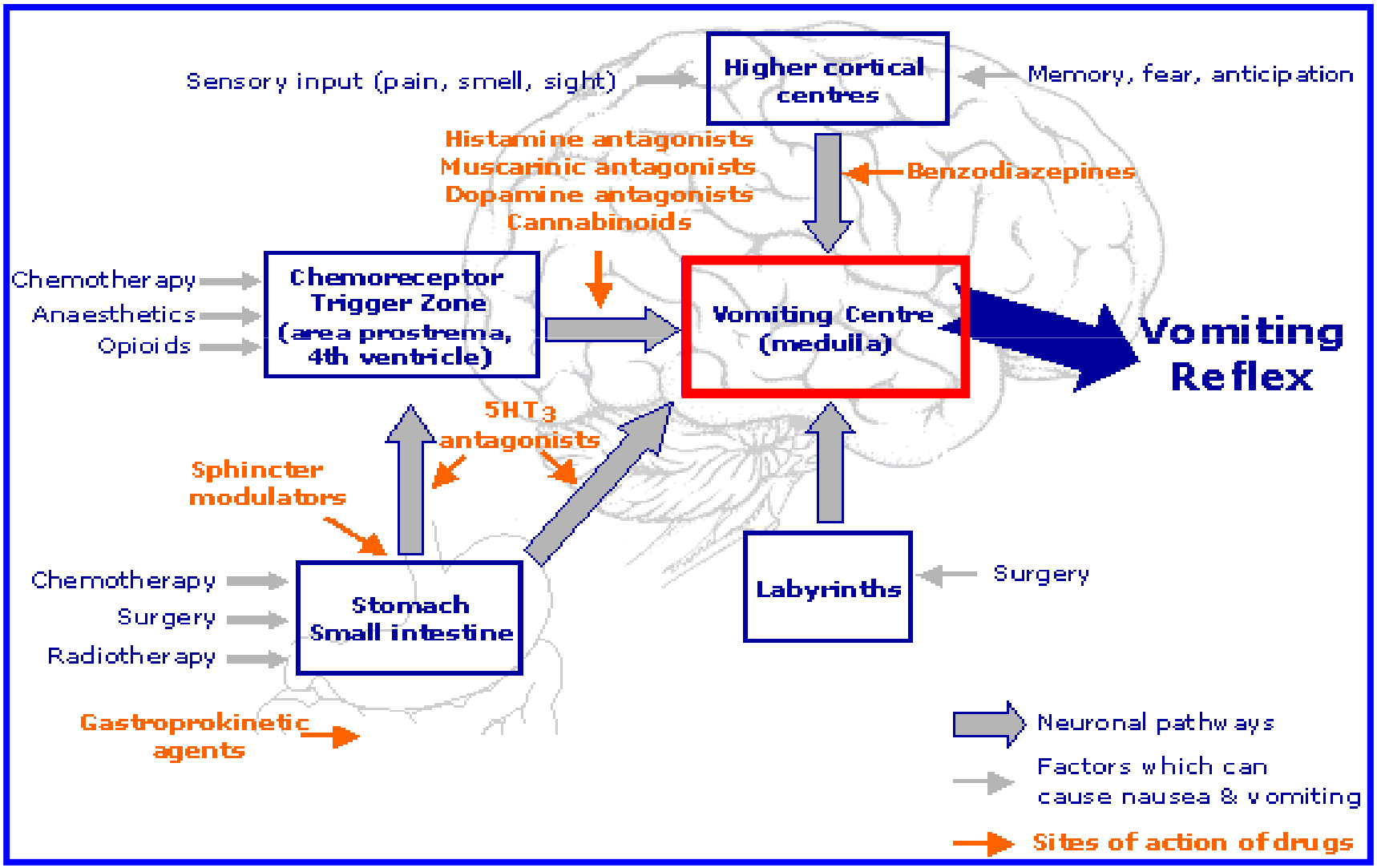
Anti-emetic drugs indications

1. **Antihistamines:** especially for vestibular disorders
2. **Anticholinergics:** especially for vestibular and GI disorders
3. **Dopamine antagonists:** especially for GI disorders
4. **Selective serotonin-3 ($5HT_3$) R-Ant:** especially to prevent chemotherapy-induced nausea/vomiting

Drugs with anti-emetic properties
Multiple mechanisms of action:

- **Promethazine (Fargan)**
  - dopamine antagonist
  - H1 antihistamine
  - anticholinergic
  - CNS sedative
  - prevention of opiate-induced nausea and vomiting
- **Hydroxyzine (Atarax)**
  - H1 antihistamine
  - anticholinergic
  - CNS sedation
  - prevention of opiate-induced nausea and vomiting

Sites of action of drugs affecting nausea and vomiting



Agonists and antagonists associated with vomiting

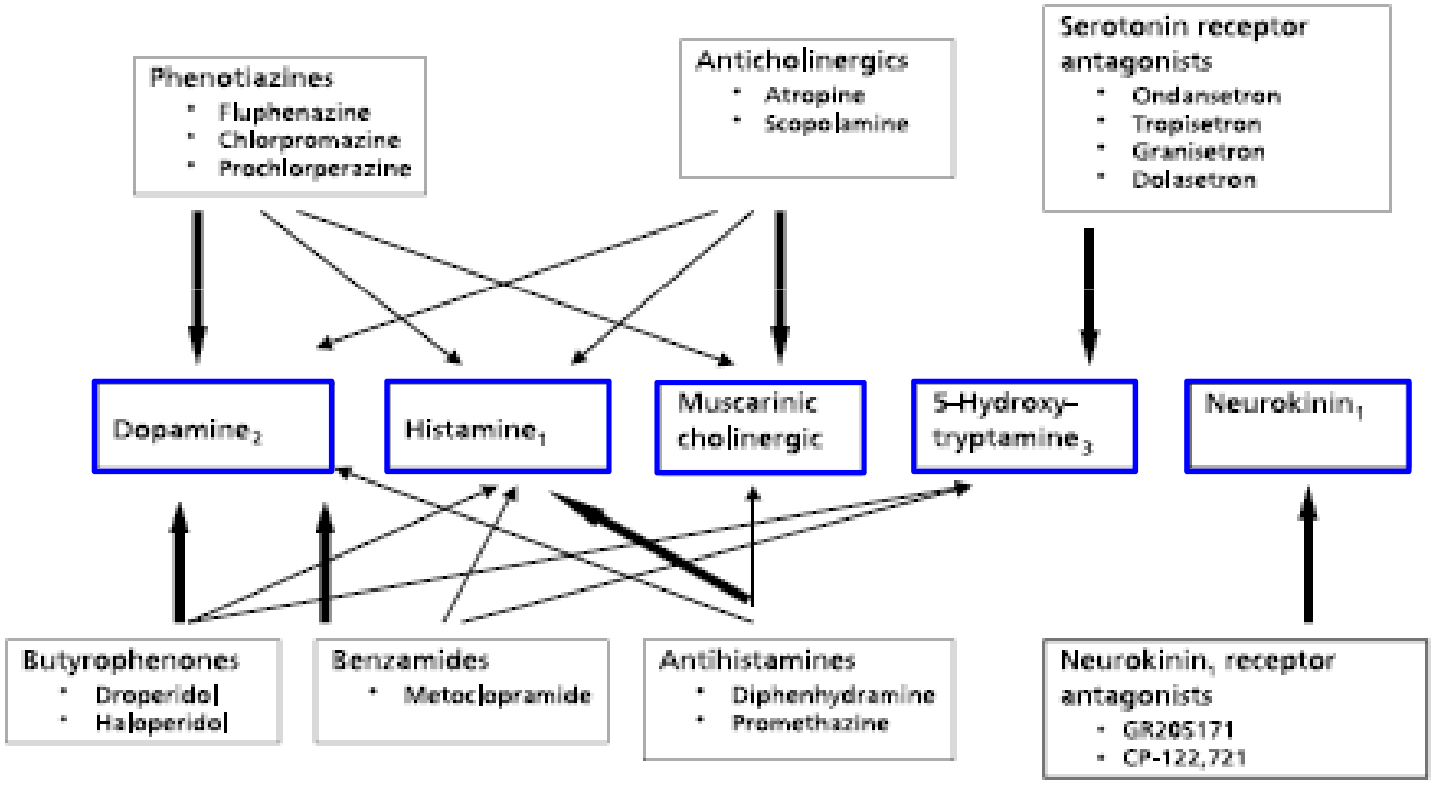


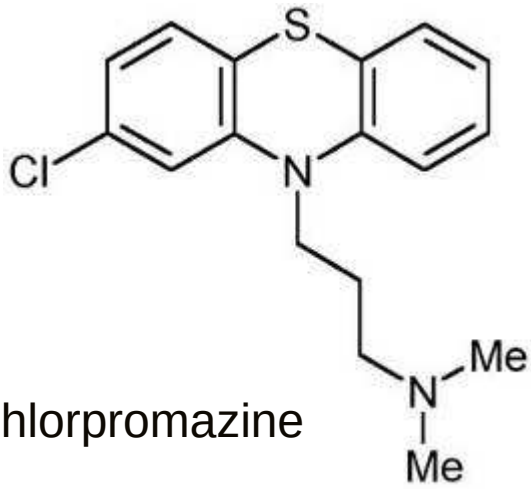
Figure 1. Agonists and antagonists associated with nausea and vomiting.

Phenothiazines

Chlorpromazine (Largactil)

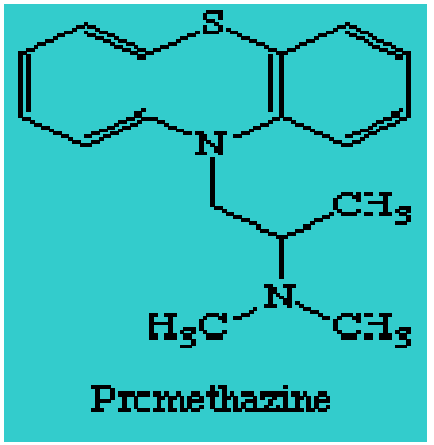
Prochlorperazine (Stemetil)

Promethazine (Fargan)



chlorpromazine

- All antipsychotic agents
- ***D_2 receptors antagonist in CTZ and CNS***
- SIDE EFFECTS: extra pyramidal symptoms, sedation, dizziness, blurred vision, skin reactions, orthostatic hypotension



Butyrophenones

Aloperidol (Serenase, Haldol)

- ***D_2 receptor antagonist + α blocker***
- Acts at both CTZ and area postrema
- SIDE EFFECTS: extra pyramidal symptoms (EPS), sedation, QTc prolongation with *torsade de pointes* (little evidence at antiemetic doses (Gan et al. Anesthesiology 2002).

  - high doses: possible hypotension (by α blockade)

Benzamides

Metoclopramide (Plasil)

- ***Specific dopamine D_2 antagonist***
- ↑ LES tone which enhances gastric motility
- Short (1-2 hours) duration of action
- SIDE EFFECTS: extrapyramidal symptoms, restlessness, drowsiness, fatigue, hypotension and bradycardia (or tachycardia)

Cisapride: hase been removed from use for cardiac side effects

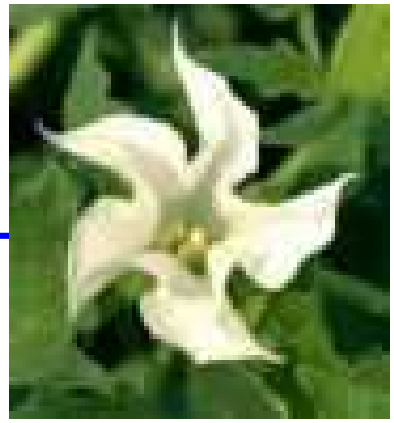
What about atypicals antipsychotics?

- 2nd generation neuroleptics
- reduced incidence of EPS
- Olanzapine (Zyprexa®)
- multiple publications support role as anti-emetic

Receptor	Olanzapine	Haloperidol
D2	+++	+++++
H1	++++	+
M1	++++	+
5HT2	++++	+++

Contents of above table extracted from Clinical Handbook of Psychotropic Drugs, 16th Edition

Anticholinergics



Scopolamine (Erion, Addofix)

- ***Inhibit cholinergic and muscarinic CNS receptors.***
- Crosses the blood-brain barrier.
- More effective against motion-induced **emesis** than against motion-induced **nausea.**
- SIDE EFFECTS: sedation, dry mouth, urinary retention, blurred vision, confusion, disorientation, hallucinations

Antihistamines

Dimenhydrinate, **Hydroxyzine**, **Cyclizine**

- ***Block acetylcholine in the vestibular apparatus and histamine H_1 receptors in the nucleus of the solitary tract.***
- SIDE EFFECTS: blurred vision, urinary retention, dry mouth, and sedation

Cyclizine has similar efficacy to **Ondansetron**; side effects: sedation and dry mouth (anticholinergic).

5-HT_3 (Serotonin) Antagonists

Ondansetron (Zofran®)
Granisetron (Kytril®)
Tropisetron (Navoban®)
Dolasetron (Anzemet®)

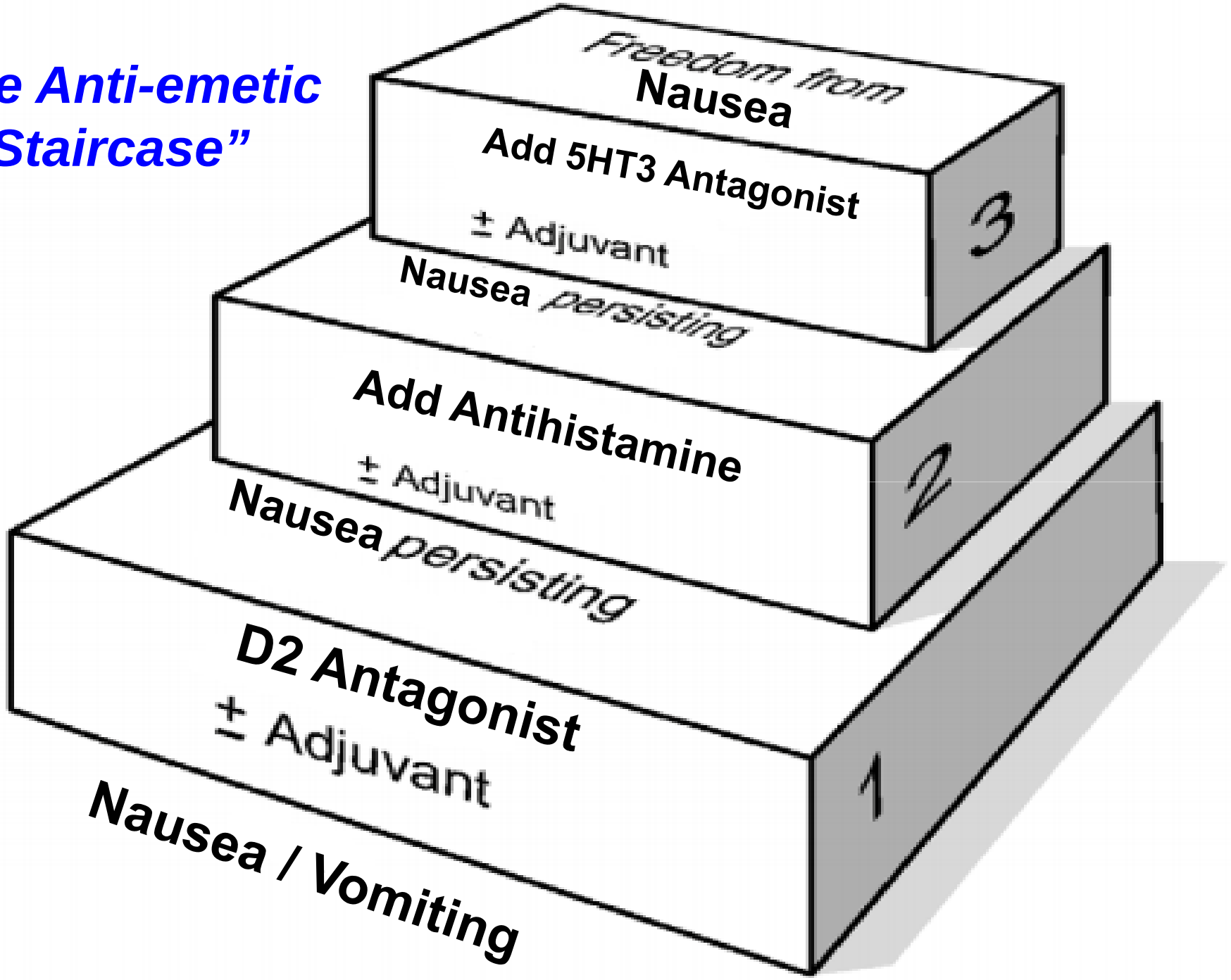
No large difference in efficacy

- No sedation, extra pyramidal reactions, adverse effects on vital signs or laboratory tests, or drug interactions with other anesthetic medications.
- SIDE EFFECTS: headache, dizziness, flushing, elevated liver enzymes, constipation

Adjunctive antiemetic agents

- **Dexamethasone (Decadron)**
  - along with other anti-emetics for prevention of cancer chemotherapy-induced emesis
- **Dronabinol (Marinol)**
  - for prevention of cancer chemotherapy-induced emesis refractory to other agents
  - [also for anorexia and weight loss in AIDS]

he Anti-emetic Staircase”



Dexamethasone

Strong synthetic steroid

Hypotheses:

- inhibition of prostaglandin synthesis
- ↓ tryptophan
- release of endorphins
- change in CSF opening pressure

\+ psychological effects of steroids

- *dexamethasone has a delayed onset of antiemetic actions which might need a **few hours to work**.*

DRONABINOL

MARINOL® C III

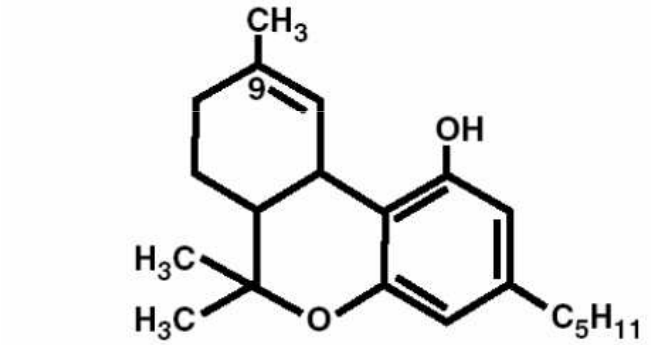
(Dronabinol)

Capsules

℞ only

DESCRIPTION

Dronabinol is a cannabinoid designated chemically as (6*aR-trans*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol. Dronabinol has the following empirical and structural formulas:



$C_{21}H_{30}O_2$ (molecular weight = 314.47)

Dronabinol, the active ingredient in MARINOL® Capsules, is synthetic delta-9-tetrahydrocannabinol (delta-9-THC). Delta-9-tetrahydrocannabinol is also a naturally occurring component of *Cannabis sativa L.* (Marijuana).

INDICATIONS AND USAGE

MARINOL® (Dronabinol) Capsules is indicated for the treatment of:

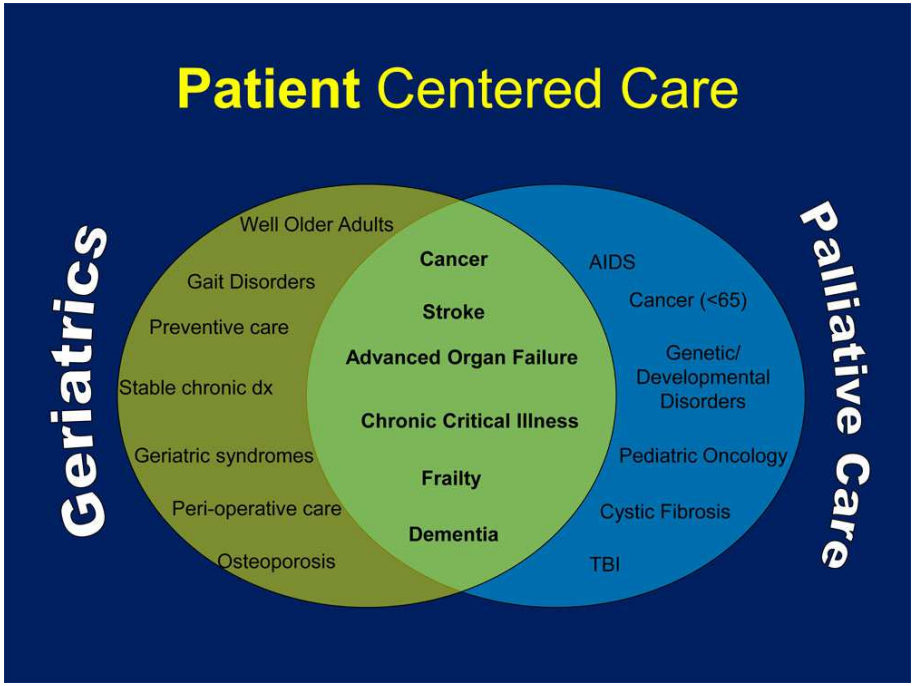
1. anorexia associated with weight loss in patients with AIDS; and

2. nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

Table 4. Select Antiemetic Agents, Common Uses, and Side Effects

Class of medication	*Common uses*	*Common side effects*
Anticholinergic* (scopolamine [Maldemar]	Possible adjunct for cytotoxic chemotherapy, prophylaxis and treatment of motion sickness	Drowsiness, dry mouth, vision disturbances
Antihistamines (cyclizine [Marezine], diphenhydramine [Benadryl], dimenhydrinate [Dramamine], meclizine [Antivert])	Migraine, motion sickness, vertigo	Drowsiness
Benzodiazepines (alprazolam [Xanax], diazepam [Valium], lorazepam [Ativan])	Adjunct for chemotherapy-related symptoms	Sedation
Butyrophenones (droperidol [Inapsine†], haloperidol [Haldol])	Anticipatory and acute chemotherapeutic nausea and vomiting, postoperative nausea and vomiting	Agitation, restlessness, sedation
Cannabinoids (dronabinol [Marinol])	Refractory chemotherapy-related nausea and vomiting	Ataxia, dizziness, euphoria, hypotension, sedation
Corticosteroids (dexamethasone)	Adjunct for chemotherapy-related symptoms	Increased energy, insomnia, mood changes
Phenothiazines (chlorpromazine [Thorazine†], prochlorperazine, promethazine [Phenergan])	Migraine, motion sickness, postchemotherapy nausea and vomiting, postoperative nausea and vomiting, severe episodes of nausea and vomiting, vertigo	Extrapyramidal symptoms (e.g., dystonia, tardive dyskinesia), orthostatic hypotension, sedation
Serotonin 5-hydroxytryptamine antagonists‡ (dolasetron [Anzemet], odansetron [Zofran], granisetron [Kytril], palonosetron [Aloxi])	Postchemotherapy nausea and vomiting, severe nausea and vomiting	Asthenia, constipation, dizziness, mild headache
Substituted benzamides* (metoclopramide [Reglan], trimethobenzamide [Tigan])	Diabetic gastroenteropathy, gastroparesis	Extrapyramidal side effects (e.g., akathisia, dyskinesia, dystonia, oculogyric crises, opisthotonos), fatigue, hyperprolactinemia

Nausea & vomiting in palliative care



Nausea & vomiting in palliative care

- Occurs in 40-70% patients with advanced cancer
- 1/3 will have more than 1 contributing factor
- 1/3 will need more than 1 anti-emetic

Nausea & vomiting in palliative care

- Neoplasia
- Metastases
- Paraneoplastic syndrome
- Meningeal irritation
- Anxiety
- Side effect of Drugs
- Mucosal irritation
- Mechanical obstruction

Nausea & vomiting in palliative care

Assess and treat the cause, if possible, and appropriate whilst respecting the patients wishes:

- Biochemical: hypercalcaemia, uraemia, dehydration
- Raised intracranial pressure: possible cerebral secondaries
- Drug Induced: Opioids
- Gastric Stasis: constipation and ascites due to potential liver metastasis
- Fear and Anxiety: fear of dying, breathlessness

Gastric stasis: drug management

Cause	Drug	Dose	Comments
Gastric Stasis Ascites GI Tract infiltration	**1) Metoclopramide**	10-20mg po three times a day or 40-80mg sc infusion/24 hours	Parkinsonian side-effects Abdominal cramps may occur
	2) Domperidone	10mg po/30mg PR three times a day	Abdominal cramps may occur
	3) Levomepromazine	6.25-12.5mg po at night 6.25-12.5mg sc infusion/24 hours	May cause drowsiness, hypotension Parkinsonian side-effects

Chemically-induced nausea

- Drugs (10-30% on initiation of opioid)
  - antibiotics, anticonvulsants, antidepressants, cytotoxics, steroids, digoxin, NSAID's
- Metabolic
  - renal or hepatic failure, hypercalcaemia, hyponatraemia, ketoacidosis
- Toxins
  - ischaemic/obstructed bowel, tumour effect, infection

Chemically-induced nausea

Cause	Drug	Dose	Comments
Biochemical/drug e.g. Hypercalcaemia, uraemia, opioids	**1) Haloperidol**	0.5-5mg po/sc at night 5-10mg sc infusion/24 hours	Sedative and anxiolytic Parkinsonian side-effects
	2) Metoclopramide	10-20mg po three times a day/ 40-80mg sc infusion/24 hours	Abdominal cramps may occur Parkinsonian side-effects

Raised intracranial pressure

- Intracranial tumour
- Cerebral oedema
- Intracranial bleed
- Meningeal infiltration by tumour
- Skull metastases
- Cerebral infection

Raised intracranial pressure

Cause	Drug	Dose	Comments
Raised intracranial pressure	**1) Dexamethasone**	4-16mg taken once a day or in two divided doses, morning and lunchtime	Dry mouth, blurred vision, sedation, confusion, constipation
	2) Cyclizine	25-50mg po three times a day or 50-150mg sc infusion/24 hours	
	3) Prochlorperazine	5-10mg po/12.5mg im three times a day	Parkinsonian side-effects, may cause drowsiness

Fear and Anxiety

Cause	Drug	Dose	Comments
Fear and Anxiety	**1) Haloperidol**	0.5-5mg po/sc at night 5-10mg sc infusion/24 hours	Sedative and anxiolytic Parkinsonian side-effects
	2) Lorazepam	0.5-1mg po prn	May cause drowsiness

Summary

- Nausea and vomiting are features of many GI and non-GI diseases and disorders.
- Regardless of its cause, treatment of nausea and vomiting should initially focus on ***replacing volume and electrolyte deficits.*** Later on, nutritional deficits must be addressed.
- Regardless of its cause, nausea and vomiting can cause several GI and non-GI complications.
- Elucidation of the cause is often possible, and ***treatment of the underlying cause*** will usually be successful.
- Effective ***symptomatic therapies*** for nausea and vomiting are available when the cause is unclear or when the treatment of the underlying cause takes time to work.