

FARMAKOTERAPI OBAT PADA SISTEM PENCERNAAN II

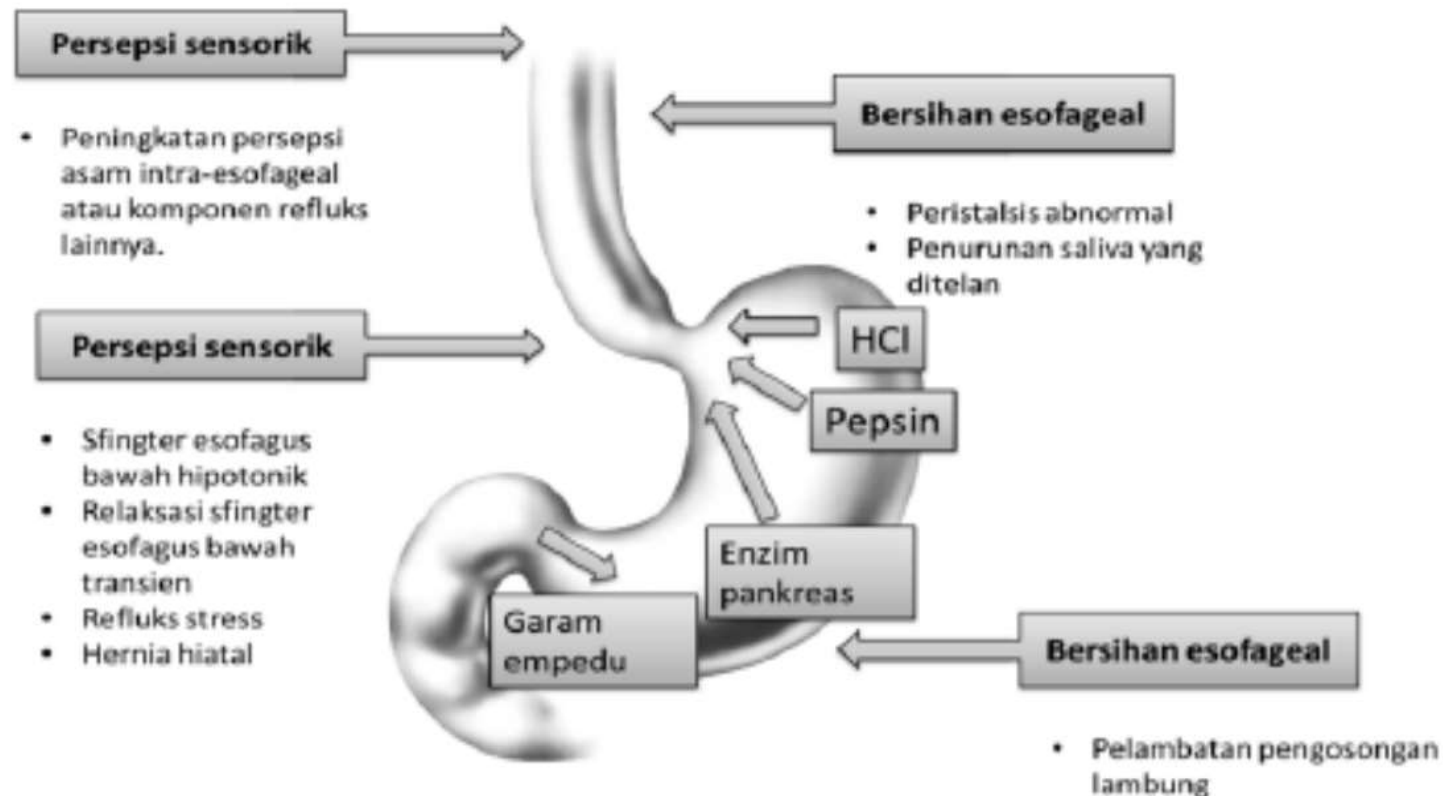


GASTRO-ESOPHAGEAL REFLUX DISEASE (GERD)

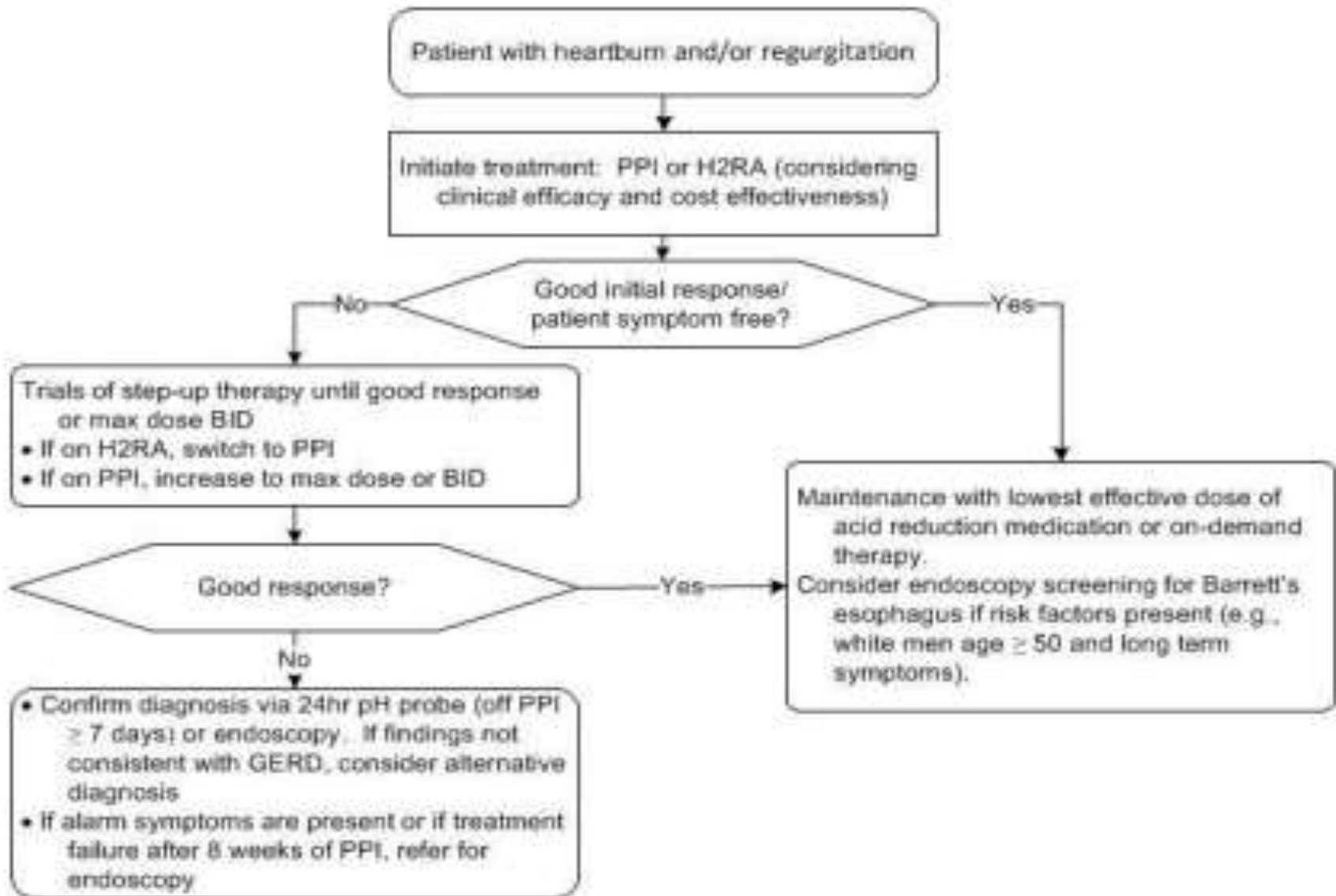
PATOFISIOLOGI

=suatu gangguan di mana isi lambung mengalami refluks secara berulang ke dalam esofagus, yang menyebabkan terjadinya gejala dan/atau komplikasi yang mengganggu.

- a. Erosive Esophagitis/ERD
- b. Non-Erosive Reflux Disease/NERD



TX GERD



LIFE MODIFICATION IN GERD

Elevate head of bed 6-8 inches

Decrease fatty meals

Stop smoking

Avoid recumbency/sleeping for 3-4 hours
postprandially

Avoid certain foods: chocolate, alcohol, peppermint,
caffeinated coffee and other beverages, onions,
garlic, fatty foods, citrus, tomato

Avoid large meals

Weight loss

OBAT YANG DAPAT MENGINDUKSI GERD

Obat yg menurunkan tekanan LES (*lower esophageal sphincter*)

- calcium channel blockers,
- B-agonists,
- α -adrenergic agonists,
- theophylline,
- nitrates,
- PDE-5 inhibitors (e.g., sildenafil, tadalafil, vardenafil),
- anticholinergics,
- narcotics, and
- some sedatives (benzodiazepines).

Obat yg mengiritasi esofagus

- NSAIDS,
- ferrous sulfate, and
- bisphosphonates

TX GERD

Drug	Dose Equivalents ^a	Dosage ^b
H2 antagonists cimetidine (Tagamet HB) cimetidine (Tagamet) famotidine (Pepcid) ranitidine (Zantac) ranitidine (Zantac)	200 mg BID 400 mg BID 20 mg BID 150 mg BID 300 mg nightly	200 mg BID 400 mg BID 20 mg BID 150 mg BID 300 mg nightly
PPIs lansoprazole (Prevacid) omeprazole (Prilosec) pantoprazole (Protonix) rabeprazole (Aciphex)	30 mg daily 20 mg daily 40 mg daily 20 mg daily	15/30 mg daily before breakfast 20/40 mg daily before breakfast 40 mg daily before breakfast 20 mg daily before breakfast

Medicine	Mechanism of Action	Adverse Effects
Proton Pump Inhibitors (PPIs)	Omeprazole Lansoprazole Rabeprazole Esomeprazole Pantoprazole Inhibition of the gastric H ⁺ /K ⁺ -ATPase (proton pump) enzyme system	Headache Abdominal pain Diarrhea Nausea Vomiting Constipation Flatulence Vitamin B12 deficiency Osteoporosis
H2 Receptor Blockers	Cimetidine Famotidine Nizatidine Ranitidine Blocking the action of histamine at the histamine H2 receptors of parietal cells	Headache Anxiety Depression Dizziness Cardiovascular events Thrombocytopenia
Antacids	Aluminum hydroxide Magnesium hydroxide Increases gastric pH to greater than four, and inhibits the proteolytic activity of pepsin Causes osmotic retention of fluid	Frequency not defined: Nausea Vomiting Hypophosphatemia Chalky taste Constipation Abdominal cramping Diarrhea Electrolyte imbalance
Potassium-Competitive Acid Blocker	Vonoprazan Inhibits H ⁺ , K ⁺ -ATPase in gastric parietal cells at the final stage of the acid secretory pathway	Nasopharyngitis Fall Contusion Diarrhea Upper respiratory tract inflammation Eczema Constipation
Cytoprotective Agents	Misoprostol Sucralfate Stimulate mucus production and enhance blood flow throughout the lining of the gastrointestinal tract	Back pain Diarrhea Abdominal pain Headache Constipation

POTASSIUM-COMPETITIVE ACID BLOCKER (P-CAB)

PPI

contoh : Omeprazole, Lansoprazole

PPI memasuki kanalikulus sel parietal dalam bentuk tidak aktif

membutuhkan aktivasi asam.

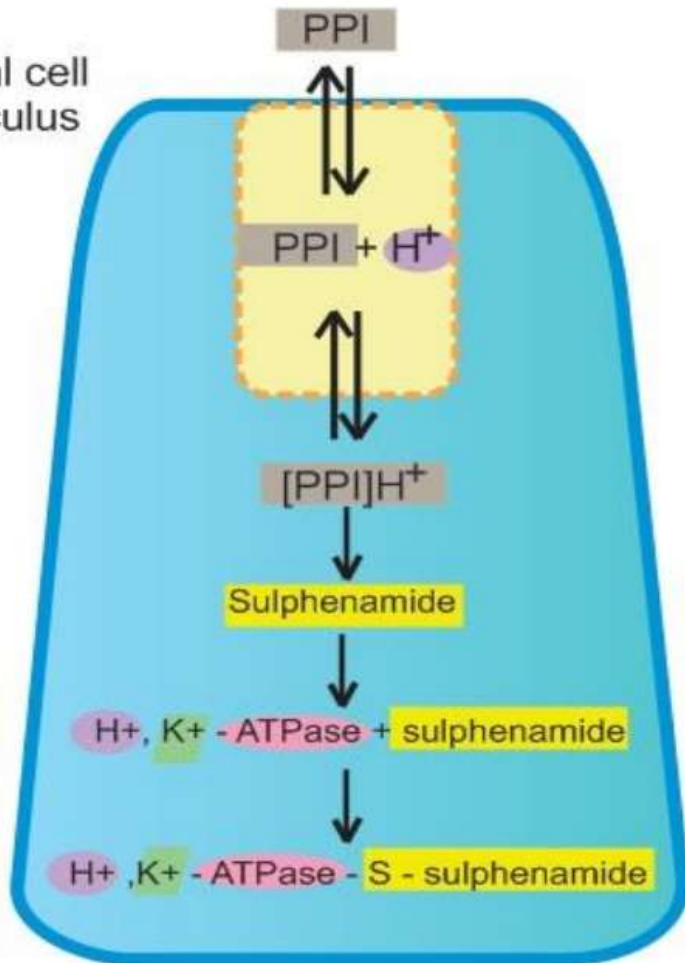
terprotonasi pro-drug akan dikonversi menjadi sulfenamida dan berikatan secara kovalen dengan gugus sistein $H^+/K^+-ATPase$ yang menyebabkan inaktivasi $H^+/K^+-ATPase$.

P-CAB

- Contoh : Vonoprazan , Tegoprazan
- P-CAB memasuki kanalikulus sel parietal dalam bentuk aktif,
- memiliki stabilitas dalam lingkungan asam, dan tidak memerlukan aktivasi asam.
- P-CAB yang terprotonasi akan membuat ikatan non-kovalen dengan $H^+/K^+-ATPase$, dengan demikian
- menonaktifkan $H^+/K^+-ATPase$ dengan laju disosiasi yang lebih lambat dan waktu yang lebih lama.

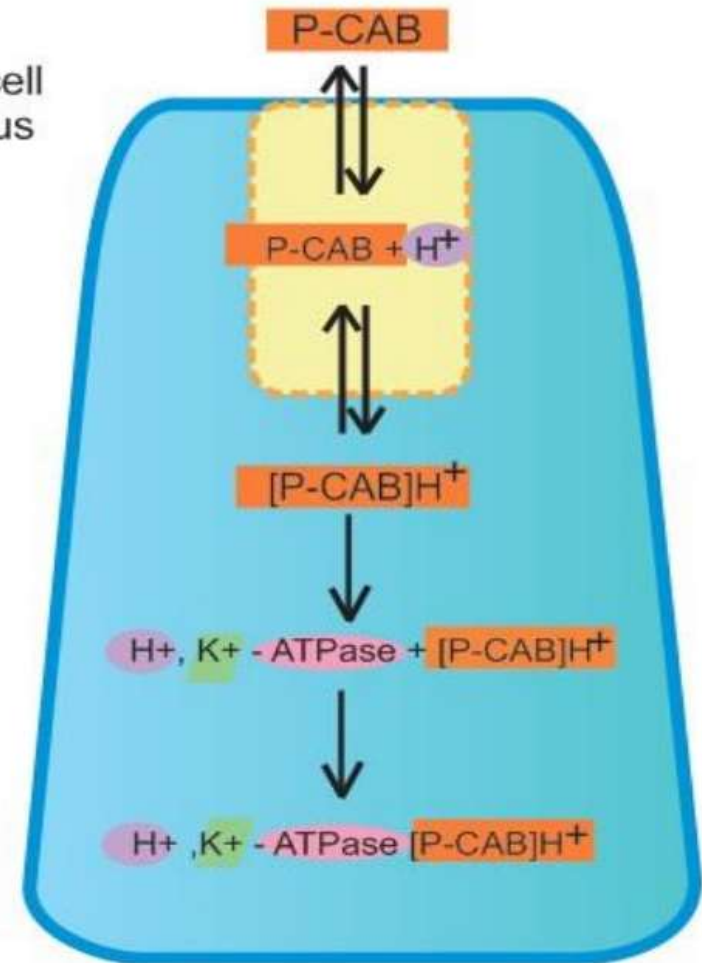
PPI VS P-CAB

Parietal cell
canaliculus



*The PPIs are inactive in their native form
*PPI is unstable in acid

Parietal cell
canaliculus



**Vonoprazan has already in active form
**Vonoprazan is stable in acid situation

Tabel 2. Efektivitas Terapi Obat untuk GERD³⁷

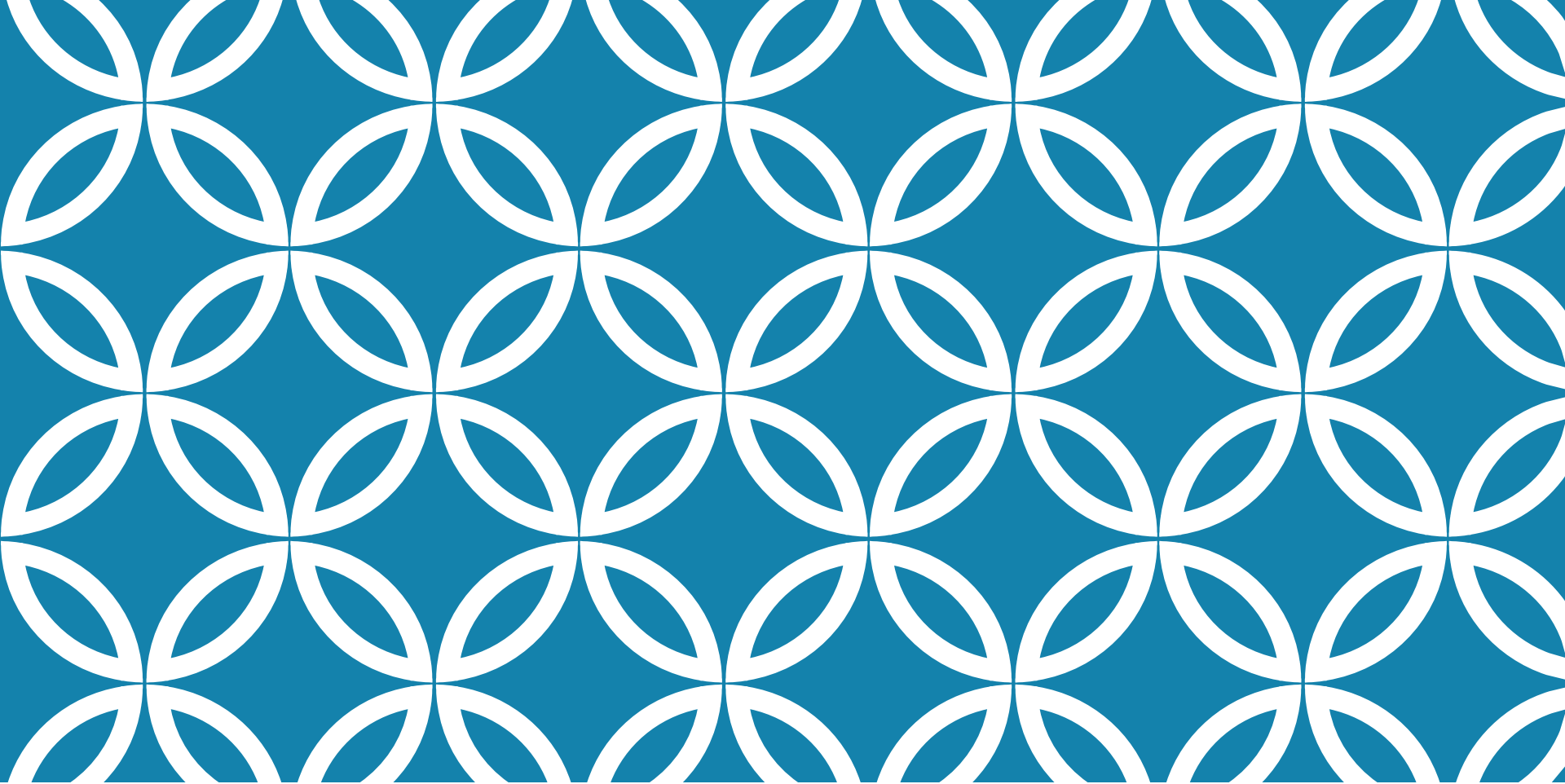
Jenis Obat	Perbaikan Gejala	Penyembuhan Lesi Esofagus	Pencegahan Komplikasi	Pencegahan Kekambuhan
Antasida	+1	0	0	0
Prokinetik	+2	+1	0	+1
Antagonis Reseptor H2	+2	+2	+1	+1
Antagonis Reseptor H2 dan Prokinetik	+3	+3	+1	+1
Antagonis Reseptor H2 Dosis Tinggi	+3	+3	+2	+2
<i>PPI</i>	+4	+4	+3	+4
Pembedahan	+4	+4	+3	+4

Tabel 3. Dosis *PPI* untuk Pengobatan GERD^{38,39}

Jenis <i>PPI</i>	Dosis Tunggal	Dosis Ganda
Omeprazole	20 mg	20 mg 2 kali sehari
Pantoprazole	40 mg	40 mg 2 kali sehari
Lansoprazole	30 mg	30 mg 2 kali sehari
Esomeprazole	40 mg	40 mg 2 kali sehari
Rabeprazole	20 mg	20 mg 2 kali sehari

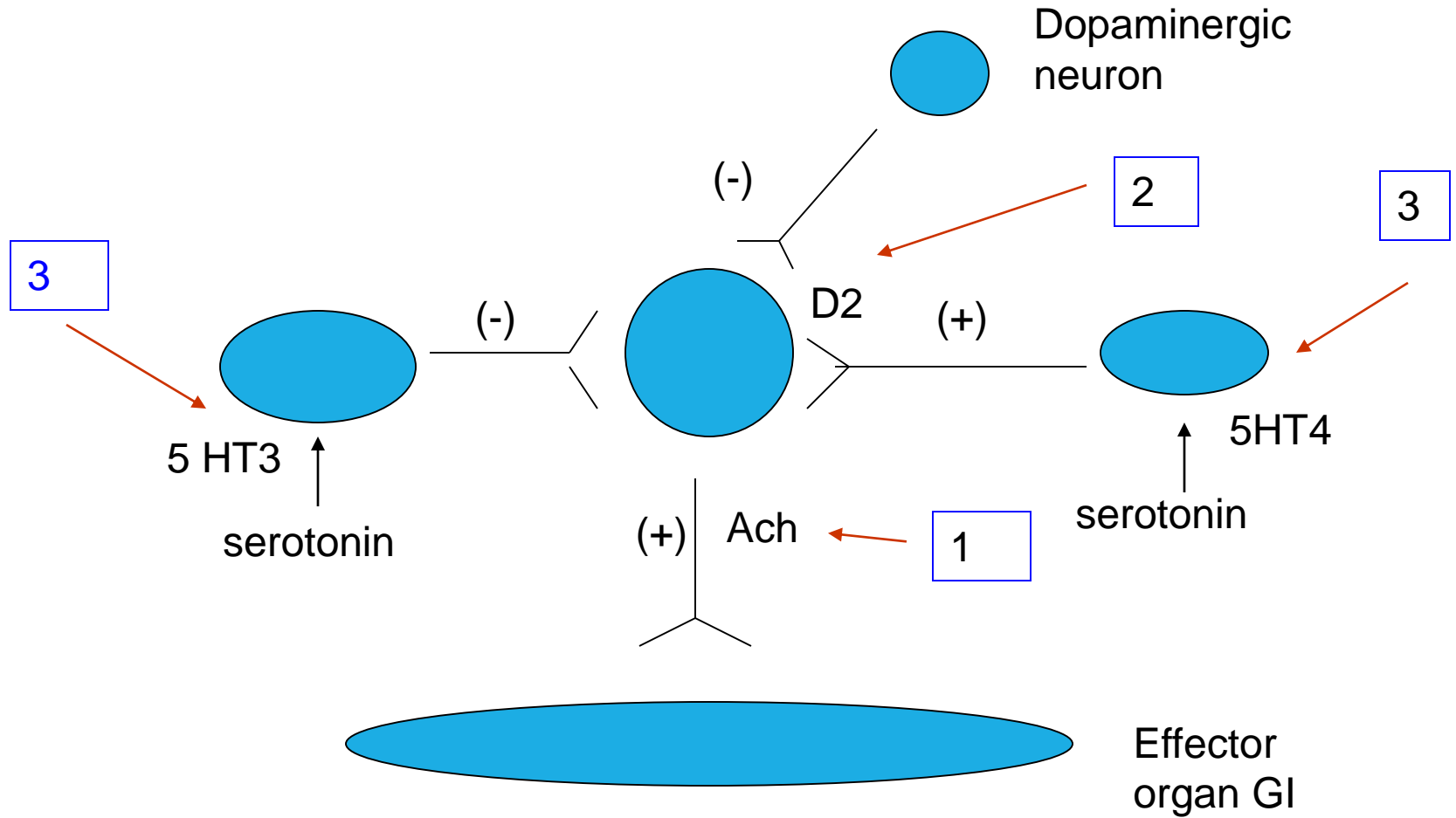
TRANSIENT RELAXATIONS OF THE LOWER OESOPHAGEAL SPHINCTER (TLOSRS) INHIBITOR

- a. *NO synthase blockade (L-NMMA)*
- b. *Cholecystokinin-1 (CCK₁) – Receptor blockade (e.g. with loxiglumide)*
- c. *5-HT₃ – Receptor blockade (e.g. with ondansetron) (granisetron)*
- d. *Muscarinic receptor blockade (e.g. with atropine)*
- e. *μ-receptor stimulation (e.g. with morphine)*
- f. *GABA_B – Receptor stimulation (e.g. with baclofen)*



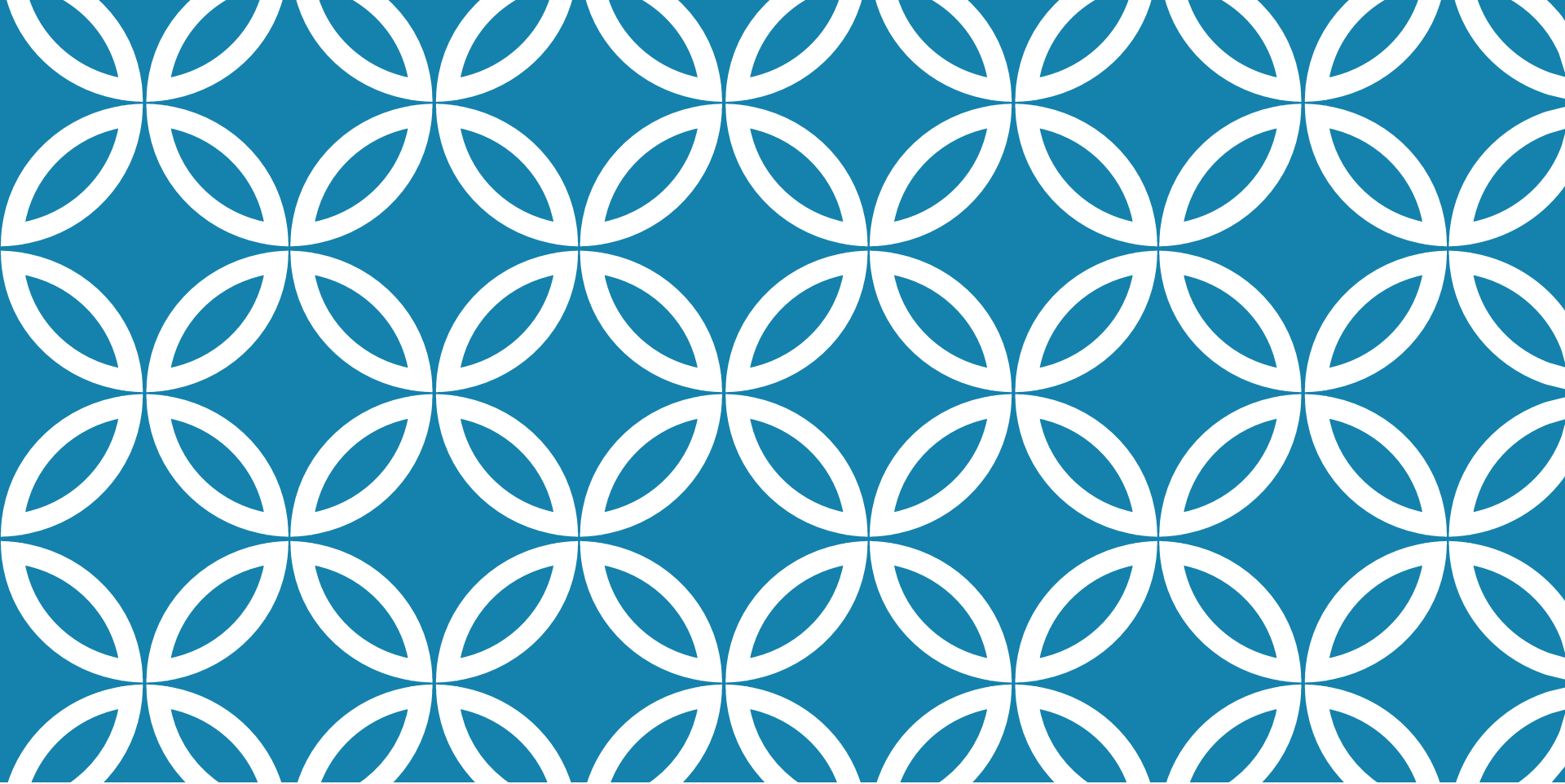
PROKINETICS AGENT

Conceptual model of prokinetic agents



Classification of prokinetic agents

Mech. Of action	General pharm. class	Example of drug	Used medications
Aktivasi R/ Musc.	Cholinergic agents	Betanechol neostigmin	Costipation pseudoobstruction
Inhibisi R/D2	Antagonis R/Dopamin	Metoclopramide Domperidone	GERD
Aktivasi R/5HT4 Inhibisi R/5HT3	Agonis R/Serotonin Antagonis R/ Serotn	Cisapride Metoclopramide	Gastroparesis
Aktivasi R/Motilin	Motilin like agents	Erytromycin	Gastroparesis



ANTI EMETIC AGENT

DIFFERENTIAL DIAGNOSIS OF NAUSEA AND VOMITING

Central nervous system

Closed head injury⁴
Increased intracranial pressure
 Cerebrovascular accident
 (infarction/hemorrhage)
 Hydrocephalus
 Mass lesion
 Meningitis/encephalitis/abscess
 Pseudotumor cerebri
Migraine
Seizure disorders²
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
 Pneumonia³
 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/withdrawal⁶
Radiation therapy
Toxins
 Arsenic⁷
 Organophosphates/pesticides⁸
 Ricin⁹

Metabolic

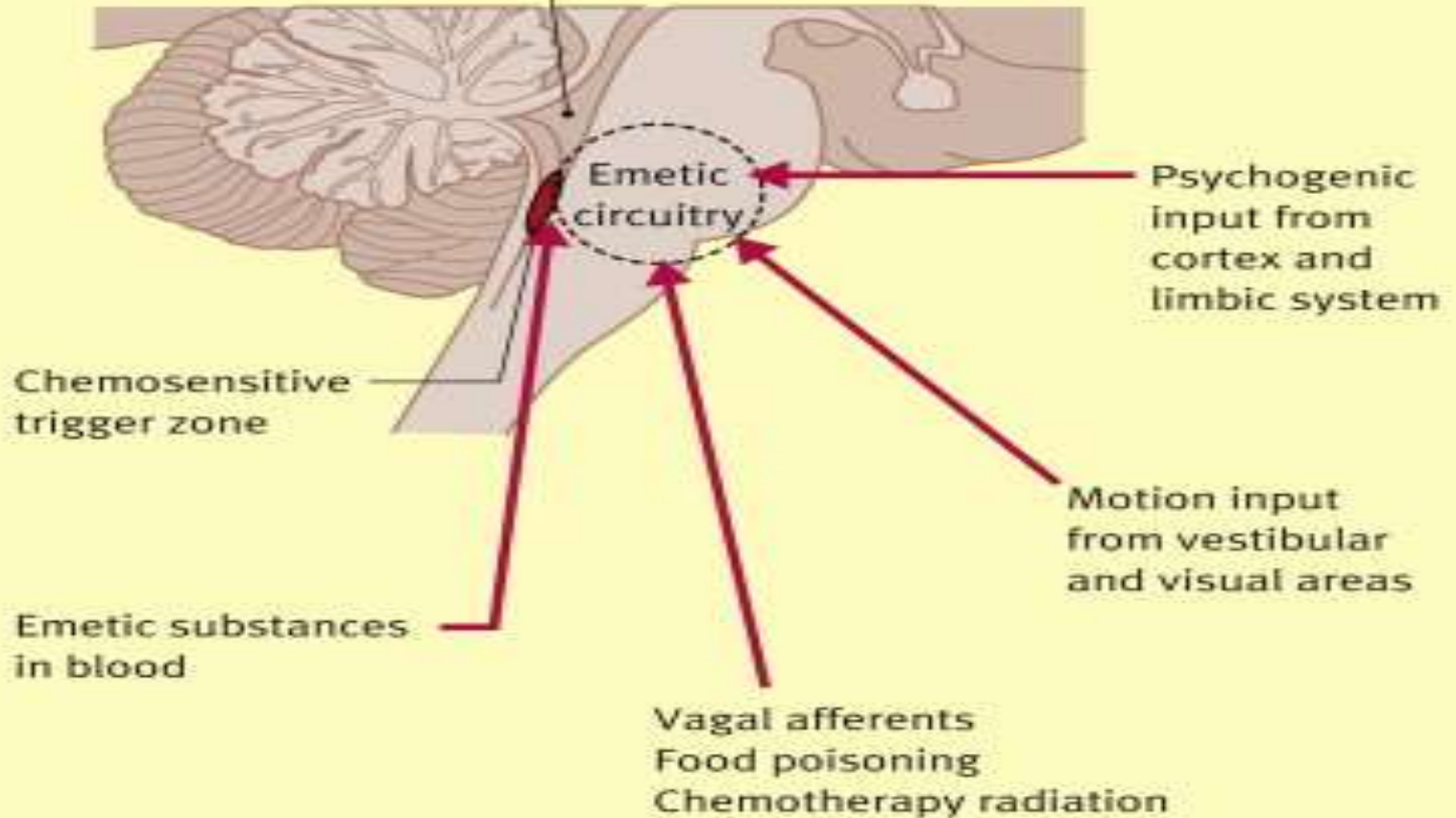
Adrenal disorders
Diabetic ketoacidosis
Paraneoplastic syndromes
Parathyroid disorders
Pregnancy
Thyroid disorders
Uremia

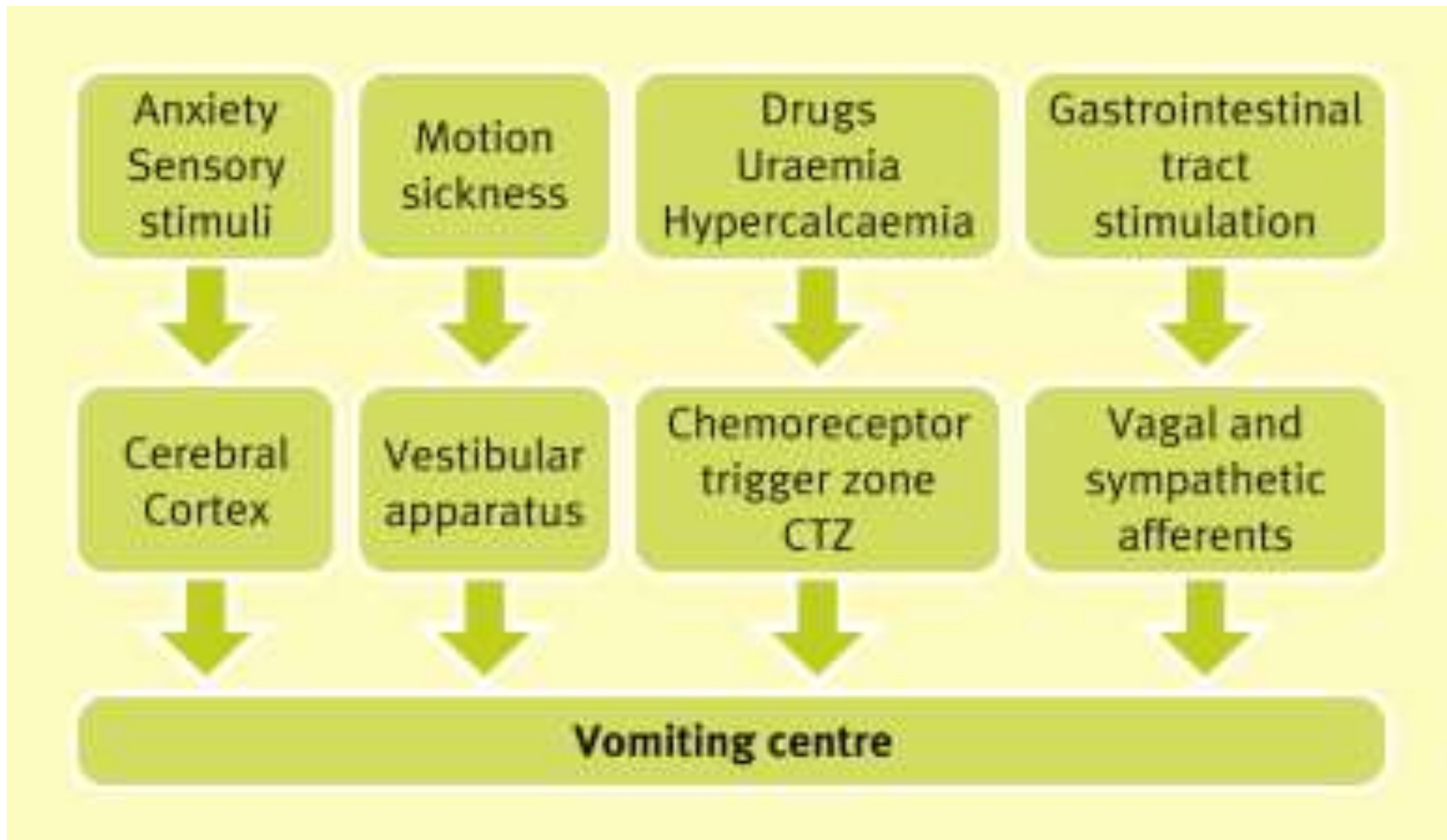
Miscellaneous

Acute glaucoma⁵
Acute myocardial infarction
Nephrolithiasis¹⁰
Pain
Psychiatric disorders
 Anorexia nervosa
 Anxiety
 Bulimia nervosa
 Conversion disorder
 Depression

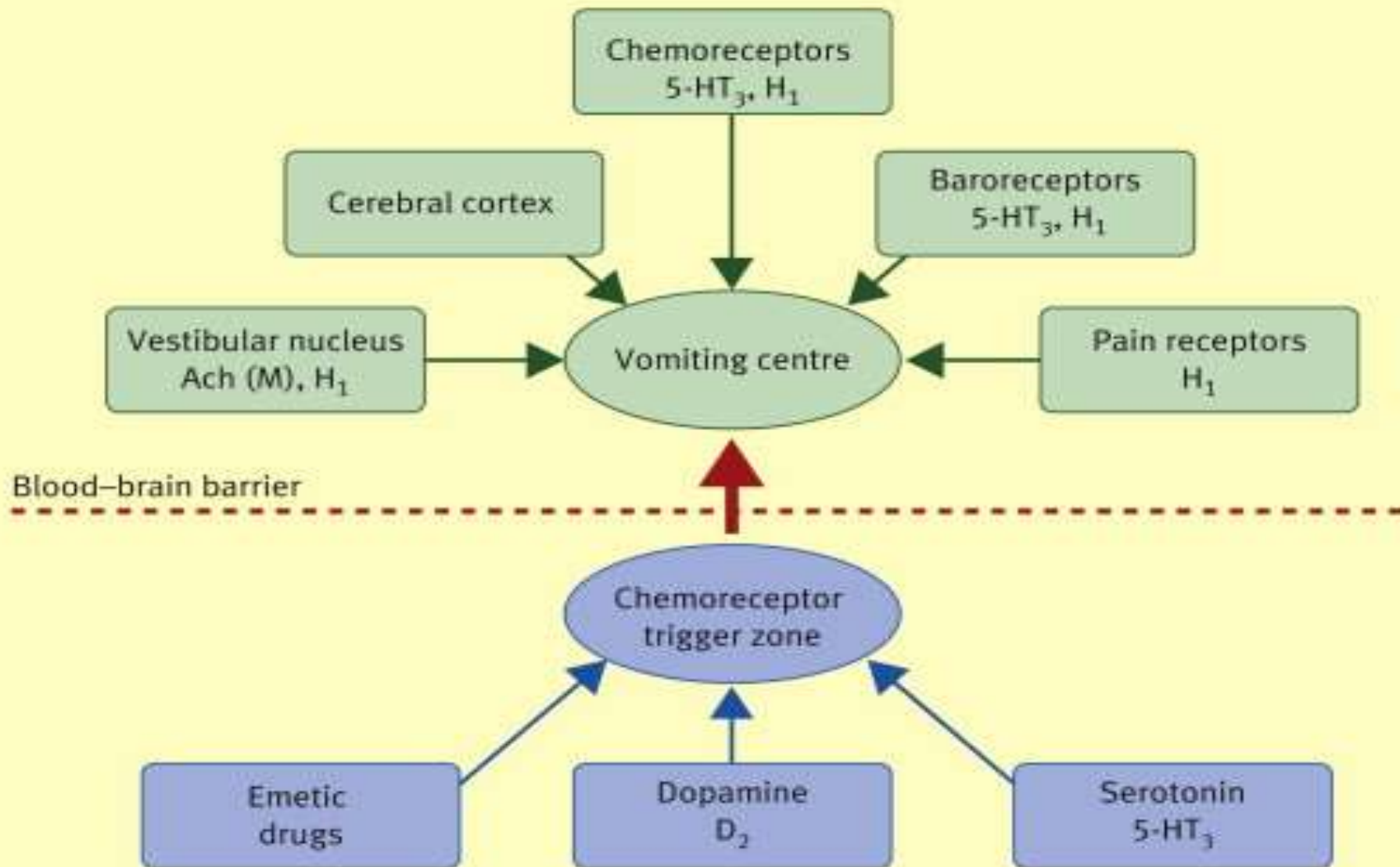
Factors that initiate vomiting

Fourth ventricle



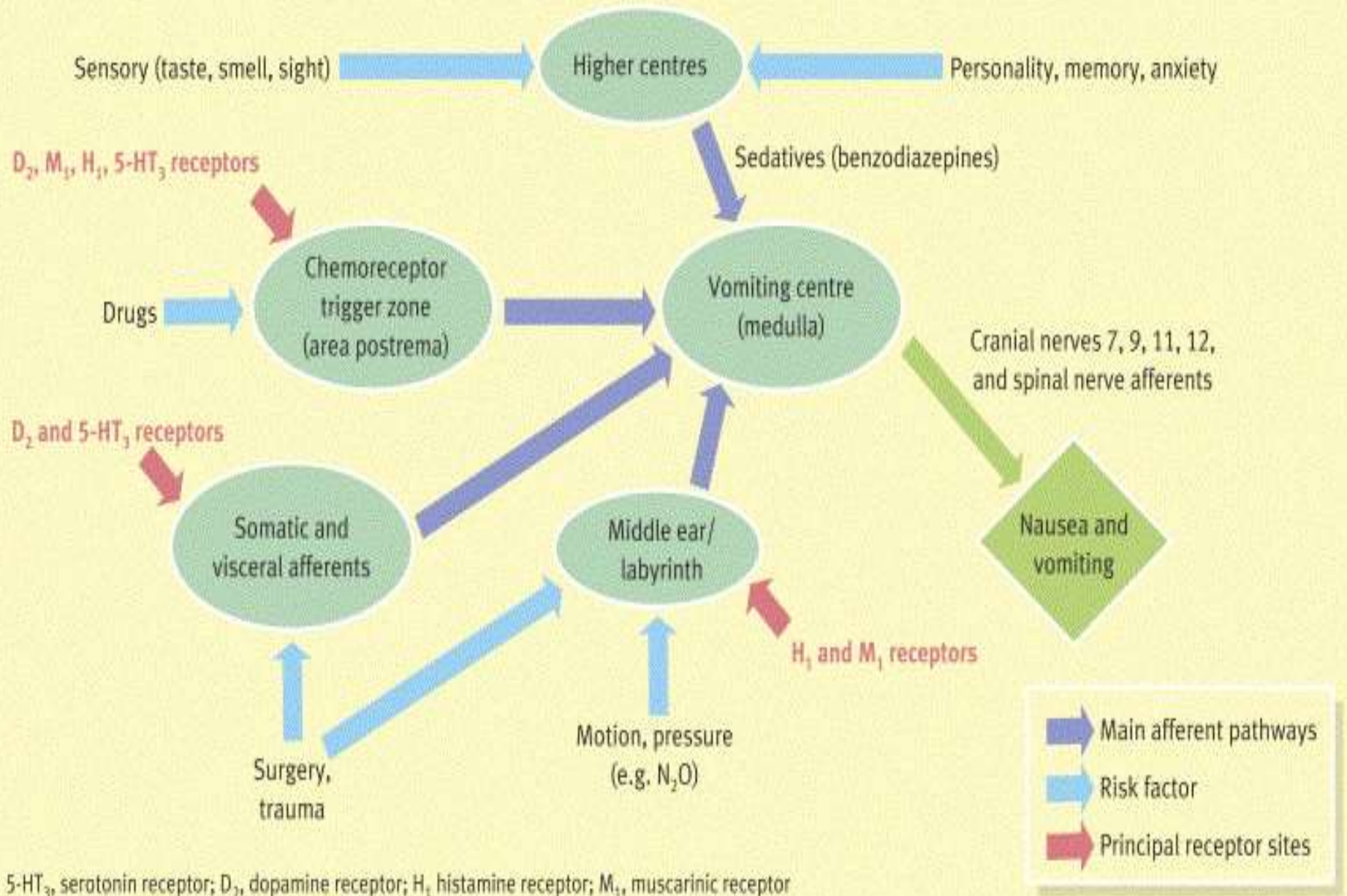


Integration of inputs to the vomiting centre



Each input is shown with its predominant neurotransmitter.

Nausea and vomiting



5-HT₃, serotonin receptor; D₂, dopamine receptor; H₁, histamine receptor; M₁, muscarinic receptor

ANTI-EMETIC AGENT (1)

<i>Class of medication</i>	<i>Common uses</i>	<i>Common side effects</i>
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

ANTI-EMETIC AGENT (2)

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], ondansetron [Zofran], granisetron [Kytril], palonosetron [Aloxi])

Postchemotherapy nausea and vomiting, severe nausea and vomiting

Asthenia, constipation, dizziness, mild headache

Substituted benzamides* (metoclopramide [Reglan], trimethobenzamide [Tigan])

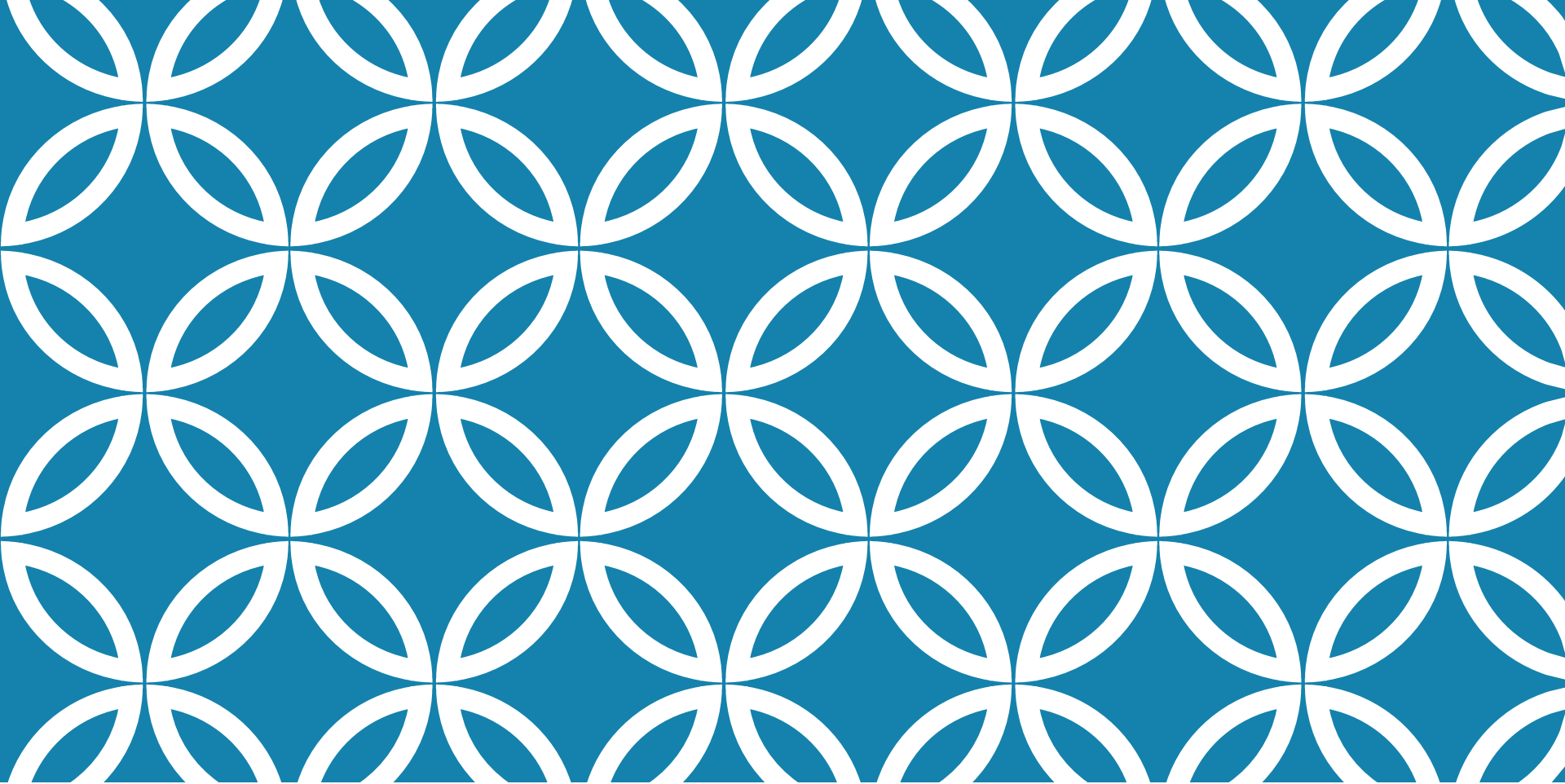
Diabetic gastroenteropathy, gastroparesis

Extrapyramidal side effects (e.g., akathisia, dyskinesia, dystonia, oculogyric crises, opisthotonos), fatigue, hyperprolactinemia

*—Use limited by high occurrence of side effects.

†—Not available in the United States.

‡—Low incidence of side effects.



PHARMACOTHERAPY OF INFLAMMATORY BOWEL DISEASE

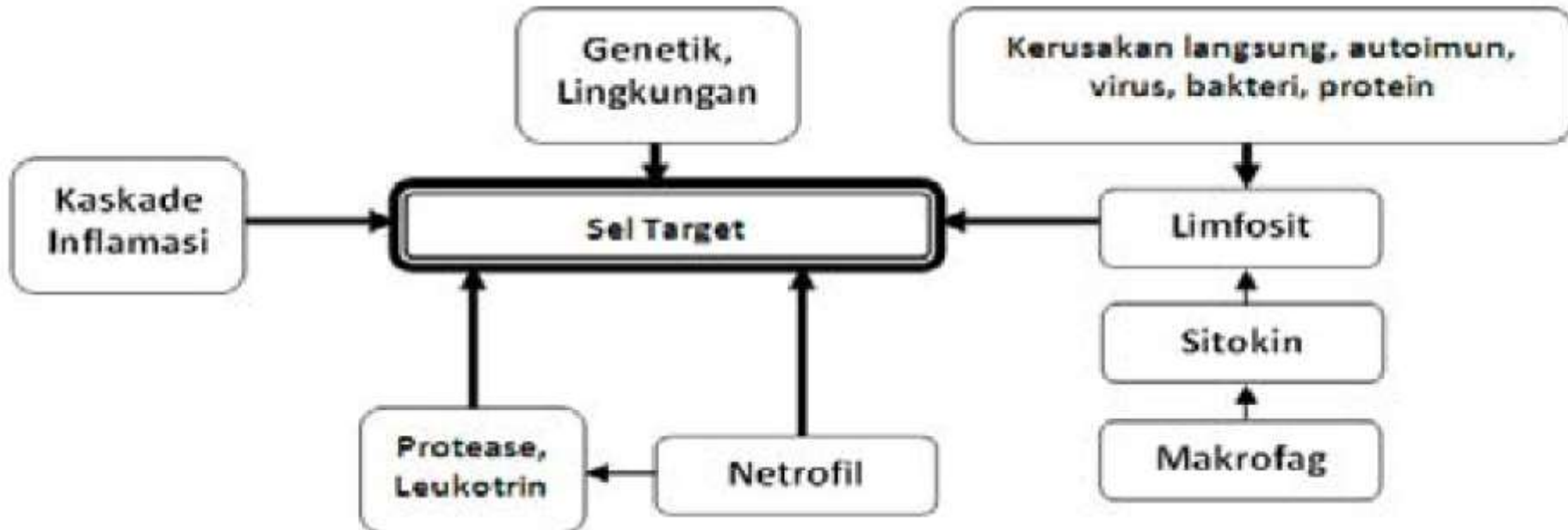
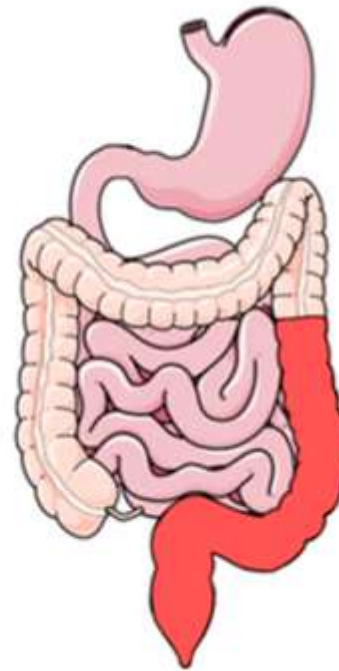
Crohn's Disease

- May affect any part of the GIT
- Discontinuous patchy inflammation
- Transmural (affects the full thickness of the bowel wall)



Ulcerative colitis

- Affects only large intestine
- Continuous inflammation
- Mucosal and submucosal layers are affected



REGIMEN TX ULCERATIF COLITIS

Active disease

5-ASA enema or p.o. (2-4 g/d, 2-3 x/d)
5-ASA suppositories (3 X 500 mg/d)

Glucocorticoides (1 mg/kg d p.o.)
in severe cases 100 mg/d i.v.
5-aminosalicylate (3-4 g/d)
+ rectal topical therapy

Parenteral nutrition, i.v. steroids,
cyclosporine A (4 mg/kg, i.v.),
or surgery

Pancolitis →

Left-sided
colitis →

Therapy-
refractory
disease →

Remission

5-ASA (1.5-3 g/d)
or *E.coli* Nissle

5-ASA enema (2-4 g/d, 2-3 x/wk)
5-ASA supp (1 X 500 mg/d)

Azathioprine or 5-ASA,
(postoperative: no therapy)

Alternative in therapy-refractory disease:
infliximab 5 mg/kg KG i.v.

REGIMEN TX PADA PENYAKIT CROHN

Mild active disease



5-ASA 3 g/d p.o.

Moderate to severe active disease



Glucocorticoids 1 mg/kg/d p.o. or in severe cases i.v.

Steroid-dependent and steroid refractory disease



Azathioprine (2-3 mg/kg) or 6-MP (1-1.5 mg/kg) or MTX 25 mg i.m./wk

Therapy-refractory disease and/or fistulizing disease



Azathioprine (2-3 mg/kg) and infliximab (5 mg/kg)

Additional nutritional supplemental therapy

5-ASA (5-AMINOSALISILIC ACID)

Contoh : mesalazin, sulfasalazine, balsalazide, Olsalazine

Mesalazine-containing compounds have a wide variety of **anti-inflammatory actions**:

- Inhibition of leucocyte migration
- Reduced activation of NFκB
- Reduced synthesis of leucotrienes, thromboxanes, and prostaglandins

Indications

These agents are indicated in the:

- Treatment of mild to moderate UC
- Maintenance of remission in UC/CD

DRUG OF CHOICE

Condition	Drug of choice
• Peptic ulcer	
- Gastric ulcer	Proton pump inhibitors (PPI)
- Duodenal ulcer	PPI
- Stress ulcer	PPI
- NSAID-induced	PPI
- H. pylori associated	Lansoprazole + Amoxicillin + Clarithromycin
- Zollinger Ellison syndrome	PPI
- Gastro Esophageal Reflux Disease	PPI
• Vomiting	
- Chemotherapy induced	5-HT ₃ antagonists like palonosetron
- Levo-dopa induced	Domperidone
- Migraine associated	Metoclopramide
- Drug or disease associated	Metoclopramide
- Post-operative	Ondansetron
- Radiation induced	Ondansetron
- Cisplatin - induced	
* Early	5-HT ₃ antagonists
* Delayed	Aprepitant
- Prophylaxis of motion sickness	Hyoscine
- Pregnancy (Morning sickness)	Doxylamine + Pyridoxine
• Opioid induced constipation	Methyl naltrexone
• Diarrhea in carcinoid syndrome	Octreotide
• To prevent dehydration in diarrhea	ORS
• Crohn's disease	Corticosteroids
• Ulcerative colitis	5-ASA derivatives
• Hepatic encephalopathy	Lactulose

LAXATIVES

Luminally active agents

Bulk-forming

- Dietary fibre
- Bran
- Psyllium
- Methylcellulose

Surfactant (stool softner)

- Docusate
- Liquid paraffin
- Mineral oil

Osmotic

- *Saline laxatives*
 - $MgSO_4$
 - $Mg(OH)_2$
 - Sodium phosphate
- *Non-digestible sugars and alcohols*
 - Lactulose
 - Sorbitol
 - Mannitol
- Poly ethylene glycol

Stimulant purgatives

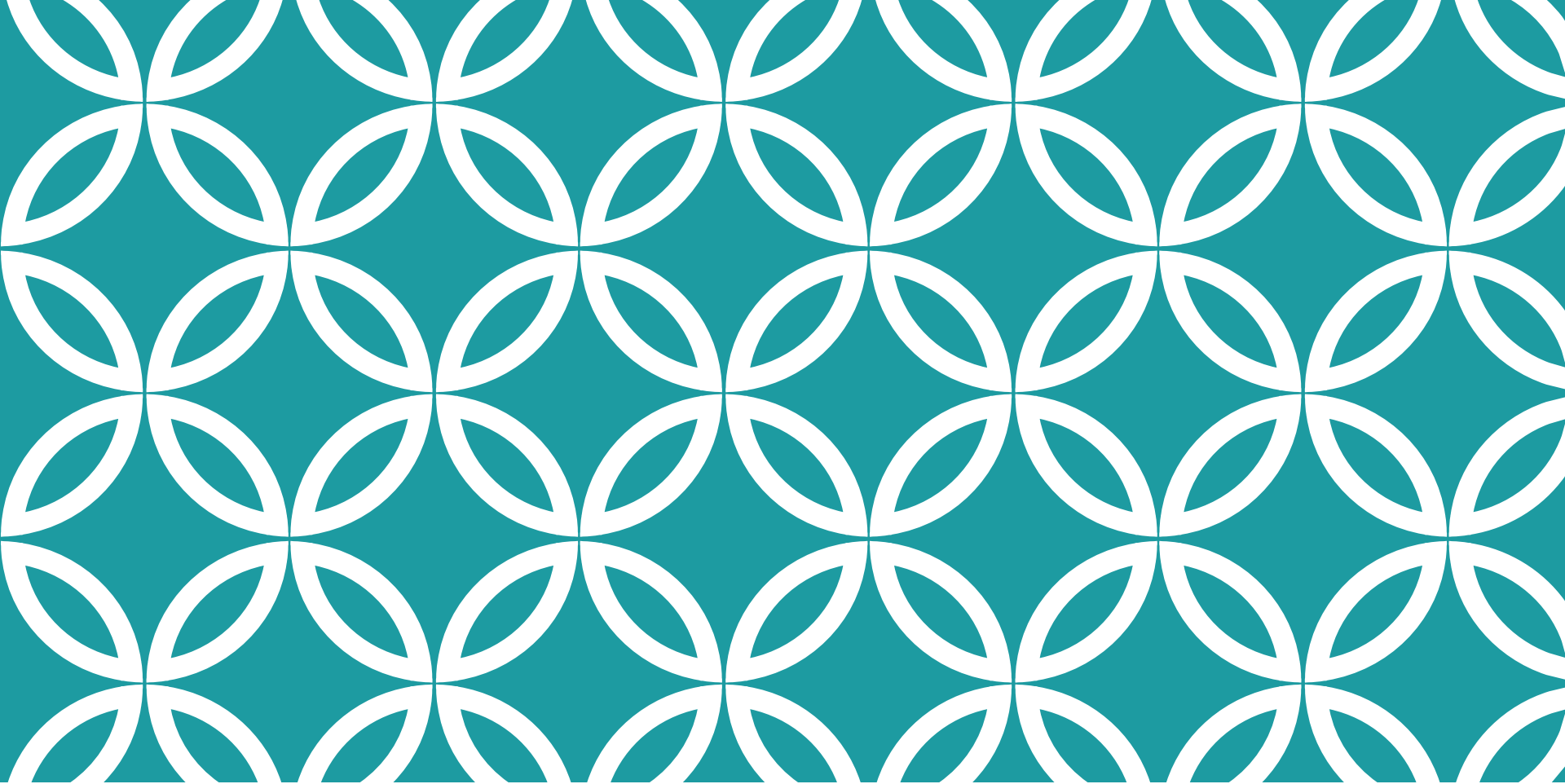
- Diphenylmethanes
 - Bisacodyl
 - Sodium picosulfate
 - Phenolphthalein
- Anthraquinones
 - Senna
 - Cascara
- Castor oil

Prokinetics

- $5HT_4$ agonists
 - Prucalopride
- D_2 Antagonists
 - Metoclopramide
 - Domperidone
- Macrolides
 - Erythromycin

New agents

- Chloride secretory agents
 - Lubiprostone
 - Linaclotide
- Opioid receptor antagonists
 - Methylnaltrexone
 - Alvimopan



TERIMA KASIH |