Antiemetics, laxatives and antidiarrheal drugs

Dr. Balázs Varga

University of Debrecen, Faculty of Medicine,
Department of Pharmacology and Pharmacotherapy

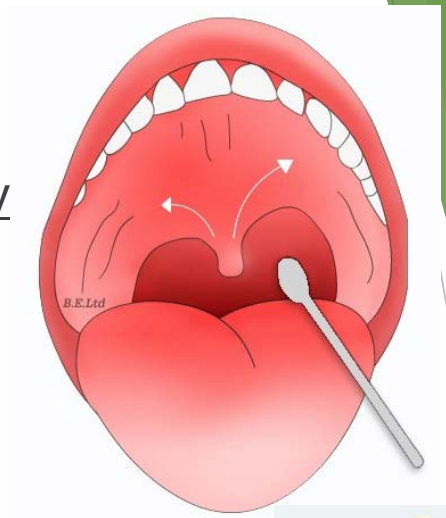
Emesis (vomiting)

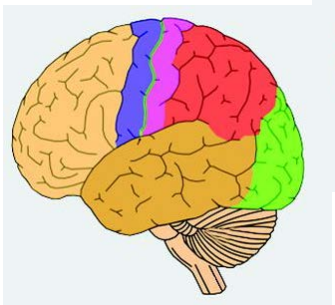
- Act of forceful expulsion of gastric contents through the mouth
  - Often preceeded by nausea
- Normally protective mechanism:
  - To eliminate harmful substances from the stomach and duodenum
  - Prevention of ingestion of noxious substances (sight, smell, taste, texture)
- Unwanted side effect ➔ needs to be attenuated
  - Pregnancy
  - Labyrinth-stimulation
  - Drugs/chemotherapy etc.

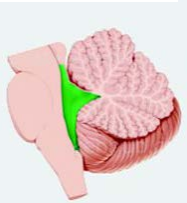
Physiology of emesis

- Vomiting is initiated involunatrily, reflexively
  (the reflex can also be triggered voluntarily)

- Parts of the vomiting-reflex:
  - Inputs
    - Mechano- or chemoreceptors in
      - (Oro)Pharynx (pharyngeal/gag reflex)
      - Stomach
      - Intestines
      - Inner ear (osseous labyrinth)
      - Chemosensitive trigger zone
    - Neuronal input from higher CNS areas



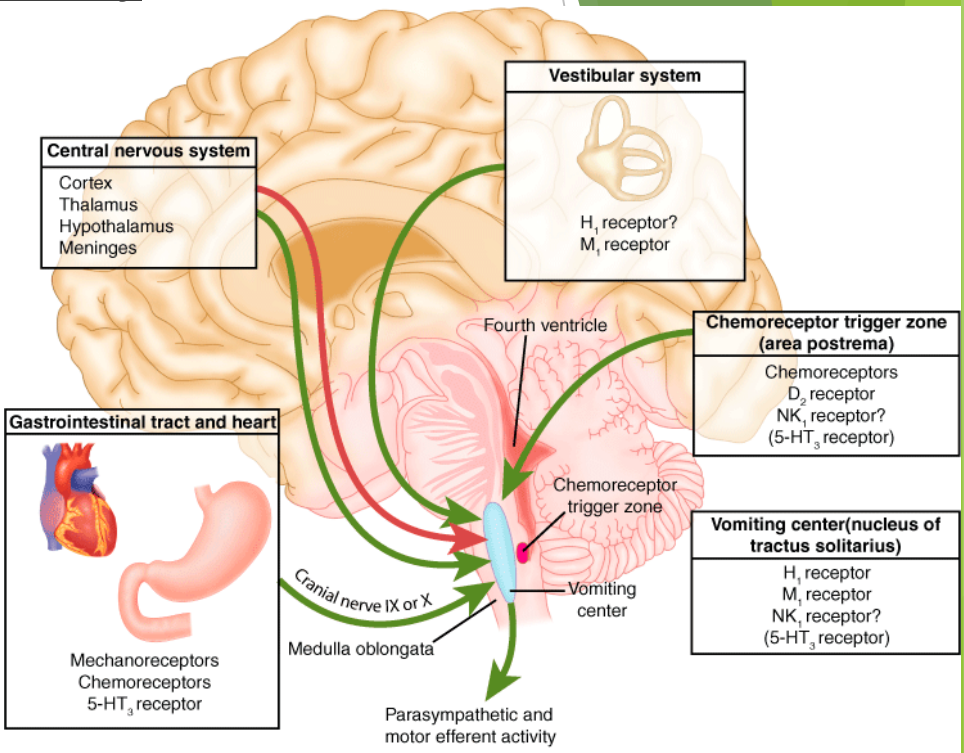




Physiology of emesis

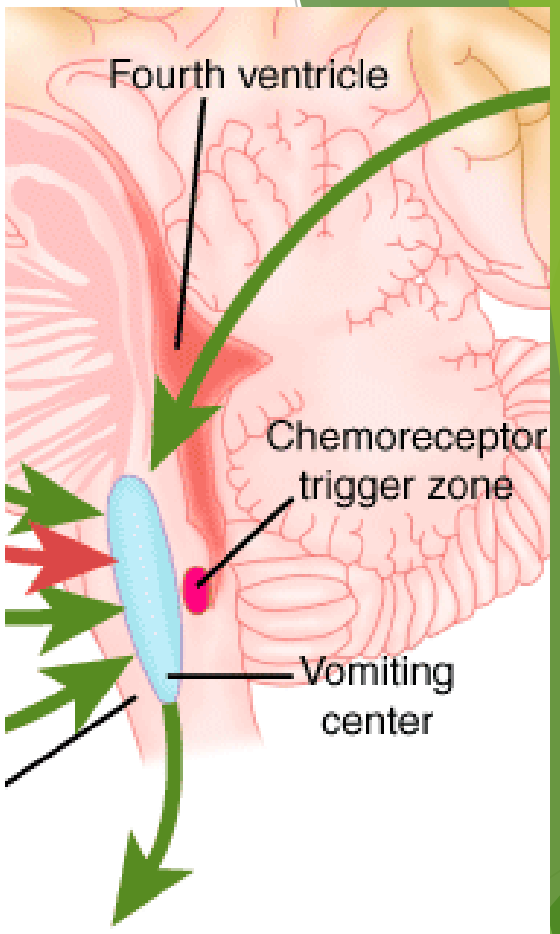
- Vomiting is initiated involunatrily, reflexively
  (the reflex can also be triggered voluntarily)

- Parts of the vomiting-reflex:
  - Inputs
    - Mechano- or chemoreceptors in
      - (Oro)Pharynx (pharyngeal/gag reflex)
      - Stomach
      - Intestines
      - Inner ear (osseous labyrinth)
      - Chemosensitive trigger zone
    - Neuronal input from higher CNS areas
  - Afferentation
    - From soft palate: cranial nerve V (trigeminal nerve)
    - From pharynx: CN IX (glossopharyngeal nerve)
    - From viscera: CN X (n. vagus)
    - From inner ear: CN VIII (vestibulocochlear nerve)
    - Neuronal pathways from higher CNS areas



Physiology of emesis

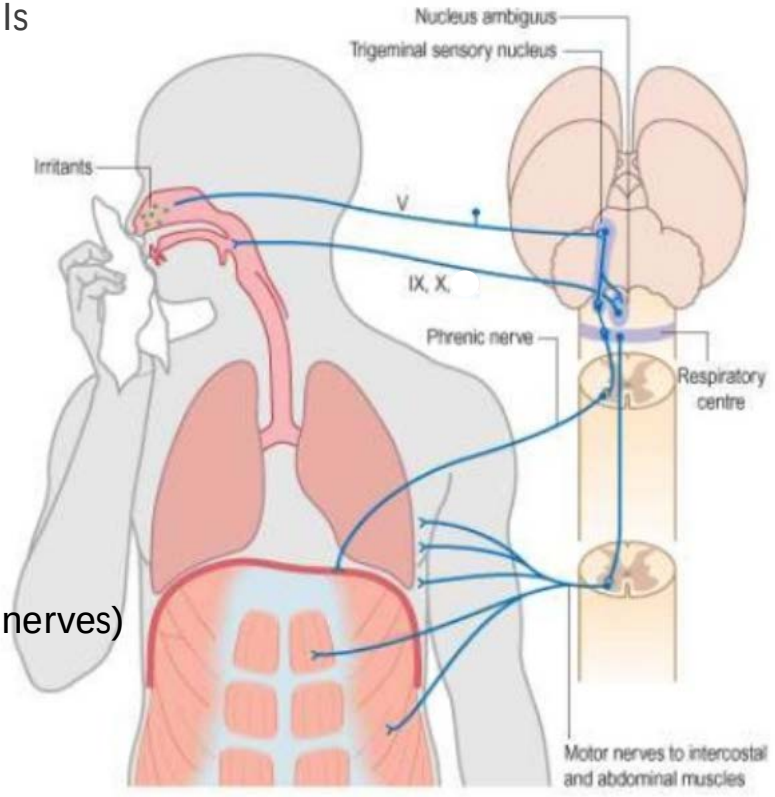
- Parts of the vomiting-reflex (cont.):
  - Vomiting center (area postrema)
    - Located in medulla oblongata in brainstem at the inferoposterior limit of the fourth ventricle
    - Densely vascularized structure
    - No tight junction between capillary endothelial cells
      - = it is a „circumventricular organ”
      - = no blood-brain-barrier exists here
      - Neither towards blood nor towards liquor



Physiology of emesis

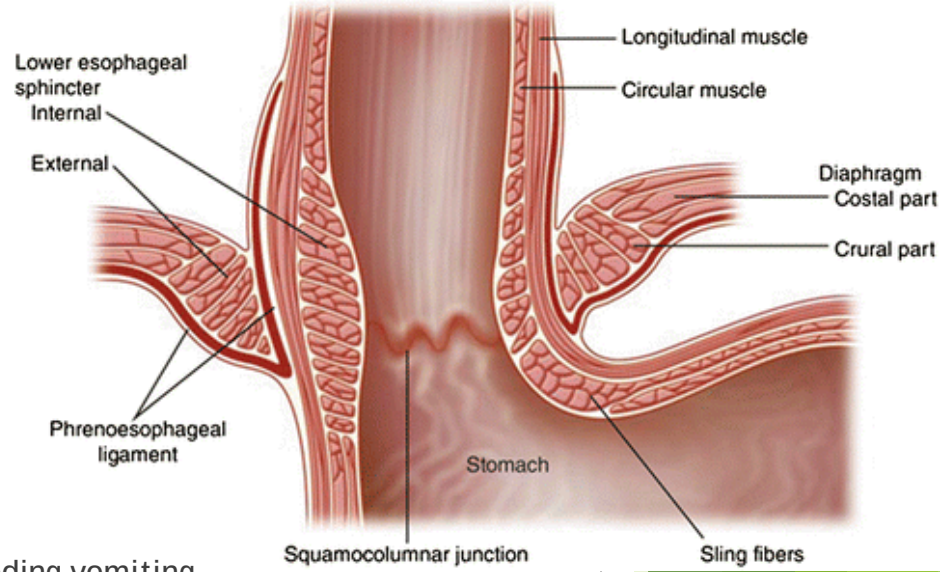
- Parts of the vomiting-reflex (cont.):
  - Vomiting center (area postrema)
    - Located in medulla oblongata in brainstem at the inferoposterior limit of the fourth ventricle
    - Densely vascularized structure
    - No tight junction between capillary endothelial cells
      - = it is a „circumventricular organ"
      - = no blood-brain-barrier exists here
      - Neither towards blood nor towards liquor
  - Efferentation
    - Parasympathetic & motor nerves namely:
      - To (oro)pharynx (CN IX, X)
      - To diaphragm (phrenic nerve)
      - To abdominal and intercostal muscles (spinal nerves)
      - To gut (CN X)

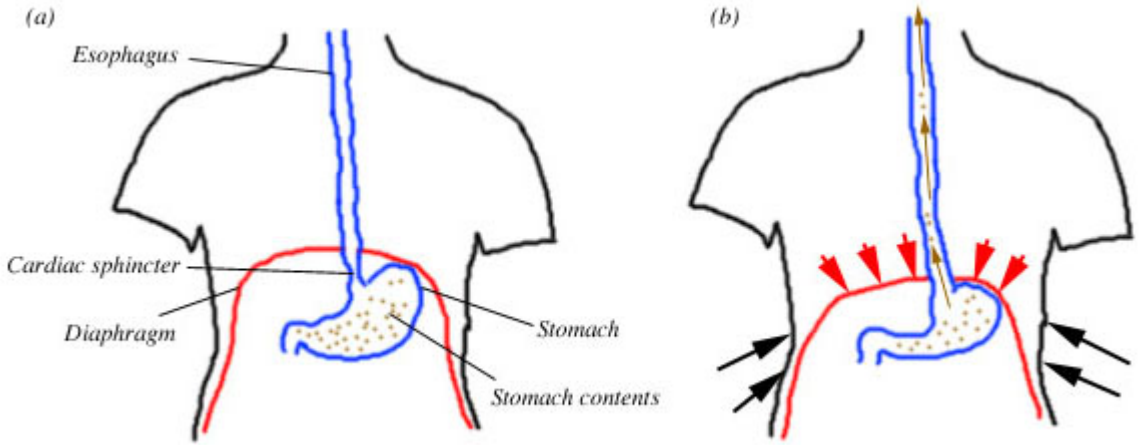
Similarity to cough-reflex



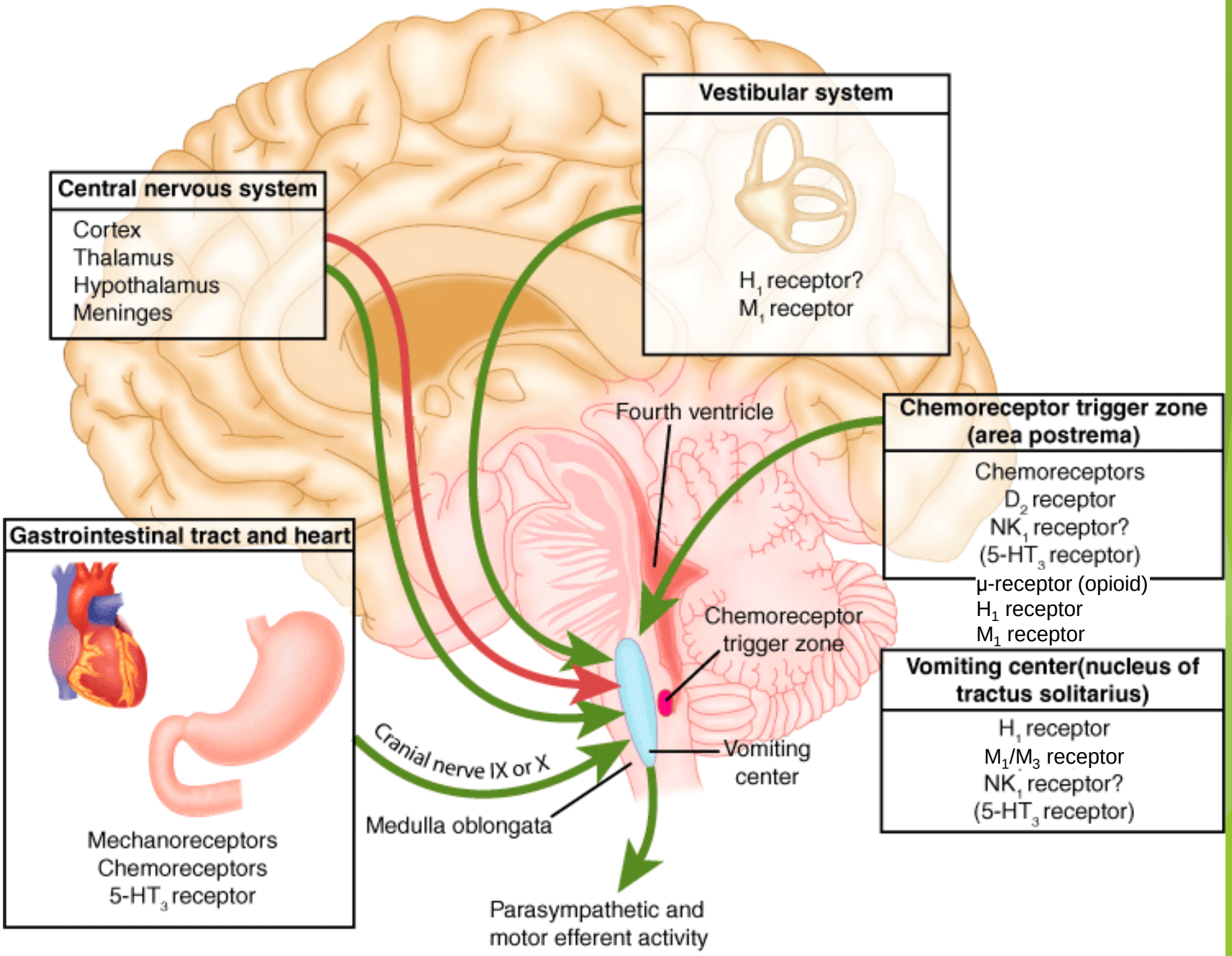
Physiology of emesis

- Parts of the vomiting-reflex (cont.):
  - Muscle contraction
    - Pre-ejection phase:
      - gastric relaxation
      - retroperistalsis
    - Retching:
      - rhytmic action of respiratory muscles preceding vomiting
      - Contraction of abdominal and intercostal muscles and diaphragm against a closed glottis
    - Ejection:
      - intense contraction of abdominal muscles
      - Relaxation of crural section(/sling) of dihpragm (lower esophagal sphincter)
      - Relaxation of upper esophagal sphincter





Neurotransmitters involved in emesis



Emetic drugs

- Required when an undesirable substance has been ingested, e.g.:
  - acute poisoning (EXCEPT corrosive substances e.g. acids/alkali)
  - Alcoholic intoxication
  - Removal of foreign bodies from esophagus

- According to site of action:
  - Centrally acting (directly on CTZ/VC):
    - Apomorphine
      - i.m. / s.c. 2-8mg
      - induces vomiting in 5-10 mins
      - Causes sedation ➔ contraindicated in respiratory depression
  - Peripherally acting:
    - Mustard seed (1 tablespoonful ground powder in 2dl water),
    - hypertonic sodium chloride (1 spoonful in 2 dl water)
  - Both (irritating gastric mucosa & through CTZ):
    - Ipecacuanha (emetin) (larger doses)
      - As syrup: Infants 5ml, children 10-15ml, adults 15-30ml
      - Induces vomiting in 15 mins

Contraindications of emetic drugs

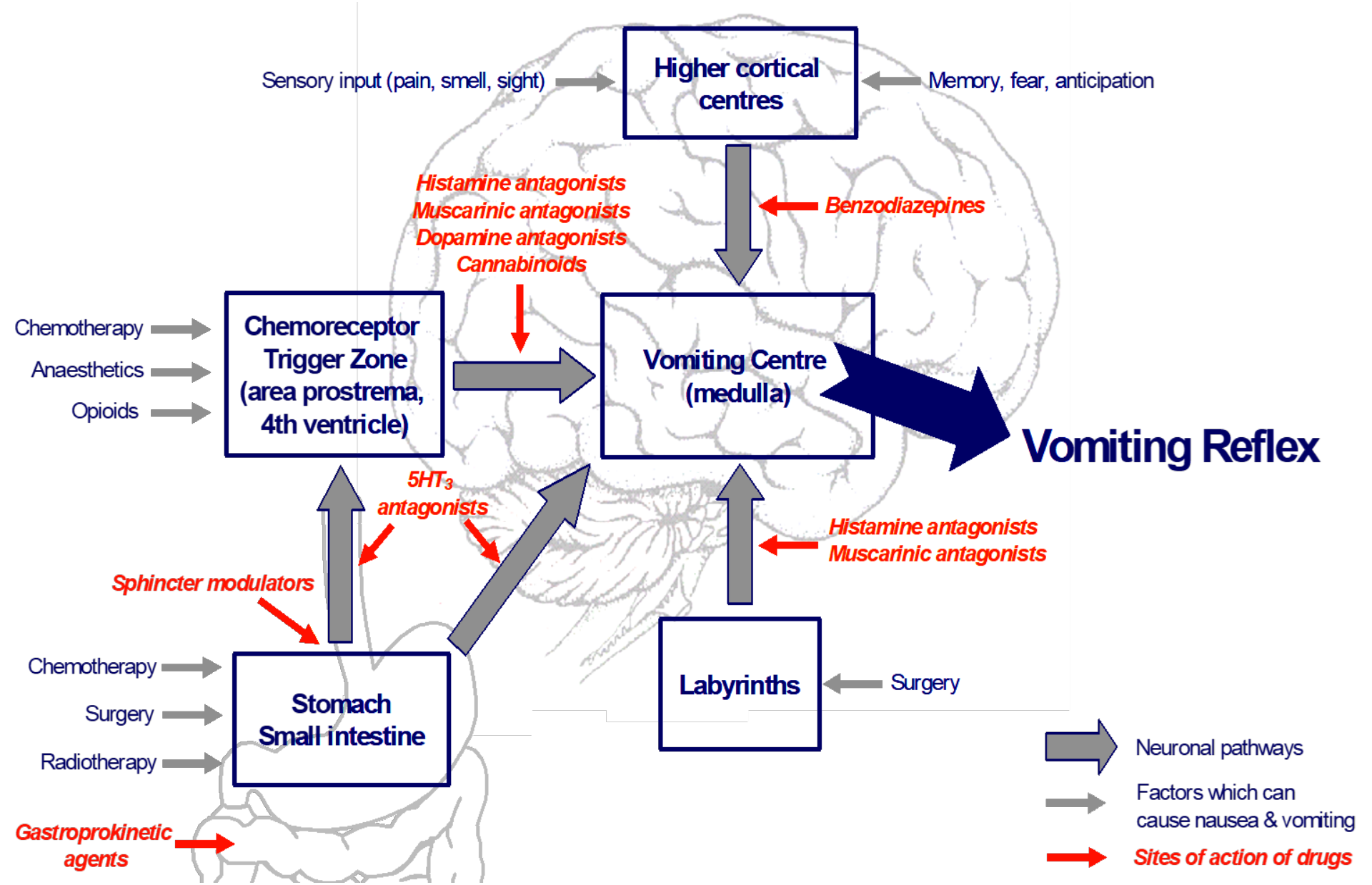
- Corrosive (acid/alkali) poisoning
- Unconscious patients
- Weak / debiliated patients
- Peptic ulcer
- Aneurysm
- Severe heart diseases
- Threatening abortus

- Too many ➔ instead ➔ consider gastric lavage

Antiemetics - Classification

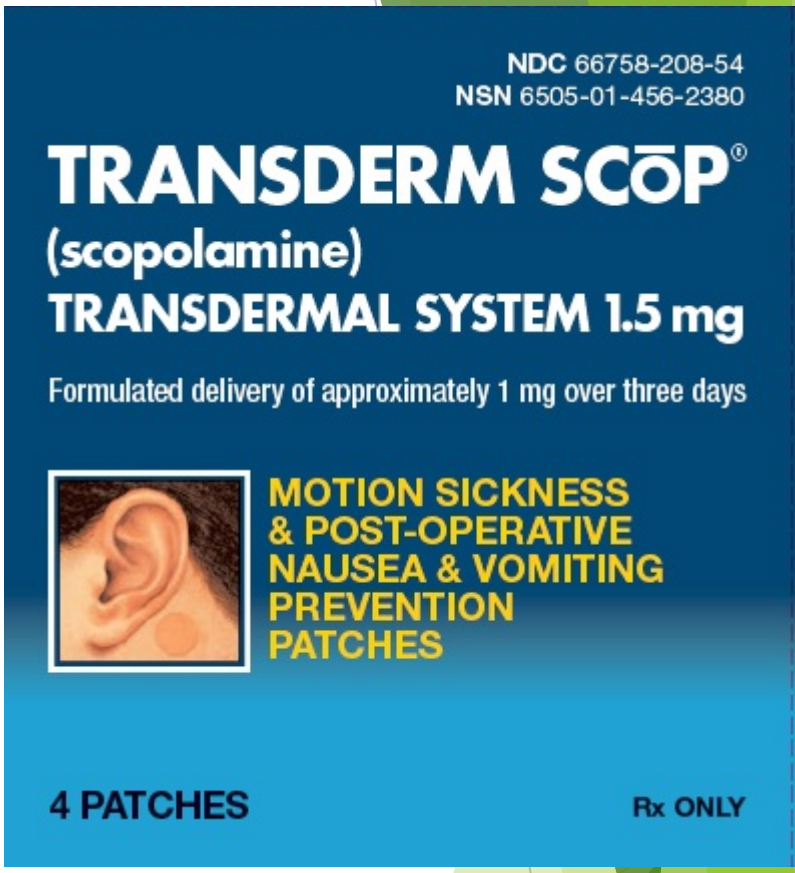
- Anticholinergic (muscarinic antagonists)
  - Scopolamine (hyoscine)
- Antihistamines (H_1 receceptor blockers)
  - Promethazine, diphenhydramine, dimenhydrinate, cyclizine, etc.
- D_2 antagonists (antipsychotics)
  - Haloperidol, chlorpromazine, promethazine (here as well), prochlorperazine, etc.
- Prokinetics
  - Domperidone, metoclopramide, cisapride, mosapride, etc
- 5-HT_3 antagonists (-setrons)
  - Ondansetron, granisetron, tropisetron etc.
- Neurokinin 1 antagonists
  - Aprepitant, fosaprepitant
- Cannabinoids
  - Dronabinol, nabilone
- Benzodiazepines
  - Diazepam, lorazepam etc.
- Glucocorticoids (adjuvants)
  - Dexamethasone, methylprednizolone, etc.

Antiemetics – Which to use?



Anti-cholinergics

- Scopolamine (Hyoscine) (0.2 - 0.4 mg oral/i.m.)
  - Most effective for motion sickness
  - Non-selective Antagonist on Muscarinic AcCh-rec.
  - Brief duration of action ⇔ but transdermal patch
  - Side effect:
    - Sedation
    - Other cholinergic side effect (e.g. dry mouth, blurred vision)
  - Less side effect with TTS applied behind the auricle



Anti-histamines

- Mainly 1st generational anti-histamines (2nd and 3rd gen are mainly anti-allergics)
- Non-selective blockers of H_1-rec,
  - also antagonists on
    - Muscarinic acetylcholine-receptors
    - 5-HT-receptors
    - D_2-receptors
- Sedative side-effect (due to anti-muscarinic/anti-histaminic action)
- Promethazine
  - H_1-rec inhibitor ➔ **antiemetic**, antiallergic
    D_2-rec inhibitor ➔ antipsychotic, **antiemetic**
  - Used in pregnancy (morning sickness)
  - Used by NASA for space motion sickness
- Diphenhydramine
- Dimenhydrinate (Daedalon(etta)®)= combination of diphenhydramine & 8-chlorotheophylline
- Cyclizine, Meclizine – also anti-cholinergic actions
- Anti-motion-sickness drugs are more effective 0.5-1 hr before starting journey

Anti-psychotics

- D2-rec antagonists ➔ antipsychotic, **antiemetic** actions
- Antiemetic dose is much lower than antipsychotic doses
- Should not be administered until the cause of vomiting has been diagnosed

- Haloperidol, droperidol
- chlorpromazine, promethazine (here as well), prochlorperazine, etc.

- Uses:
  - Drug induced post-anaesthetic nausea and vomiting
  - Disease induced vomiting – gastroenteritis, uraemia, liver disease
  - Chemotherapy induced nausea and vomiting (CINV)
  - Morning sickness: preferably drugs should be avoided – reassurance & dietary modifications ; except in hyperemesis gravidarum

- Adverse effects: extrapyramidal symptoms (EPS) and muscle dystonia

Prokinetic drugs

- **Indications:** postoperative, chemotherapy-, radiotherapy-, MIGRAINE-emesis
- **Metoclopramide**, Mosapride, Cisapride, Alizapride, Prucalopride, Tegaserod, Zacopride
  - D2-rec antagonist ➔ antiemetic and prokinetic actions
  - 5-HT3 antagonist (at higher doses) ➔ antiemetic actions
  - 5-HT4 agonist ➔ prokinetic actions (= also antiemetic)
    - increase peristalsis of stomach, duodenum, jejunum
    - Relax pylorus sphincter
    - Increase tone of lower esophagal sphincter
  - Well tolerated, but serious side effects include: ➔ not for longer than 12 weeks
    - movement disorder like tardive dyskinesia: extrapyramidal symptoms (EPS)
    - Galactorrhea, gynecomastia
  - Secreted into breast milk ➔ not for lactating mothers; $T_{1/2}$ ~ 4-6hrs
- Domperidone
  - Peripherally selective D_2-rec antagonist ➔ but CTZ is outside CNS ➔ antiemetic as well +prokinetic (=which is also antiemetic)
    - Peripherally selective = low CNS-penetration (domperidon is a substrate for P-glycoprotein transporter = actively pumped out from CNS)
    - BUT galactogogue effects still exist
  - Less severe side effects than metoclopramide ➔ for children as well
  - Kinetics: 15% bioavailability – high 1st pass metabolism; excreted in urine; $T_{1/2}$ ~ 7-8hrs

5-HT3 antagonists

- Alosetron, Azasetron, Bemesetron, Cilansetron, Dolasetron, **Granisetron**, Lerisetron, **Ondansetron**, Palonosetron, Ramosetron, **Tropisetron**, Zatosetron
- Indications: radiation-, chemotherapy-, postoperative emesis
- No D2 affinity ➔ No extrapyramidal side effects
- Different $t_{1/2}$: e.g. ondansetron 4-9hrs, palonosetron 40hrs
  - Given 1x or 2x daily depending on this
- Adverse effects: mild (headache, constipation)
- Kinetics: 60-70% bioavailability – first pass metabolism;
  Metabolized as glucuronid and sulfate ➔ eliminated in faeces and urine.

Neurokinin 1 antagonists

- **Aprepitant**, Casopitant, Ezlopitant, **Fosaprepitant**, Maropitant, Netupitant, Rolapitant, Vestipitant
- Newer oral antiemetics
- Non-peptide, selective, NK1 rec.-antagonists
  - NK1 = substance-P receptor (neurokinin receptor)
    - Located in CTZ and vomiting centre
    - Also in hypothalamus and amygdala;
    - and on surface of many different cells throughout the body
  - Substance-P is a 11 amino acid peptide neurotransmitter
    - Associated with inflammatory processes and pain (among many others)
- Uses:
  - chemotherapy induced nausea & vomiting (CINV)
    - also for difficult-to-control **delayed phase CINV** (as opposed acute phase responds to 5HT-3 antagonists)
  - Post-operative nausea & vomiting (PONV)
- Adverse reactions: weakness, fatigue, flatulence
- Kinetics: well absorbed orally, metabolized by liver, excreted in faeces/urine, $T_{1/2}$ ~ 10-13hrs

Cannabinoids

- On the market:
  - Nabilone (=THC-analog) (Cesamet®)
  - Dronabinol (= synthetic THC) (Marinol®)
  - Nabiximol (= cannabis extract = THC+cannabidiol) (Sativex®)
- Mechanism of action:
  - (endo)cannabinoid receptor 1 (CB1) agonists
    - Gi signaltransduction; mainly on GABAergic neurons
    - Also located in vomiting center
- (Potential) Use:
  - Against moderately emetogenic chemotherapy
- Adverse effect:
  - Dronabinol, Nabiximol – psychoactive
  - Nabilone – neurological adverse effects
- Kinetics:
  - significant 1st pass metabolism
    metabolites excreted slowly (days to weeks) in faeces & urine

Laxatives and antidiarrheal drugs

Laxatives

- In Latin the word *Laxare* means „to loosen”
- Drugs that promote evacuation of bowels
  - to relieve constipation
  - to clear bowels prior to surgery or examination
- Based on intensity:
  - **Laxative** (or aperient): milder action, elimination of soft but formed stool, eases defecation
  - **Purgative** (or cathartic): stronger action, result in more fluid evacuation, accelerates defecation

Classification of laxatives/purgatives

- Bulk forming
  - Dietary fibers
- Stool softeners, Lubricants
  - Docusate, Liquid paraffin
- Osmotic
  - Salts
  - Lactulose
  - Glycerin
- Stimulant
  - Glycerin
  - Diphenylmethanes
    - Phenolphtalein
    - Bisacodyl
    - Sodium picosulfate
  - Anthraquinones
    - Senna
    - Dantron
  - Castor oil
  - Prokinetics

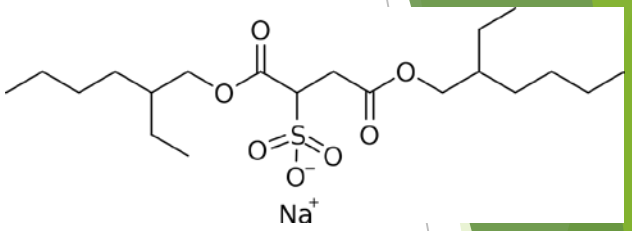
Bulk forming

- Methylcellulose, sterculia, agar, bran and ispaghula husk
- Fibers contain unabsorbable cell wall and other vegetable constituents
  - Cellulose
  - Lignins
  - Pectins
  - Gums
  - Other polysaccharides
- Mechanism of action:
  - Absorb water to increase bulk
  - Soften stool (gelatinous mass), facilitate colonic transit
  - Increase bacterial mass
  - Distend bowel to initiate reflex bowel activity
- Must be followed with large amount of fluid!
  - Without fluid, may cause constipation and obstruction
- Indication: mild laxatives, even for everyday use (prevention)

bran

ispaghula husk

Stool softeners, Lubricants



- Docusate (dioctyl sodium sulfosuccinate)
- Anionic detergent
- Mechanism of action:
  - Emulsifies colon contents and increase penetration of water/fat into faeces ➔ softens stool
  - As a detergent ➔ it can disrupt mucosal barrier ➔ enhance absorption of other drugs
    - E.g. liquid paraffin ➔ should not be combined with it
- Adverse effects:
  - Bitter taste ➔ liquid preparations may cause nausea
  - Cramps, abdominal pain
  - Hepatotoxicity on prolonged use
- Oral 50mg-400mg, in rectal enema 200mg

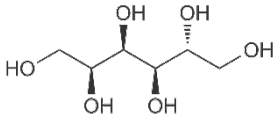
Stool softeners, Lubricants II.

- Liquid paraffin: mixture of petroleum hydrocarbons
- Mechanism of action:
  - Pharmacologically inert
  - Softens stool by lubricating it
- 15-30ml/day (as oil or in emulsion)
- Adverse effect:
  - prevent fat-soluble vitamins from being absorbed

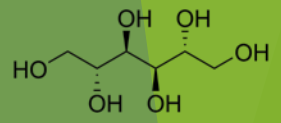
Osmotic laxatives

- Mild action
- Mechanism of action:
  - Solutes that are not absorbed ➔ retain water osmotically ➔ softens stool
  - Distend bowels ➔ increase peristalsis indirectly
  - Magnesium ions release cholecystokinin which augments motility and secretion ➔ purgative action
- Salts:
  - Magnesium-sulfate (Epsom-salt): 5-15g, bitter taste, may nauseate
  - Magnesium-hydroxide (as 8% suspension): 30ml; bland in taste, also used as antacid
  - Sodium-sulfate (Glauber's salt): 10-15g; bad taste
  - Sodium-phosphate: 6-12g, unpleasant taste
  - sodium-potassium-tartarate: 8-15g, relatively pleasant taste

Osmotic laxatives II.

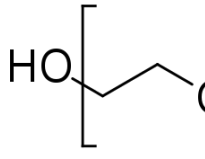


sorbitol



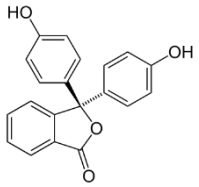
mannitol

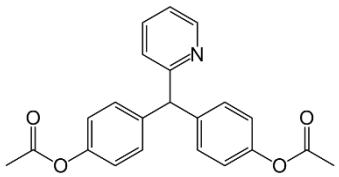
- Sorbitol (and mannitol)
  - Sugar alcohol (also found in many fruits); an isomer of mannitol (which is laxative >20g)
    - Mannitol i.v. used against increased intracranial/intraocular pressure and to treat fluid build up
  - Slow metabolism ➔ slow absorption ➔ osmotically active
  - Orally or as enema (>10g)
- Lactulose:
  - disaccharide of galactose and fructose;
  - not digested by intestinal enzymes ➔ not absorbed
  - Digested by colon bacteria to form acids (lactic, formic and acetic acids) ➔ increase osmotic pressure
  - 10g-30g before meal + plentiful of water
- Glycerol
  - colorless, odorless, viscous liquid that is sweet-tasting and non-toxic
  - Rectal suppository or enema; 2-10ml
  - Hyperosmotic AND irritates anal mucosa
- PEG – polyethylene-glycol (Macrogol)
  - Macrogol 3350 and 4000
  - Orally or as whole bowel irrigation

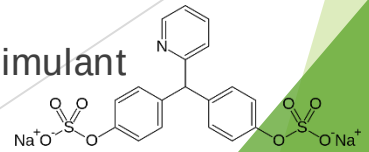


Stimulant purgatives

- Strong effects
- Mechanism of action:
  - Irritate colonic mucosa ➔ stimulate motor activity
  - Produce mild inflammation (enhanced Prostaglandin-synthesis)
  - Increase secretion
- Diphenylmethanes
  - Phenolphtalein, thymolphtalein (similar)
    - 250-500mg/day (at night)
    - Concerns with carcinogenicity ➔ not for longer than 2 weeks
    - May color the urine pink (if alkaline ➔ litmus-like indicator)
  - Bisacodyl
    - 5-10 mg
    - Contact laxative (see above) AND
    - Stimulates enteric nerves to cause colonic contractions
  - Sodium picosulfate
    - Pro-drug metabolised by bacteria ➔ metabolite is stimulant
    - 5-10 mg

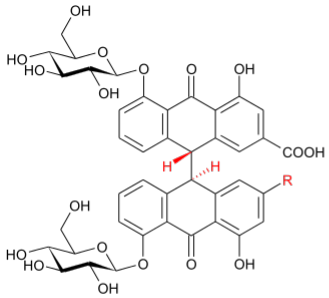




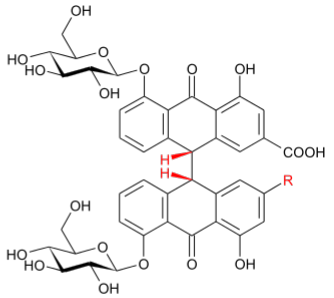


Stimulant purgatives II.

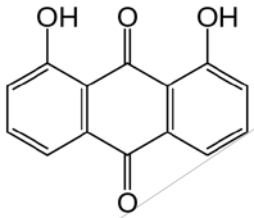
- Anthraquinones
  - Senna gylcosides (sennoside A + B)
    - Weaker than bisacodyl or castor oil
      - 10-30mg once daily
    - Mechanism of action:
      - Contact laxative (see before) AND
      - Stimulate enteric nerves ➔ stimulate peristalsis
    - Pharmacokinetics:
      - Unabsorbed in small intestine
      - Bacteria liberate active *anthrol* form
      - Enterohepatic circulation (long halflife)
    - Secreted into breast milk ➔ purgation in infant!
  - Dantron
    - In some countries used as stimulant laxative
    - May colour urine red



Sennosid A: R = COOH
Sennosid C: R = CH_2OH



Sennosid B: R = COOH
Sennosid D: R = CH_2OH



Stimulant purgatives III.

- Castor oil (vegetable oil cold-pressed from castor beans)
  - Strong purgative (>10ml) (🡐 a ususal tablespoon is ~15ml)
  - Also induces labor in pregnant women! (contracts uterus)
  - For enhanced hair/beard conditioning
    - supposed anti-dandruff properties.
    - high in linoleic acid,
      - restores dry follicles,
      - adds shine and
      - promotes follicle growth.

Prokinetics

- Metoclopramide, Cisapride, Mosapride, **Prucalopride**, **Tegaserod**, Zacopride
- Mechanism of effect:
  - 5-HT_4-agonists ➔ stimulate the peristalsis = they are called prokinetics

    Metoclopramide is also D_2-receptor antagonist and 5-HT_3-receptor antagonist ➔ used as antiemeticum

    Zacopride is also 5-HT_3-receptor antagonist (antiemetic)
- Application:
  - Against ulcer („antiulcer" drugs)
  - Gastrooesophageal reflux
  - Used to increase motility in gastoparesis, and constipation
  - In irritable bowel syndrome (spastic colon)

Antidiarrheals

Diarrhea

- Too frequent
- Too hasty passage of
- Poorly formed stool (loose watery stool)
- 3 or more in 24h

- Due to excess water in faeces.
- Causes of diarrhea:
  - Osmotic – lactase deficiency
  - Secretory – cholera, enterotoxigenic E.coli, Salmonella, Staph. Aureus, Clostridium difficile, Entamoeba histolytica etc.
  - Deranged intestinal motility – thyrotoxicosis
  - Altered mucosal morphology – viral gastroenteritis (e.g. Rota)
  - Inflammation of mucosa and exudation into lumen – autoimmune processes (IBD)
  - Allergic diarrhea – food allergy
  - Drug induced diarrhea
  - Tumour-related changes in intestines

Diarrhea II.

- Some molecular mechanisms:
  - cholera, enterotoxigenic E.coli, Salmonella, Staph. Aureus –
    - activate adenylyl cyclase (cAMP-production) ➔ enhance anion (Cl^-) secretion ➔ Na cannot be absorbed but retain in faeces ➔ osmotically drains water ➔ diarrhea
  - Clostridium & Entamoeba
    - increase cGMP-production in a similar manner
  - Rota virus
    - inhibits Na+K+ATPase ➔ water would follow Na+ isosmotically ➔ reduced water absorption ➔ diarrhea
  - Tumour
    - may secrete 5-HT ➔ also increases cAMP-production ➔diarrhea
    - (Thyroid medullary carcinoma secretes calcitonin ➔ increases cAMP➔ diarrhea)
  - Excess of bile acids
    - also cause diarrhea by activating adenylyl cyclase
  - Inflammation
    - Prostaglandines and intracellular Ca2+ also stimulate the secretory process

Antidiarrheals

- Treatment of fluid depletion
- Maintenance of nutrition
- Drug therapy

Rehydration

- Oral rehydration
  - Indication:
    - mild (5-7% BW) to
    - moderate (7-10%) fluid loss
  - From the very beginning

New formula WHO-ORS			
Content		Concentrations	
NaCl	2.6 g	Na+	75 mM
KaCl	1.5 g	K+	20 mM
Trisod.citrate	2.9 g	Cl-	65 mM
Glucose	13.5 g	Citrate	10 mM
Water	1 L	Glucose	75 mM
Total osmolarity 245 mOsm/L			

- Intravenous rehydration
  - Indication:
  - severe >10% BW fluid loss OR
  - losing >10ml/kg/h OR
  - Unability to take enough oral rehydration (e.g. weakness, vomiting, dementia, etc.)

Intravenous rehydration solution		
NaCl	5 g	85 mM
KaCl	1 g	13 mM
NaHCO3	4 g	48 mM
Glucose	13.5 g	10 mM
Water or 5% glucose solution	1 L	

Nutrition

- Contrary to public belief, patients of diarrhea should not be starved
  - Fasting decreases disaccharidase enzymes AND
  - Reduces absorption of salt, water and nutrients ➔ may lead to malnutrition if diarrhoea is prolonged or recurrent
- Simple foods should be given as soon as the patient can eat
  - Breast milk or ½-strenght cow milk
  - Boiled potato, rice, chicken soup (low fat), toasted bread, plain biscuits
  - (Banana)

Drug therapy

- Specific antimicrobial drugs
- Probiotics
- Drugs for inflammatory bowel disease (see lecture)
- Nonspecific antidiarrheal drugs
  - Adsorbants
  - Antisecretory agents
  - Antimotility agents

Antimicrobials for diarrhea

Only good in infectious cases!

- Bacterial diarrhea is only a fraction of cases
- Even if bacterial diarrhoea, antimicrobials alter the course of illness only in selected cases
- Antimicrobials may prolong the carrier state

- Useful in severe disease (but not in mild cases):
  - Enterotoxic E.coli, Campylobacter (, or viral)
  - Trimethoprim+sulfamethoxazole comb., norfloxacin/ciprofloxacin, doxycycline
- Antimicrobials regularly useful in:
  - Cholera, clostridium etc
  - Amoebiasis, Giardiasis

- BUT careless administration of antibiotics may lead to e.g. Clostridium infection (= 20% of antibiotic-associated diarrhea is due to *Clostridium difficile*)

Probiotics

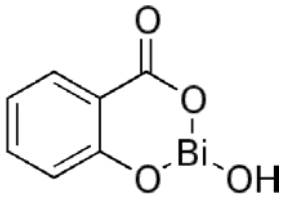
- Mechanism of action:
  - Restore and maintain healthy gut flora ➔
  - Competitive exclusion of enteric pathogens
  - producing lactic acid, bacteriocin etc.
    - Inhibit growth of pathogens
  - Produce butyric acid
    - Increase enterocyte turnover
    - Neutralize dietary carcinogens
  - Trigger cytokine synthesis from enterocytes

- Diarrheal illnesses and antibiotic use are associated with aterations
  - in the population
  - in the composition
  - in the balance of gut microflora.

- Organisms used for recolonisation:
  - Lactobacillus sp.
  - Bifidobecterium
  - Streptococcus faecalis
  - Enterococcus sp.
  - Saccharomyces boulardii (yeast)

Adsorbants

- Mechanism of action:
  - Adsorb bacterial toxins and/or bacteria themselves
  - Coat/protect the mucosa
- Activated charcoal/carbon
  - a form of carbon processed to have small, low-volume pores that increase the surface area (1g = 3000 m^2)
  - Also for treatment of poisoning
  - Colors the stool black
- Bismuth subsalicylate (pink bismuth)
  - Combines with HCl ➔ bismuth oxychloride + salicylic acid
  - Adsorbant + Anti inflammatory, bactericid
  - Also decreases prostaglandine synthesis ➔ reduce secretion
  - Pink colored
- Kaolin(ite)
  - $Al_2Si_2O_5(OH)_4$
  - Main component of porcelain
- Attapulgite (palygorskite) (another clay material)
  - $(Mg,Al)_2Si_4O_{10}(OH)\cdot 4(H2O)$
- Pectin
  - Gelling agent, purified carbohydrate



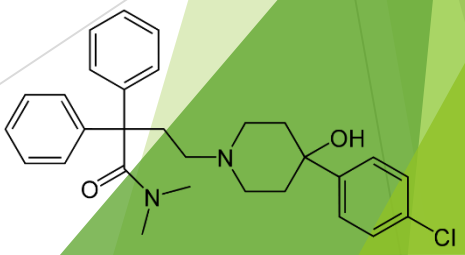
Antisecretory agents

- Racecadotril
  - A dipeptide prodrug
    - Its active metabolite is called Thiorphan
  - Mechanism of action
    - Enkephalinase inhibitor ➔
    - Increase local enkephalin concentration in intestinal mucosa ➔
    - Lower mucosal cAMP ➔
    - Unlike opioids it has antisecretory actions! (δ-receptors)
  - can be used by infants as well
    - While opioids are contraindicated in children
- Bismuth subsalicylate (see former slide)
- Octreotide
  - Somatostatin analogue (peptide)
  - Has antisecretory/antimotility actions
  - 50-250ug s.c.
- Anticholinergic agents
  - Atropinic drugs can reduce bowel motility and secretion; poor efficacy

Antimotility agents

- Antimotility agents should not be given in bacterial diarrhea ➔ slow clearing
- Mechanism of action:
  - Opioid-derivatives ➔ μ -receptor agonist action
    - μ-receptors = Decrease intestinal motility
    - δ-receptors = Decrease intestinal secretion

- Loperamide
  - Loperamide is a substrate for P-glycoprotein ➔
    - efflux from brain and even from blood ➔
    - bad absorption
    - can hardly pass Blood-brain barrier
  - Still may cause mild physical dependence
    - Mild opiate withdrawal following abrupt discontinuation of long-term treatment
    - NOT for children under 2 years
    - NOT for pregnants and breast-feeding mothers (may pass)



Antimotility agents II.

- Diphenoxylate
  - Synthetic opioid (chemically related to pethidine)
  - Prominent antidiarrheal actions
- Side effect:
  - Can pass blood-brain barrier ➔ CNS effects
    - Combined with subpharmacologic dose of atropin ➔ to prevent abuse
  - NOT for children, pregnant and breast-feeding women