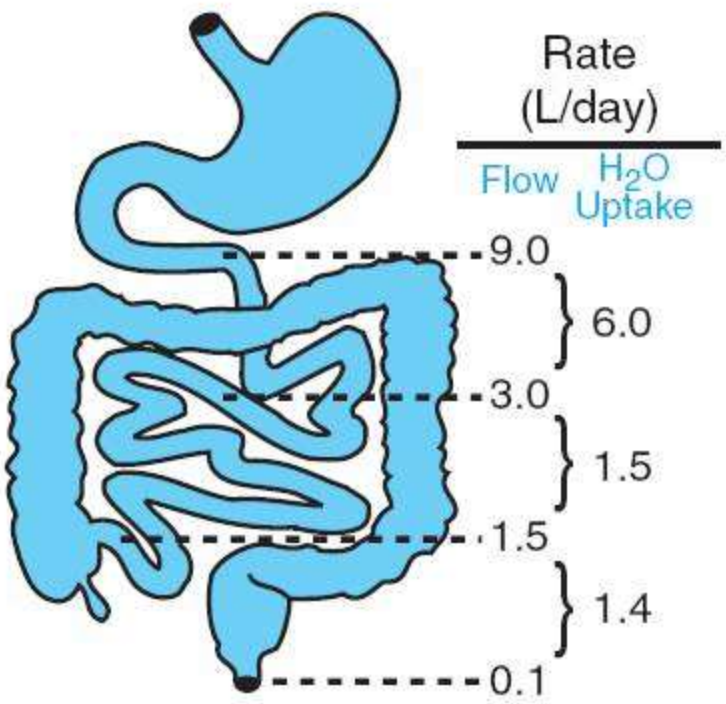
# Topics

- Laxatives
- Antidiarrheal drugs
- Drugs used in the treatment of irritable bowel syndrome (**IBS**)
- Antiemetic drugs
- Drugs used for **IBD** (Crohn's / UC)

# Laxatives

GI water intake and absorption ⟶ water content ⟶ stool volume / consistency

- input: 9 L (2 L diet + 7 L endogenous)
- colon: max. absorptive capacity: ~4-5 L
- change in secretion and/or absorption
  - neurohumoral mechanisms
  - pathogens
  - **drugs**
  - altered motility ⟶ transit time ⟶ absorp.
- constipation
  - defined by **stool frequency** (min 3x weekly)
  - BUT it is a frequent complaint
    - difficulty in initiation or passage
    - passage of firm or small-volume feces
    - feeling of incomplete evacuation



# Drugs causing constipation

- antacids
  - e.g. aluminium hydroxide
- anticholinergics
  - atropin, scopolamin
  - some antiparkinsonian drugs (benztropin, biperiden)
  - antihistamins ($H_1$ blockers)
  - phenothiazines
  - tricyclic antidepressants
- opioids
- verapamil
- smooth muscle relaxants

# Clinical use of laxatives

- *constipation*
- *emptying colon*
  - before surgical, radiological, and endoscopic procedures

- *laxation*
  - the evacuation of formed fecal material from the rectum
- *catharsis*
  - the evacuation of unformed, usually watery fecal material from the entire colon

# General mechanism of action of laxatives

- ↑ intraluminal fluid retention
  - hydrophilic – attract water
  - osmotic – hyperosmolality
- ↓ net fluid absorption
  - altered fluid and electrolyte transport
- altered motility
  - ↓ nonpropulsive
  - ↑ propulsive

# Classification of laxatives

- **Luminally active agents** (↑ intraluminal fluid retention)
  - Bulk forming agents (bran, psyllium)
  - Stool surfactant agents - softeners (docusate, mineral oil)
  - Osmotic laxatives (nonabsorbable salts / sugars)
- **Nonspecific stimulants or irritants**
  - diphenylmethanes (bisacodyl)
  - anthraquinones (senna and cascara)
  - castor oil
- **Chloride channel activators**
  - lubiprostone / linaclotide
- **Prokinetic agents**
  - 5-$HT_4$ receptor agonists
  - opioid receptor antagonists

# Luminally active agents 1.

- **Bulk forming laxatives** (hydrophilic colloids)
  - ***bran*** (contains > 40% fiber)
    - wheat bran - **lignin** (insoluble, poorly fermentable by bacteria)
  - ***psyllium***
    - fermented by bacteria → colonic bacterial mass ↑
  - ***methylcellulose / Ca-polycarbophil***
    - poorly fermentable, absorb water, ↑ fecal bulk

*Plantago ovata* (ispaghula/isabgol)

Psyllium husk

AEs:
bloating
flatus

Fiber: resists enzymatic digestion and reaches the colon unchanged

# Luminally active agents 2.

- **Softeners**
  - ***docusate*** salts
    - aninonic surfactants
    - widespread use but marginal efficacy
  - ***glycerin*** suppository
  - ***mineral oil*** – mixture of aliphatic hydrocarbons
    - clear viscous oil / indigestible / limited absorption
    - lubricate and softens stool (↓ water absorption)
    - clinical use: prevent and treat fecal impaction
    - undesired effects
      - ↓ absorption of fat-soluble vitamins
      - foreign body reactions in the mucosa
      - lipid pneumonitis ← aspiration (rare)

# Luminally active agents 3.

- **Osmotic laxatives**
  - Saline laxatives
    - magnesium cations or phosphate anions
      - magnesium sulfate / magnesium hydroxide (milk of magnesia) / sodium phosphate)
    - for colonic preparation - larger doses (purgatives)
    - caution in:
      - renal insufficiency / cardiac disease / preexisting electrolyte abnormalities / diuretic therapy
  - Nondigestable sugars and alcohols
    - hydrolyzed in the colon to short-chain fatty acids → colon propulsive ↑
    - lactulose = galactose + fructose
    - sorbitol, mannitol
    - adverse effects: abdominal discomfort / flatulence

# Luminally active agents 4.

- **Osmotic laxatives**
  - **Balanced PEG (PEG-electrolyte solutions)**
    - for **colonic cleansing** – large dose (4 L over 2-4 hours !)
      - e.g. prior to gastrointestinal endoscopic procedures
      - PEG is inert. not absorbed and osmotically active
    - constipation treatment in difficult cases – small dose
      - 250-500 ml daily
    - no significant intravascular fluid or electrolyte shifts
      - no net transfer of ions
      - isotonic mixture of Na-sulfate, $NaHCO_3$, NaCl, KCl
    - no cramps and flatus

# Stimulant (irritant) laxatives 1.

- direct effects on
  - enterocytes, enteric neurons, GI smooth muscle
  - but **specific target is not clear** (PG, NO, Na-K ATPase)
- inflammation induction (low-grade, limited)
- ↑ water and electrolite / ↑ motility
- only for short term admininstration
  - less than ≈ 10 days (but may be required long-term)
  - risk of atonic colon ?

# Stimulant (irritant) laxatives 2.

- Diphenylmethane derivatives
  - ***bisacodyl***
    - delayed effect (hydrolysis in the bowel)
  - ***phenolphtalein***
    - carcinogenic ?
- Anthraquinone derivatives
  - ***senna, cascara, aloe***
    - plantal origin
    - monoanthrones (e.g. rhein) → drying → dianthrones → colonic bacteria → active irritating monoanthrones
      - tricyclic anthracene nucleus – carcinogenicity ?
      - activation is required → delayed effects
- Castor oil
    - derived from the bean of the castor plant (*Ricinus communis)*
    - ricin ↔ triglyceride of **ricinoleic acid**
    - seldom used ← taste / damage of epithelium / enteric neurons

# Chloride channel activators

- **lubiprostone**
  - type 2 chloride channel (ClC-2) activator
  - FDA: 2006
- **linaclotide**
  - guanylyl cyclase-C agonist
  - FDA: 2012 / EMA: 2012
- approved for
  - chronic constipation
  - constipation predominant irritable bowel syndrome (IBS)

# Lubiprostone

- enhance fluid secretion
  - prostanoid activator of $Cl^-$ channels – $EP_4$ rec.
  - improved stool consistency / volume
  - reflex activation of motility
- indications
  - chronic constipation
  - IBS with constipation
- poor bioavailability – intraluminal activity
  - but pregnancy category C (= animal studies have shown an adverse effect on the fetus)
- with long-term therapy: no loss of efficacy

# Linaclotide

- chemistry
  - 14 amino acid peptide
- mechanism of action
  - binds to and **↑ guanylyl cyclase-C** → ↑ cGMP → ↑ cystic fibrosis transmembrane conductance regulator (CFTR) → ↑ Cl rich secretion → improved stool consistency / ↑ volume → reflex activation of motility
- pharmacokinetics
  - minimal absorption
- clinical characteristics
  - indications
    - chronic constipation
    - IBS with constipation
    - with long-term therapy: no loss of efficacy
  - adverse effects
    - diarrhea (rarely severe)
  - contraindications
    - in children and pregnancy

# Opioid receptor antagonists

- **methylnaltrexone**

- μ antagonist
- does not cross BBB
- **chronic**
- sc. inj.

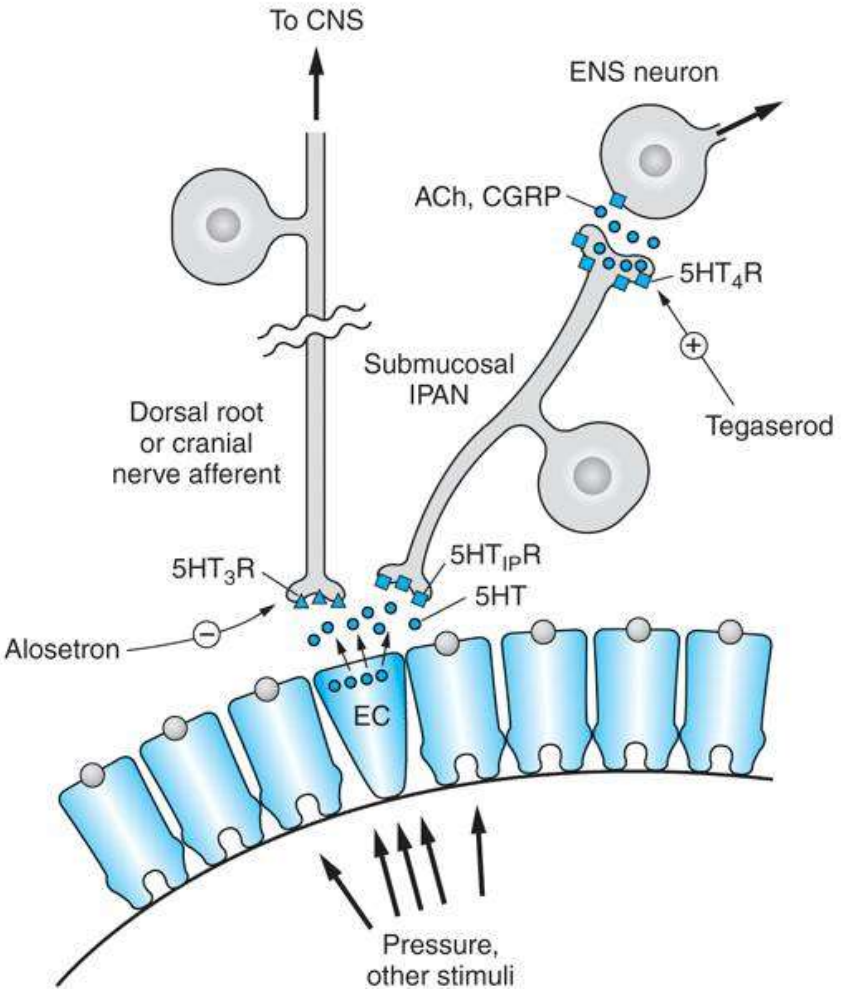
- **alvimopan**

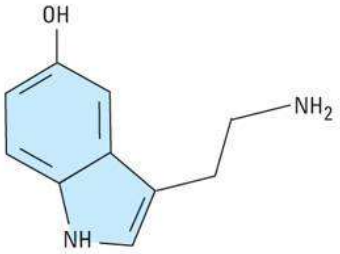
- μ antagonist
- does not cross BBB
- **short term postop.**
- oral
- possible CV toxicity ?

# $5HT_4$ receptor agonists

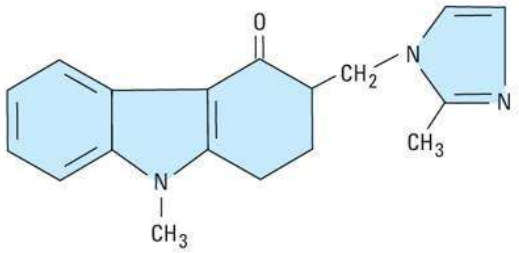
tegaserod → **prucalopride**

- $5HT_4$ partial agonist – presynaptic!
- tegaserod structurally similar to serotonin
- ↑ peristaltic reflex, intestinal secretion
- ACh, calcitonin-gene related peptide release ↑
- ind: chronic constipation / IBS-C
- high cost
- AEs: diarrhea, headache
- **tegaserod: serious CV toxicity ($5\text{-}HT_{1B}$)!! (withdrawn)**



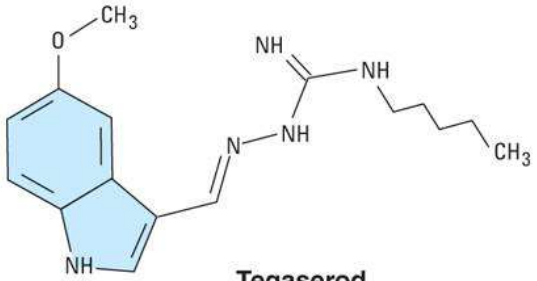



**Serotonin**



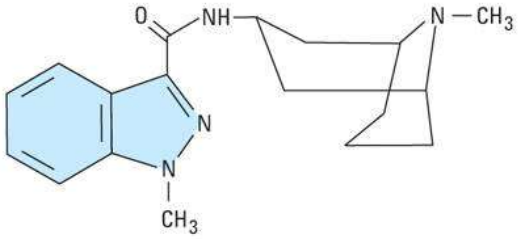

**Ondansetron**

5-$HT_3$ antagonist



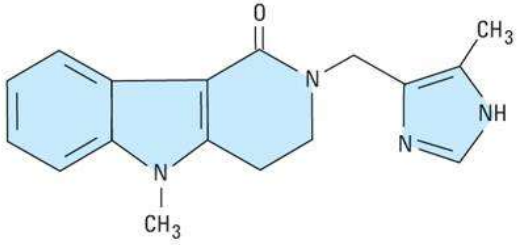

**Tegaserod**

5-$HT_4$ agonist



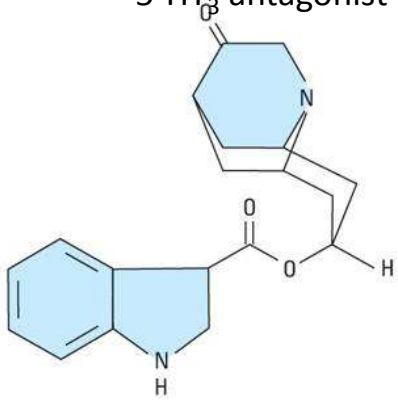

**Granisetron**

5-$HT_3$ antagonist




**Alosetron**

5-$HT_3$ antagonist




**Dolasetron**

5-$HT_3$ antagonist

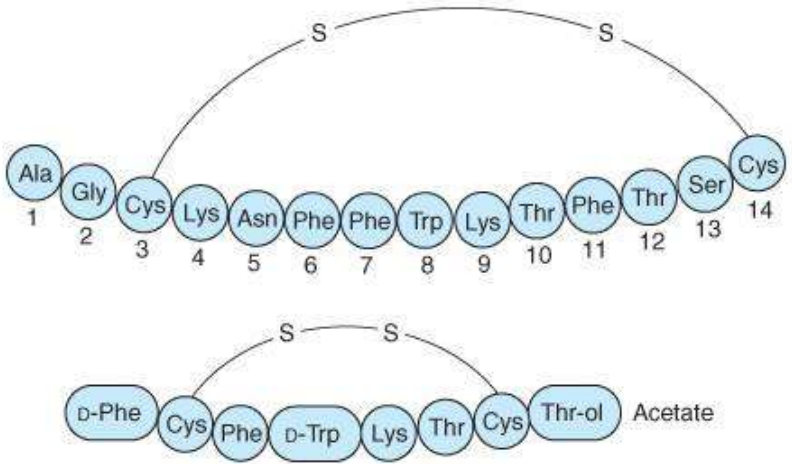
# Antidiarrheal drugs

**DO – mild acute**
**DON'T – bloody / fever / worsening**

- Opioid agonists
  - **loperamide** – does not cross BBB
  - **diphenoxylate** – combined with atropine (to prevent abuse)
  - difenoxin – active metabolite of diphenoxylate
- Colloidal bismuth compounds
  - **bismuth subsalicylate**, bismuth subcitrate
  - <1% bismuth is absorbed but stored
  - protective layer / direct antimicrobial effects / binds enterotoxins
  - clinical use
    - wide, non-specific / prevention of traveler's diarrhea / *H. pylori* eradication
    - black stools
- Kaolin and **pectin**
  - hydrated Mg-Al silicate / indigestible polymeric carbohydrate (from apples)
  - **absorbents** of bacteria, toxins, and fluid
  - may bind other medications
- Bile salt binding resins
  - cholestyramine, colestipol – in case of malabsorption
- Octreotide

# Octreotide

- synthetic octapeptide – see somatostatin
- iv. ($t_{1/2}$≈1.5 h), sc. , depot im. inj.
- 45x more potent than somatostatin in inhibiting GH release but only twice as potent in reducing insulin secretion
- Effects of somatostatin:
  - blocks: gastrin, cholecystokinin, glucagon, growth hormone, insulin, secretin, pancreatic polypeptide, vasoactive intestinal peptide, and 5-HT
  - ↓intestinal fluid secretion and pancreatic secretion
  - ↓gastrointestinal motility and gall bladder contraction
  - contraction of vascular smooth muscle - ↓portal /splanchnic blood flow
  - ↓secretion of anterior pituitary hormone - GH



# Clinical use of octreotide (Sandostatin®)

- carcinoid / VIPoma
  - secretory diarrhea
- other diarrhea
  - higher doses (100-250 µg sc.)
  - chemotherapy-induced diarrhea, diarrhea associated with HIV, diabetes-associated diarrhea
- acromegaly
- esophagus variceal bleeding

*Adverse effects*

steatorrhea, nausea, abdominal pain, **gallstones**, hyperglycemia

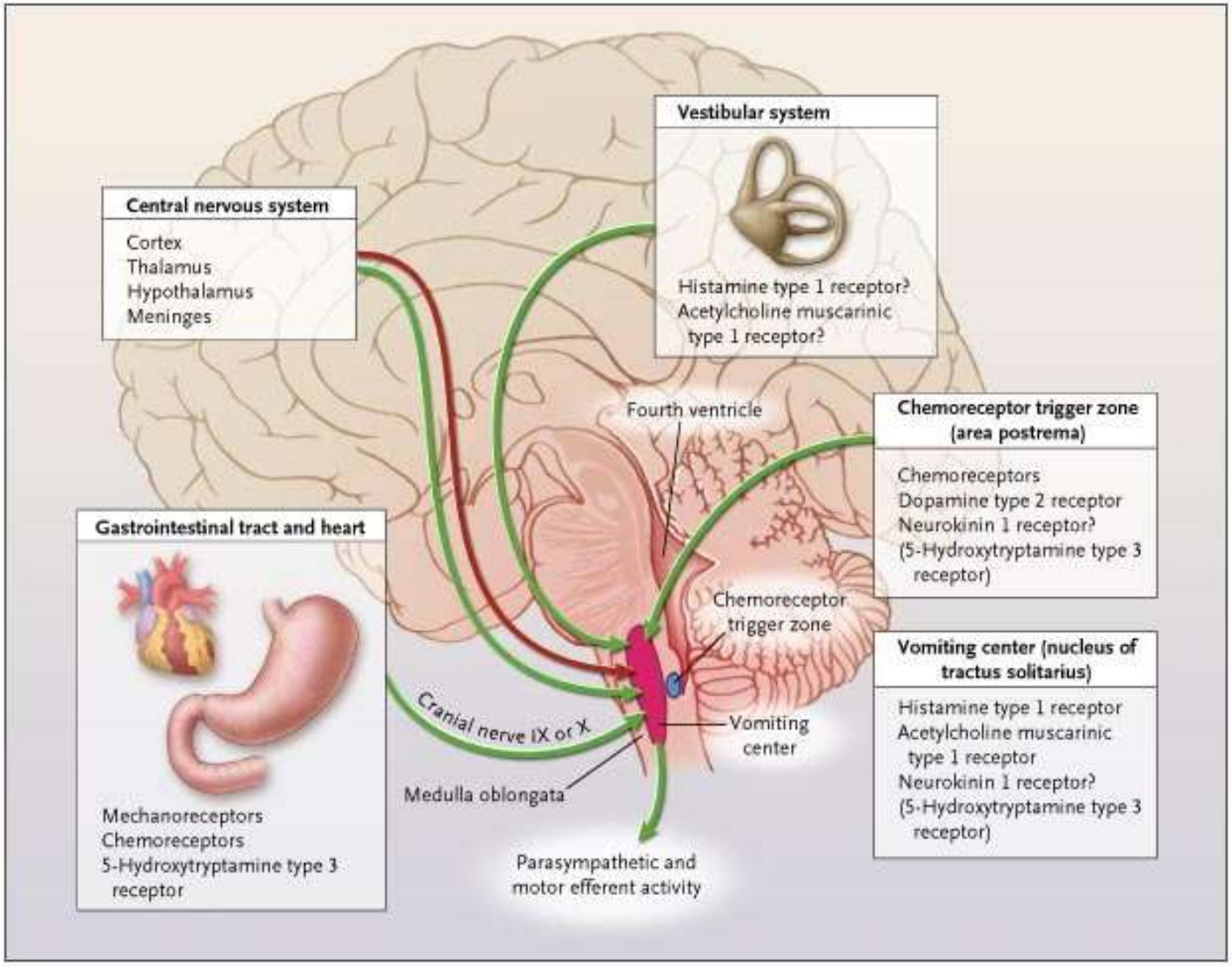
# Irritable bowel syndrome (IBS)

IBS – pain / altered bowel movements ≠ IBD

- pain / discomfort
  - anticholinergics (antispasmodics) – **efficacy ?** (anticholinergic adverse effects!)
    - dicyclomine, l-hyoscyamine
    - glycopyrrolate, methscopolamine – quaternary
  - antidepressants
    - low doses of TCAs (amitryptiline / desipramine)
    - in case of persistent abdominal pain
- constipation
  - fiber (e.g. psyllium) / osmotics (milk of magnesia / **polyethylene glycol)**
  - lubiprostone or linaclotide
  - $5HT_4$ receptor agonist – *prucalopride*
    - **constipation predominant**
    - **tegaserod was withdrawn because of CV effects**
- diarrhea
  - loperamide
  - $5HT_3$ receptor antagonists – *alosetron*
    - approved (restricted) – **diarrhea-predominant** ♀
    - high affinity binding – long duration
    - relatively serious adverse effects: constipation, ischemic colitis – only for severe cases

# Antiemetic drugs - background

- nausea, vomiting - symptom
  - adverse effect of drugs
  - infection
  - pregnancy
  - vestibular dysfunction
  - CNS disease (infection, increased pressure)
  - radiation or chemotherapy
- participating anatomical sites
  - vomiting center ($M_1$, $H_1$, $5HT_3$, $NK_1$ receptors)
  - CTZ ($D_2$, opioid receptors, 5-$HT_3$, $NK_1$)
    - outside BBB → constant monitoring of blood and CSF
  - vestibular system ($M_1$ and $H_1$ receptors) → motion sickness
  - CNS (cortex) → anticipatory
  - pharynx
  - GI tract (5-$HT_3$ receptors)


Central nervous system
Cortex
Thalamus
Hypothalamus
Meninges
Vestibular system
Histamine type 1 receptor?
Acetylcholine muscarinic type 1 receptor?
Fourth ventricle
Chemoreceptor trigger zone (area postrema)
Chemoreceptors
Dopamine type 2 receptor
Neurokinin 1 receptor?
(5-Hydroxytryptamine type 3 receptor)
Gastrointestinal tract and heart
Mechanoreceptors
Chemoreceptors
5-Hydroxytryptamine type 3 receptor
Chemoreceptor trigger zone
Vomiting center (nucleus of tractus solitarius)
Histamine type 1 receptor
Acetylcholine muscarinic type 1 receptor
Neurokinin 1 receptor?
(5-Hydroxytryptamine type 3 receptor)
Cranial nerve IX or X
Vomiting center
Medulla oblongata
Parasympathetic and motor efferent activity

# Antiemetic drugs - summary

1) 5-$HT_3$ receptor antagonists – “setrons”
2) Dopamine receptor antagonists
    1) phenothiazines, butyrophenones (antipsychotics)
    2) metoclopramide
    3) domperidone
3) $H_1$ antihistamines and anticholinergics
4) neurokinin $NK_1$ receptor antagonists
5) corticosteroids (glucocorticoids)
6) cannabinoids
7) benzodiazepines

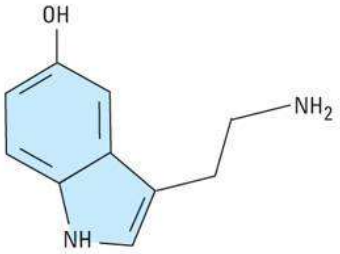
## Receptor Specificity of Antiemetic Agents

| Pharmacologic Class (Drugs in Class) | Dopamine ($D_2$) | Acetylcholine (Muscarinic) | Histamine | Serotonin |
|---|---|---|---|---|
| *Anticholinergics* | | | | |
| Scopolamine | + | ++++ | + | – |
| *Antihistamines* | | | | |
| Cyclizine | + | +++ | ++++ | – |
| Dimenhydrinate, diphenhydramine, hydroxyzine | + | ++ | ++++ | – |
| Medizine | + | +++ | ++++ | – |
| Promethazine | ++ | ++ | ++++ | – |
| *Antiserotonins* | | | | |
| Dolasetron, granisetron, ondansetron, palonosetron, ramosetron | – | – | – | ++++ |
| *Benzamides* | | | | |
| Domperidone | ++++ | – | – | + |
| Metoclopramide | +++ | – | – | ++ |
| *Butyrophenones* | | | | |
| Droperidol | ++++ | – | + | + |
| Haloperidol | ++++ | – | + | – |
| *Phenothiazines* | | | | |
| Chlorpromazine | ++++ | ++ | ++++ | + |
| Fluphenazine | ++++ | + | ++ | – |
| Perphenazine | ++++ | + | ++ | + |
| Prochlorperazine | ++++ | ++ | ++ | + |
| *Glucocorticoids* | | | | |
| Betamethasone, dexamethasone | – | – | – | – |

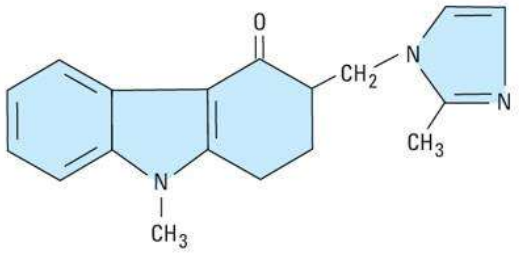
Plus signs indicate some (+) to considerable (++++) interaction. (–) indicates no effect.

# 5-$HT_3$ receptor antagonists

- selective central and **peripheral** blockade
- cancer **chemotherapy associated** & postoperative emesis only
- **ondansetron**, granisetron, dolasetron, tropisetron
  - oral, iv. once daily
- palonosetron
  - iv., longer $t_{1/2}$, ↑ affinity for receptors
- PK: extensive hepatic metabolism
- esophageal or gastric motility is not changed
- primary for prevention of chemotherapy induced emesis
  - iv. or oral
  - **in combination** with other antiemetics
- adverse effects
  - well tolerated – constipation, headache, dizziness
  - QT prolongation – dolasetron

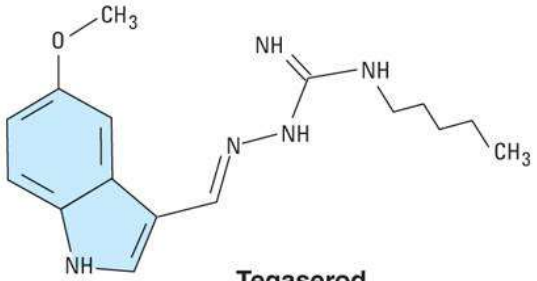



**Serotonin**



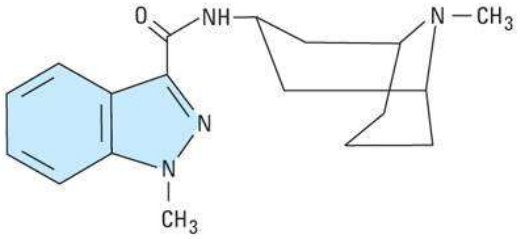

**Ondansetron**

5-$HT_3$ antagonist



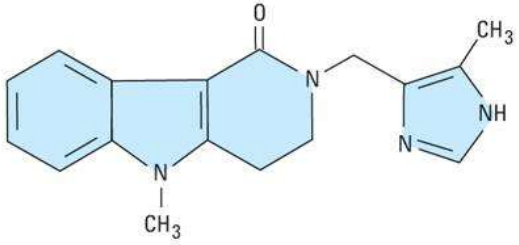

**Tegaserod**

5-$HT_4$ agonist



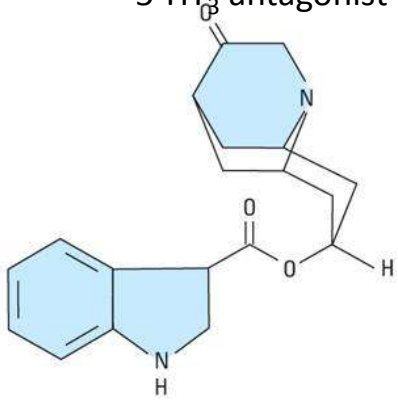

**Granisetron**

5-$HT_3$ antagonist




**Alosetron**

5-$HT_3$ antagonist

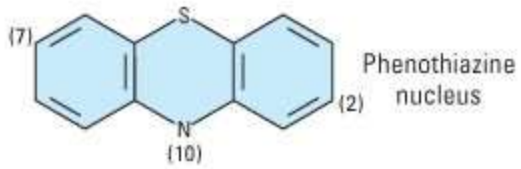


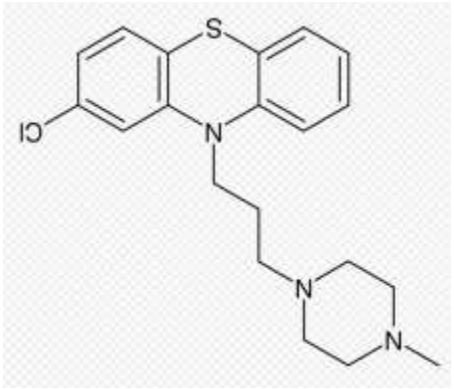

**Dolasetron**

5-$HT_3$ antagonist

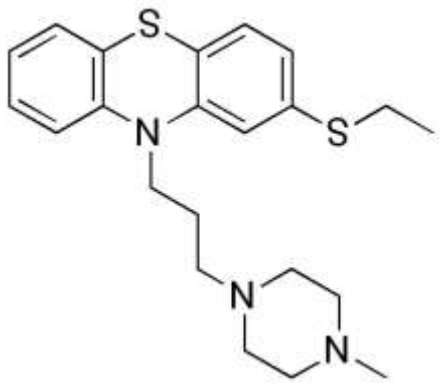
# Dopamine receptor antagonists 1.

- phenothiazines
  - antiemetic: $D_2$ and M antagonist / sedative: $H_1$ blockade

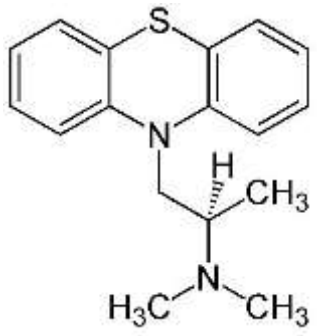



**prochlorperazine**



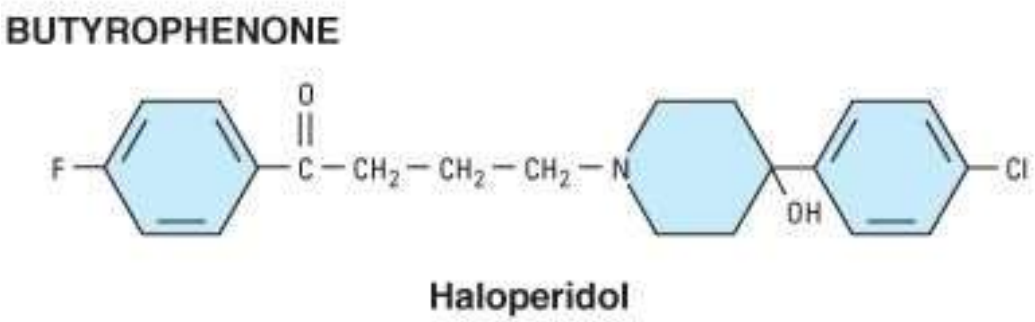

**thiethylperazine**



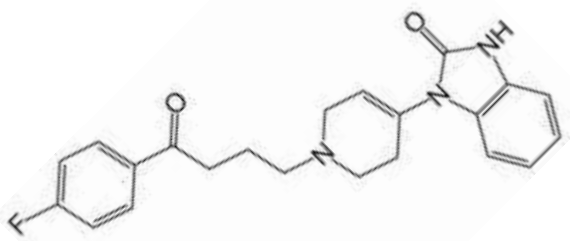

**promethazine**

# Dopamine receptor antagonists 2.

- butyrophenones – **droperidol**, im. / iv.
- other clinical uses
  - sedative
  - postoperative nausea and vomiting
  - neuroleptanalgesia
- adverse effects
  - extrapyramidal effects
  - QT prolongation – arrhythmias



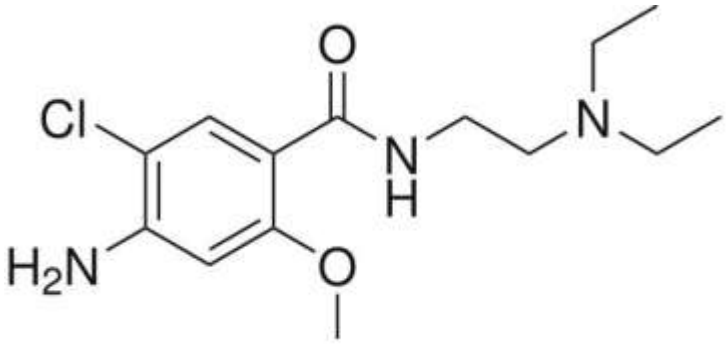

Haloperidol



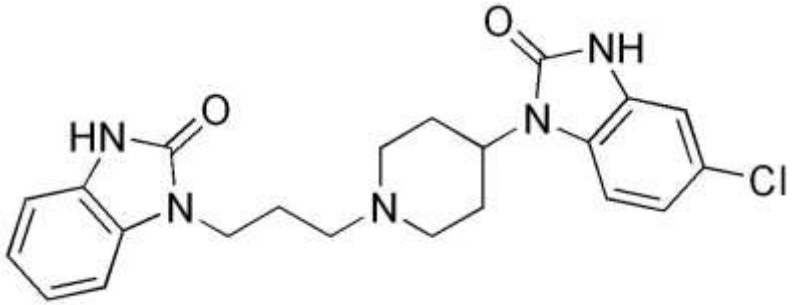

droperidol

# Dopamine receptor antagonists 3.

- **metoclopramide** / trimethobenzamide – extrap. effects
- **domperidone**



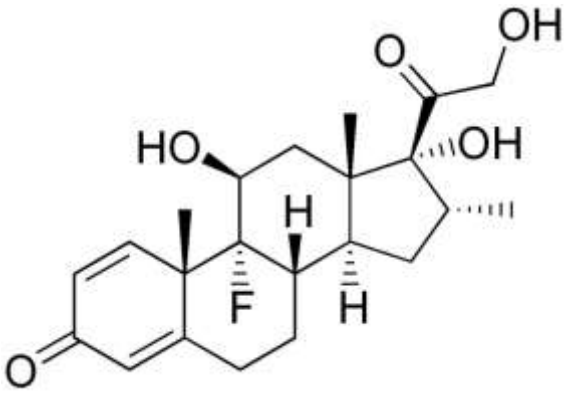

metoclopramide



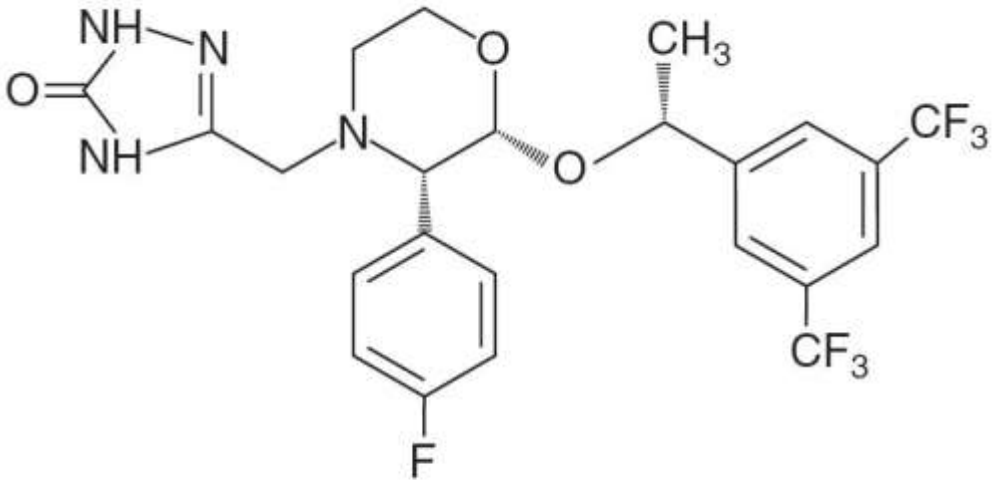

domperidone

# Corticosteroids

- **dexamethasone** / methylprednisolone
- in combination with other anti-emetics



# $NK_1$ receptor antagonist




APREPITANT

- central blockade
- acute and **delayed** chemotherapy induced emesis / oral
- used in combination (aprepitant + “setron” + dexamethasone)
- extensive metabolism – CYP3A4 – reduce dexamethasone dose!

# $H_1$ blockers and anticholinergics

- **diphenhydramine** / **dimenhydrinate** ($H_1$, M)
- meclizine ($H_1$)
- **scopolamine** (M)
- motion sickness – scopolamine patch
- combination
- AEs: dizziness, sedation, confusion, dry mouth, cycloplegia, urinary retention

# Benzodiazepines

- lorazepam, diazepam
  - anticipatory chemotherapy / anxiety caused emesis

# Cannabinoids

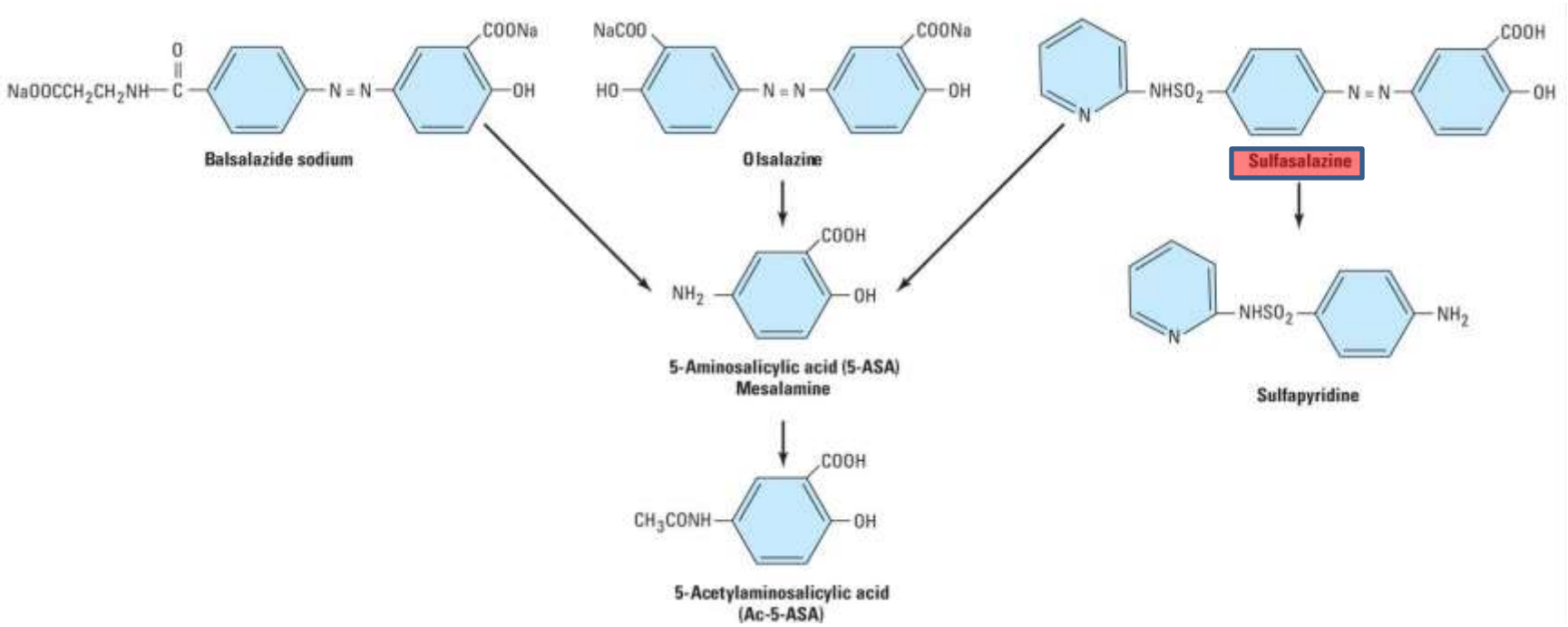
- dronabinol
  - significant first pass metabolism (oral F ≈ 10-20%)
  - appetite stimulant / antiemetic – mechanism $CB_1$ agonist?
  - when other antiemetic medications are not effective
  - central sympathomimetic activity
    - palpitations / tachycardia / “bloodshot eyes”
  - “highs” / paranoid reactions / thinking disturbances
  - **nabilone** is a closely related THC analog

# Inflammatory bowel disease = IBD

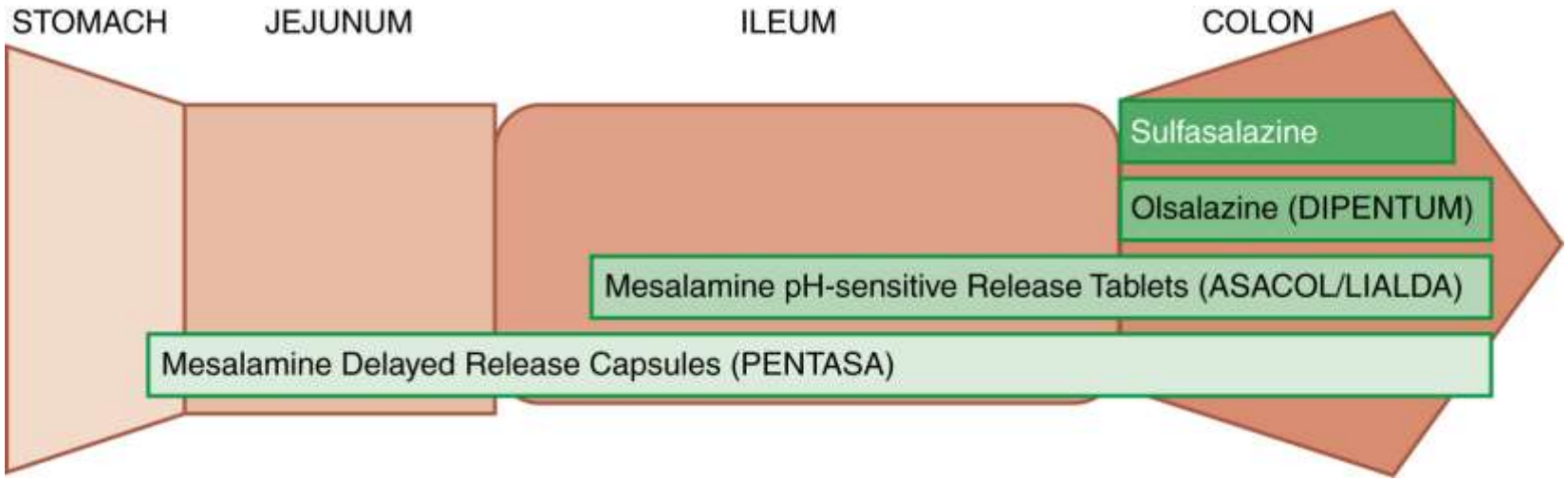
- chronic / idiopathic / inflammatory
- gastrointestinal / extraintestinal
- UC / Crohn's
- purpose of therapy: ↓ generalized inflammatory response
  - control acute exacerbations (induce remission)
  - maintain remission
  - treat complications
- drugs may be different according to purpose
  - induction: e.g. 5-ASA, corticosteroids
  - maintenance: e.g. 5-ASA, immunomodulators
- problems
  - individual differences
  - marked fluctuations in disease activity → assessing drug efficacy ?

# Drugs used for IBD (Crohn's / UC)

- aminosalicylates – 5-ASA (**5-aminosalicylic acid) =** mesalamine
- **sulfasalazine, olsalazine, balsalazide**, and various forms of **mesalamine –** deliver 5-ASA to distal parts - azoreductase



# Release of 5-ASA in the GI tract



# Aminosalicylates (5-ASA)

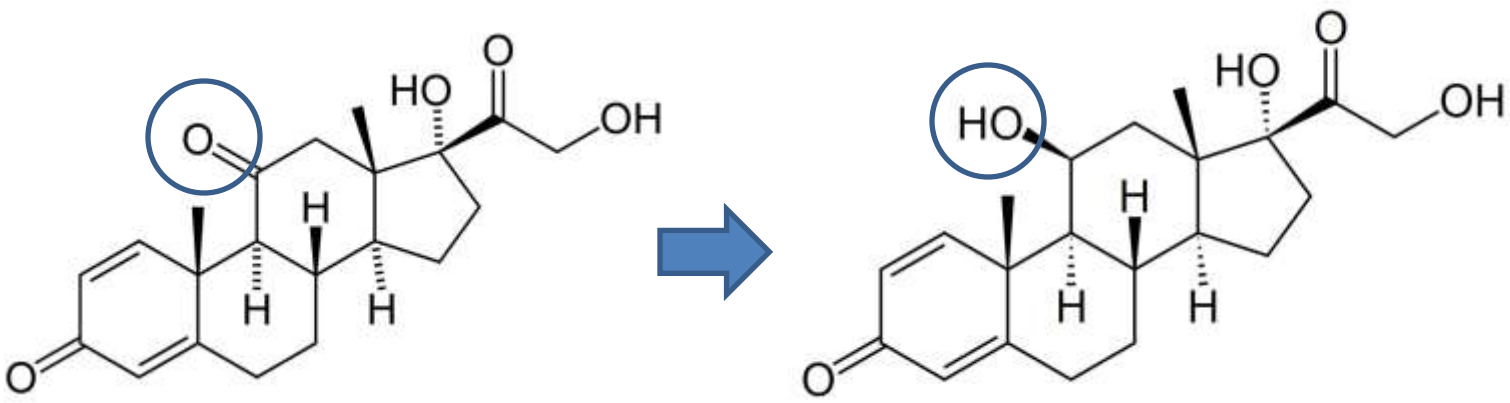
- absorption from colon is low
- mechanism of action ?
  - modulates inflammatory mediators derived from both the cyclooxygenase and lipoxygenase pathways
- indication
  - first-line agents for treatment of **mild to moderate** active **ulcerative colitis** (Crohn's ?)
- AEs (10-45%): due to sulfapyridine
    - **dose related**: headache, fatigue, nausea, GI upset
    - **hypersensitivity**: fever, rash, exfoliative dermatitis, pancreatitis, hepatitis, hemolytic anemia, bone marrow↓

# Other drugs used for IBD (Crohn's / UC)

- glucocorticoids
  - prednisone, prednisolone
- immunosuppressants
  - antimetabolites
    - purine analogs (azathioprine, 6-MP)
    - methotrexate
  - *cyclosporine*
- biological therapies
  - TNF-α antagonists
    - infliximab, adalimumab, certolizumab
  - natalizumab
- antibiotics / probiotics
  - e.g. metronidazole, ciprofloxacin, clarithromycin

# Glucocorticoids

- used in moderate / severe cases
  - responsive / dependent / unresponsive
- **for induction** and not for maintenance of remission
- intermediate duration – once daily
- slow dose tapering
- topical – enema, suppository
  - in selected cases / less effective
  - budesonide – first pass met. – low oral F

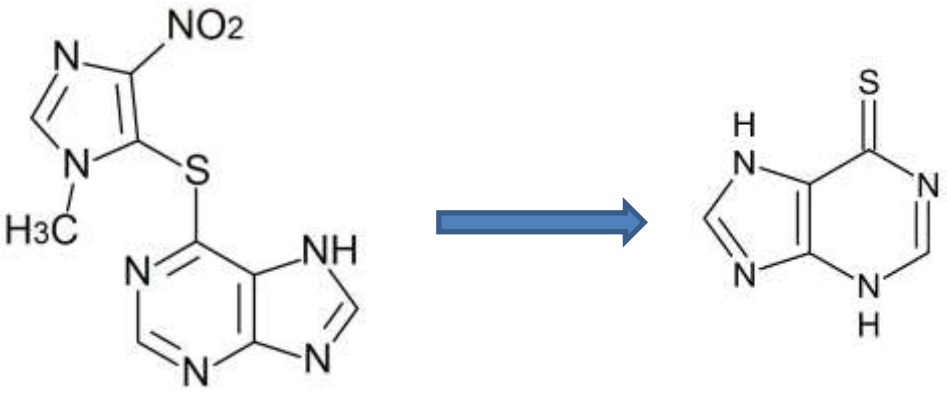



prednisone

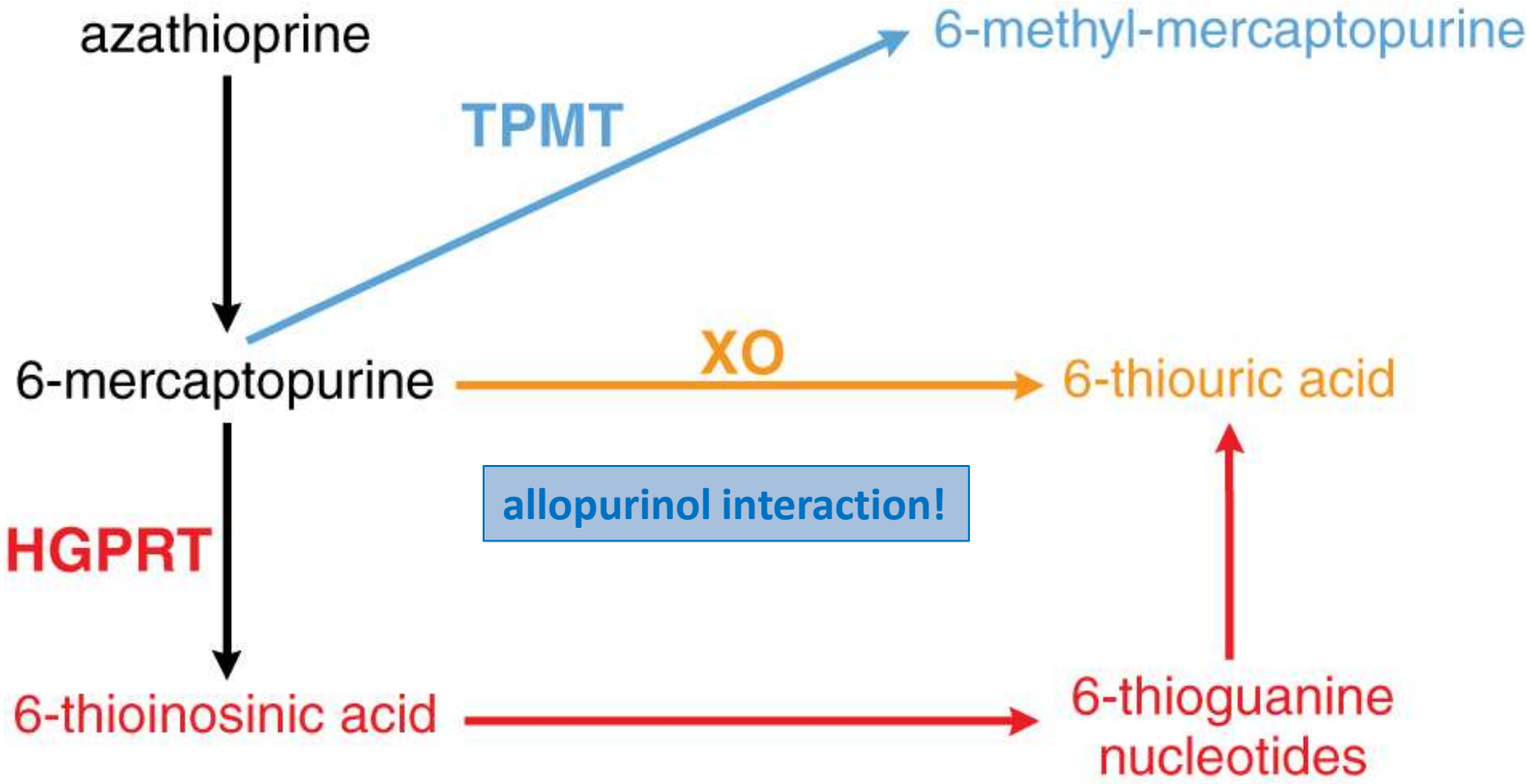
prednisolone

# Purine analogs

- antimetabolite – 6-MP leukemia treatment
- catabolism – xanthine oxidase / thiopurine methyltransferase
- anabolism – thioguanine nucleotides
- in severe / steroid resistant or dependent cases
- delay in the occurrence of effect
- **induction and maintenance** of remission (UC + Crohn's)
- AEs: pancreatitis / nausea, vomiting / bone marrow suppression
- low TPMT levels or allopurinol treatment – decrease dose




azathioprine 6-MP

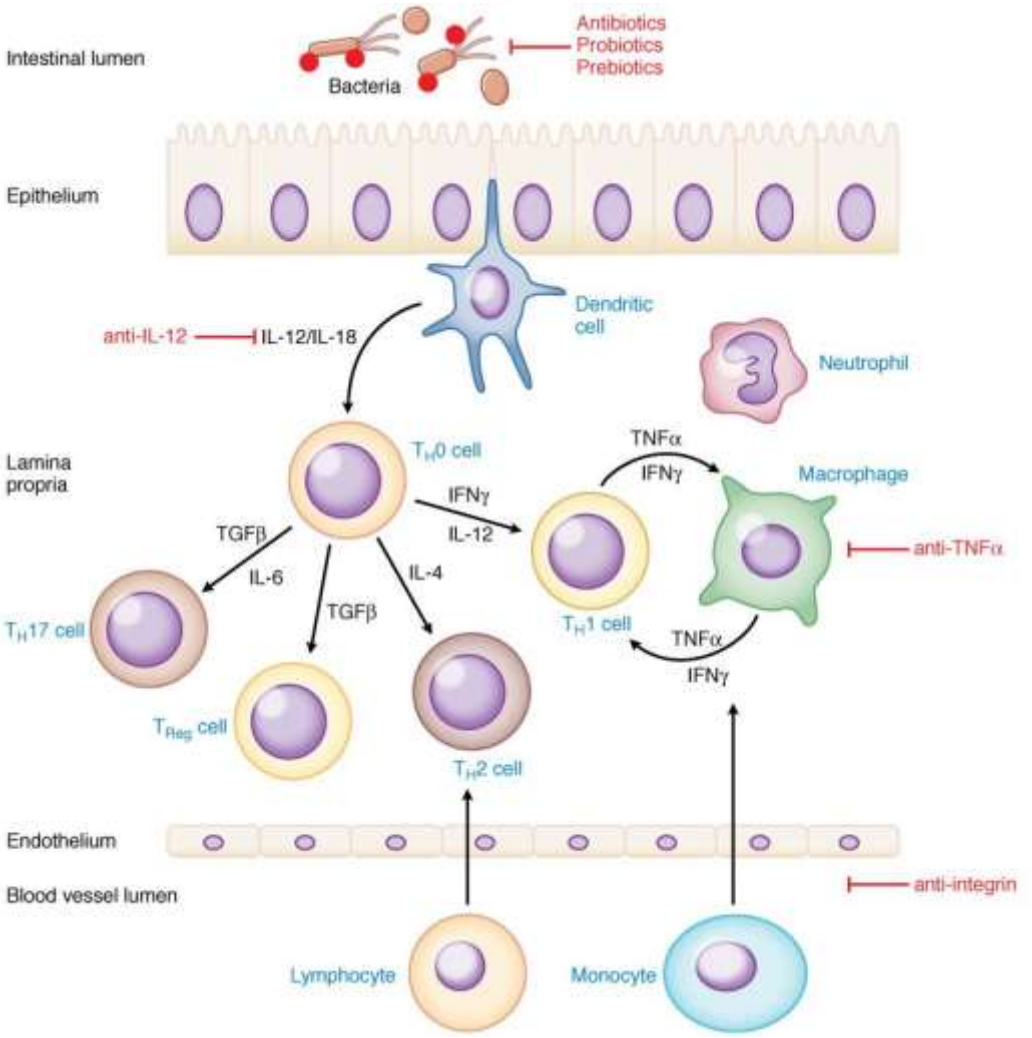



HGPRT: hypoxanthine-guanine phosphoribosyl transferase
XO: xanthine oxidase
TPMT: thiopurine methyltransferase

# Methotrexate

- antimetabolite
- also used in cancer chemotherapy
- oral, sc., im.
- inhibits dihydrofolate reductase
- low dose (15-25 mg / week sc.)
- **Crohn's** disease – **induce and maintain** remission
- rare adverse effects at low doses
    - bone marrow depression
    - megaloblastic anemia
    - alopecia
    - mucositis

# Pathogenesis of IBD




Type I helper T cell response and regulatory T cell ($T_{reg}$) dysregulation (Crohn)

# anti-TNF-α antibodies

| | Infliximab | Adalimumab | Certolizumab |
|---|---|---|---|
| Class | Monoclonal antibody | Monoclonal antibody | Monoclonal antibody |
| % Human | 75% | 100% | 95% |
| Structure | $IgG_1$ | $IgG_1$ | Fab fragment attached to PEG (lacks Fc portion) |
| Route of administration | Intravenous | Subcutaneous | Subcutaneous |
| Half–life | 8–10 days | 10–20 days | 14 days |
| Neutralizes soluble TNF | Yes | Yes | Yes |
| Neutralizes membrane-bound TNF | Yes | Yes | Yes |
| Induces apoptosis of cells expressing membrane-bound TNF | Yes | Yes | No |
| Complement-mediated cytotoxicity of cells expressing membrane–bound TNF | Yes | Yes | No |
| Induction dose | 5 mg/kg at 0, 2, and 6 weeks | 160 mg, 80 mg, and 40 mg at 0, 2, and 4 weeks | 400 mg at 0, 2, and 4 weeks |
| Maintenance dose | 5 mg/kg every 8 weeks | 40 mg every 2 weeks | 400 mg every 4 weeks |

TNF, tumor necrosis factor.

**adverse effects (!)**

infections
antibodies against antibodies
acute infusion reactions
delayed serum sickness like reaction
liver damage
increased risk of lymphomas

# Natalizumab (Tysabri®)

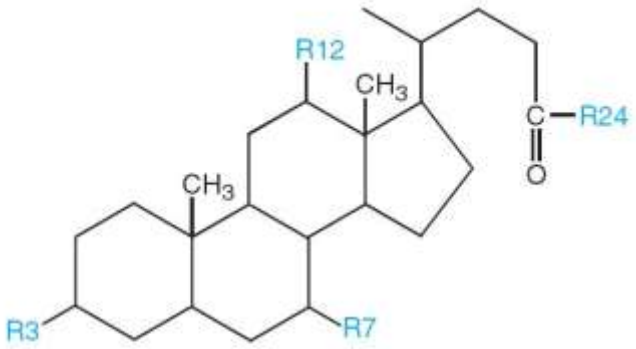
- humanized monoclonal antibody against **α4-integrin**
- indication: **severe Crohn's** disease
  - induction and maintenance of remission
- *risk: progressive multifocal leukoencephalopathy*
  - contraindicated in combination with another immunosuppressive drug
  - only in selected cases
- effective in approx. 50% of patients
  - remission is prolonged in 40% of responders

# Pancreatic enzyme supplements

- indication: exocrine dysfunction (< 10% of normal)
  - causes: CF / chronic pancreatitis / pancreatic resection
  - symptoms: maldigestion → steatorrhea, azotorrhea, vitamin malabsorption, weight ↓
- mixture of amylase, lipase, proteases (extracted from hog pancreas)
  - pancreatin / **pancrealipase** (enriched)
  - non-enteric-coated (acid suppression required) / **enteric-coated**
- administered with each meal and snack
- no significant adverse effects
  - oropharyngeal mucositis (swallow, do not chew)
  - high doses - diarrhea and abdominal pain

# Drugs used for dissolution of gallstones

- **Ursodiol** (ursodeoxycholic acid) / chenodiol (chenodeoxycholic acid)
- less lithogenic bile
  - alter relative concentrations of bile acids
  - decrease biliary lipid secretion
  - reduce the cholesterol content of the bile
- cytoprotective effects on hepatocytes
- used for
  - dissolution of small cholesterol gallstones
  - prevention of gallstones in obese patients undergoing rapid weight loss
  - early-stage **primary biliary cirrhosis**




| Bile Acid | R3 | R7 | R12 | R24 |
|---|---|---|---|---|
| Cholic acid | –OH | –OH | –OH | |
| Chenodeoxycholic acid | –OH | –OH | –H | glycine (75%) |
| Deoxycholic acid | –OH | –H | –OH | taurine (24%) |
| Lithocholic acid | $-SO_3^-$ / –OH | –H | –H | –OH (<1%) |
| Ursodeoxycholic acid | –OH | –OH | –H | |