Osteoporosis and treatment, laxatives, drugs of cholinergic transmission
Osteoporosis and treatment

Osteoporosis
1. disease of bones
2. leads to an increased risk of fracture
3. the bone mineral density (BMD) is reduced, bone microarchitecture is deteriorating, and the amount and variety of proteins in bone is altered
4. manifests mass loss and changes and structure

Type I: postmenopausal osteoporosis
- decline in production of calcitonin and sensitization of osteoclast on parathyrin - especially post-menopausal women, due to decreased production of estrogen

Type II osteoporosis: senile osteoporosis
- the cause is lack of vitamin D intake
- senile form affects men and women in old age
- occurs after age 75 and is seen in both females and males at a ratio of 2:1.
- may arise at any age and affects men and women equally
therapy and prophylaxis of osteoporosis:

- calcium
- vit. D (in drug form, fish oil)
- estrogens – in postmenopausal women
- calcitonin
- raloxifene (EVISTA) – SERM
- bisphosphonates

- vit. D3 - cholecalciferol is metabolized in the body to calcitriol
- calcitriol is an body own active form of vit. D3
- calcitriol increases the plasma concentration of calcium ions by promoting their absorption from the gastrointestinal absorption and reabsorption in the renal tubules
Bisphosphonates

- strongly inhibit the activity of osteoclasts
- derivates of medronic acid (which itself is ineffective)
- first in the 80-ty years - etidronic and clodronic acid

It was found that monosubstituted derivatives have weaker activity than disubstituted derivatives, so in the therapy are now only tiludronic and incadronic acid.
Bisphosphonates SAR:

Most used are potent disubstituted derivates with basic (alkaline) substituent:

- **Pamidronic acid**
- **Alendronic acid**
- **Risedronic acid**
- **Zoledronic acid**
- **Ibandronic acid**
Laxatives
Laxatives are used in the treatment of constipation

• Constipation is a common cause of painful defecation. Severe constipation includes obstipation (failure to pass stools or gas) and fecal impaction.

• Constipation is common; in the general population incidence of constipation varies from 2 to 30%.

• Constipation is usually easier to prevent than to treat. Following the relief of constipation, maintenance with adequate exercise, fluid intake, and high fiber diet is recommended.

• The main treatment of constipation involves the increased intake of water, and fiber (either dietary or as supplements). The routine use of laxatives is discouraged, as having bowel movements may come to be dependent upon their use. Enemas can be used to provide a form of mechanical stimulation. However, enemas are generally useful only for stool in the rectum, not in the intestinal tract.

• Many medications have constipation as a side effect. Some include (but are not limited to); opioids (e.g. common pain killers), diuretics, antidepressants, antihistamines, antispasmodics, anticonvulsants, and aluminum antacids.
Laxatives

Softeners, emollients
• Liquid paraffin

Contact laxatives
• Bisacodyl
• Castor oil
• Senna glycosides
• Sodium picosulfate

Bulk producers
• Ispaghula (psylla seeds)
• Ethulose
• Sterculia
• Linseed
• Methylcellulose
• Triticum (wheat fibre)

Osmotically acting laxatives
• Magnesium sulfate
• Lactulose
• Lactitol
• Sodium sulfate
• Mannitol
• Sorbitol
• Magnesium citrate
• Sodium tartrate
• Glycerol

Enemas
• glycerol
• sorbitol
• docusate sodium

Peripheral opioid receptor antagonists
• Methylnaltrexone bromide
• Alvimopan
Aliphatic hydrocarbons

- Medicinal **liquid paraffin** is a very highly refined mineral white oil

- **Use:**
  - as liquid paraffin oral emulsion
    - is as an occasional laxative
    - is unsuitable for regular use as it can seep from the anus and cause irritation
    - it can interfere with the absorption of fat-soluble vitamins
    - can be use in the case of accidental poisoning (if a poison has lipophilic character)
Salts of anorganic and organic acids

• Osmotically acting laxatives
  – Magnesium sulfate
  – Sodium sulfate
  – Magnesium citrate
  – Sodium tartrate
Multifunctional alcohols and carbohydrates

- Osmotically acting laxatives
  - lactulose
  - sorbitol
  - glycerol
Natural substances

**Bulk producers**
- Ispaghula (psylla seeds) = psyllium
- Ethulose
- Linseed
- Methylcellulose
- Triticum (wheat fibre)

**Contact laxatives**
- Senna glycosides (pharmacognosy)
  - rhein
- Castor oil
  - main part
    - ricinoleic acid

SAR – rhein and its derivates:
Hydroxyl group on C1 and C8 / on C8

[Chemical structures of rhein and ricinoleic acid]
Synthetic drugs

• di-phenyl-methane derivates
  – bisacodyl
  – sodium picosulfate

• SAR:
  – bis-(4-hydroxyphenyl)methane part bounded to aromatic skeleton (e.g. benzene/pyridine/heterocycle)
    • bounded directly or through polar part: -COO-, -NH-CO-
  – phenol groups can be:
    • free or
    • blocked by: ester group / acetic acid / sulfuric acid
**Synthetic drugs**

- laxatives of another structure
  - docusate sodium
    - use:

  Usually given rectally as an enema, when the colon must be free for diagnosis or surgery intervention.

**Lubiprostone**

Lubiprostone is used for the treatment of chronic constipation of unknown cause and irritable bowel syndrome associated with constipation. Lubiprostone specifically activate CIC-2 chloride channels on the apical aspect of gastrointestinal epithelial cells, producing a chloride-rich fluid secretion. These secretions soften the stool, increase motility, and promote spontaneous bowel movements.
Synthetic drugs

**Alvimopan**

Alvimopan is indicated in patients to avoid postoperative ileus following partial large or small bowel resection with primary anastomosis.

**Mechanism of action**

Alvimopan competitively binds to opioid receptor as antagonist in the gastrointestinal tract.
Synthetic drugs

**Methylnaltrexone**
- is approved for the treatment of Opioid Induced Constipation. It is generally only to be used when ordinary laxatives have failed. Because of its mechanism of action, it will not have any effect on constipation that is not OIC.

**Mechanism of action**
- Methylnaltrexone binds to the same receptors as opioid analgesics such as morphine, but it acts as an antagonist, blocking the effects of those analgesics, specifically the constipating effects on the gastrointestinal tract. Furthermore, as methylnaltrexone cannot cross the blood-brain barrier, it does not reverse the pain-killing properties of opioid agonists or cause withdrawal symptoms.
- Methylnaltrexone is unable to enter the brain primarily because it carries a positive charge on its nitrogen atom.
Drugs of cholinergic transmission

• These drugs influence the parasympathetic nervous system (PSNS), which is part of the autonomic nervous system.

• The parasympathetic system is responsible for stimulation of "rest-and-digest" activities that occur when the body is at rest, including sexual arousal, salivation, lacrimation (tears), urination, digestion, and defecation.

• These drugs bind to the cholinergic (muscarine) receptor.
• Acetylcholine is an agonist on these receptors. ACH is degraded by enzyme acetylcholinesterase (acetylcholine acetylhydrolase).

• There are five main types of muscarinic receptors: M1, M2, M3, M4, M5.
A - Cholinergic agonists
(parasympathomimetic drug)

A – 1 Direct-acting

• A-1-1 Plant alkaloids

use of cholinergic drugs:

e.g. Glaucoma, Myasthenia gravis, Atony (occurs postoperatively)
A-1-2 Acetylcholine and its analogue (Choline esters)

• 1. molecule must possess a nitrogen atom capable of bearing a positive charge, preferably a quaternary ammonium salt.
• 2. for maximum potency, the size of the alkyl groups substituted on the Nitrogen should not exceed the size of a methyl group.
• 3. The molecule should have an oxygen atom, preferably an ester-like oxygen capable of participating in a hydrogen bond.
• 4. There should be a two-carbon unit between the oxygen atom and the nitrogen atom.
• 5. Esters of carbamic acid are more metabolically stable.
A-2 Indirect-acting

A-2-1 Carbamates (Reversible cholinesterase inhibitors)

- SAR: phenyl-carbamate fragment substituted with basic (amonium) group
  - Physostigmine, Pyridostigmine, Neostigmine, Rivastigmine

A-2-2 Amonium derivates (Reversible cholinesterase inhibitors)

- ambenonium chlorid

(+)-Physostigmine

Pyridostigmine

Neostigmine

Rivastigmine
A-2-3 Organophosphates (Irreversible cholinesterase inhibitors)

- Malathion, Paraoxon

- A-3 antidote (reactivators of acetylcholinesterase)
  - used in the treatment of organophosphate poisoning

Pralidoxime

Trimedoxime
B - Cholinergic antagonists (anticholinergic drugs)

• Anticholinergic drugs are used in treating a variety of conditions:
  – Gastrointestinal disorders (e.g., gastritis, pylorospasm, diverticulitis, ulcerative colitis)
  – Genitourinary disorders (e.g., cystitis, urethritis, prostatitis)
  – Respiratory disorders (e.g., asthma, chronic bronchitis)
  – Sinus bradycardia - Hypersensitive vagus nerve
B-1 Natural drugs and their derivates

- Atropine
- Scopolamine
- Homatropine
B-2 Synthetic drugs

• B-2-1 tertiary amines

- fesoterodine
- oxybutinin
- solifenacin
- tolderodine
- propiverine
- darifenacin

Cyclopentolate  Tropicamide
B-2-2 Quaternary ammonium drugs

fenpiverinium bromide
Structure Activity relationship

• synthetic drugs - tertiary amines
  – aromatic part
  – linker
  – tertiary amine

• quaternary ammonium drugs
  – quaternary nitrogen on the tropane ring
    • lower lipophilicity, lower transfer to CNS, to the eye
    • with antispasmodic activity is connected antisecretic, anti-bronchospasm effect