Drugs used in calcium & vitamin D disorders

Objectives:

- **Recognize** the common drugs used in calcium & vitamin D disorders.
- **Classify** them according to sources & Pharmacological effects.
- **Detail** the pharmacology of each drug , regarding , Mechanism, clinical utility in affecting calcium & vitamin D

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Drug's name | Doctors' notes | Important | Extra

« لو أن الناس كلما استصعبوا أمرًا تركوه؛ ما قام للناس دنيا ولا دين! »
عمر بن عبدالعزيز

Mind Map

Calcium Hemostasis

PTH

Also synthetic form is Triparatide

- Continuous exposure of PTH which **increase bone resorption**
- Daily intermittent (متقطعه) S.C administration in the thigh of PTH which **increase bone formation**

Calcitonin

From parafollicular cells of thyroid

Used in **Paget's disease**:
disease of bone disrupts the normal cycle of bone renewal, causing bones to become weakened and possibly deformed.

Vitamin D

2 forms:
D2 from diet
D3 from sunshine

Increase plasma Ca^{2+} concentrations by:

- increases bone resorption
- increases Ca^{2+} absorption from the intestine
- increases renal Ca^{2+} reabsorption
- decreases the production of PTH by the parathyroid glands.

Calcium hemostasis

Tissues that regulate Ca^{2+} hemostasis:

Bone	Kidney	Intestine
Resorption of Ca^{2+}	Excretion of Ca^{2+}	Absorption of Ca^{2+}

Calcium

Calcium plays an essential role in many cellular processes, including muscle contraction, hormone secretion, cell proliferation, and gene expression.

Bone

- Is a dynamic organ undergoes continuous remodeling process involving resorption of old bone by osteoclast & formation of new bone by osteoblast.
- The **dominant site of calcium storage** in the body is bone, which contains nearly **99.9%** of body calcium.
- Only a **small amount** of total calcium is found in plasma & it's **regulated** by PTH & VIT D

Factors regulate Ca^{2+} metabolism & Bone remodeling

- **PTH (PARA THYROID HORMONE)** — Also has a synthetic form teriparatide (PTH analoge)
- **Vitamin D**
- **Calcitonin** — Its an antagonist for PTH

PTH and vit. D play a central role in the regulation of bone metabolism

PTH

Parathyroid hormone (PTH)

Characteristic

- It is released from the parathyroid gland and it plays an essential role in controlling of Ca^{++} & Po^{4-}, It is secreted in response of low plasma Ca^{++} level to increase plasma Ca^{2+} levels by:"
- **PTH** enhances intestinal Ca^{2+} absorption in the presence of permissive amounts of vitamin D.
  1. **PTH** stimulate bone resorption by stimulating osteoclast cell (in bone) to increase outward flux of Ca^{2+} to restore serum Ca level.
  2. **PTH** stimulates the **active** reabsorption of Ca^{2+} from the kidney.
- Secretion of PTH is **inversely** related to Ca^{2+}.

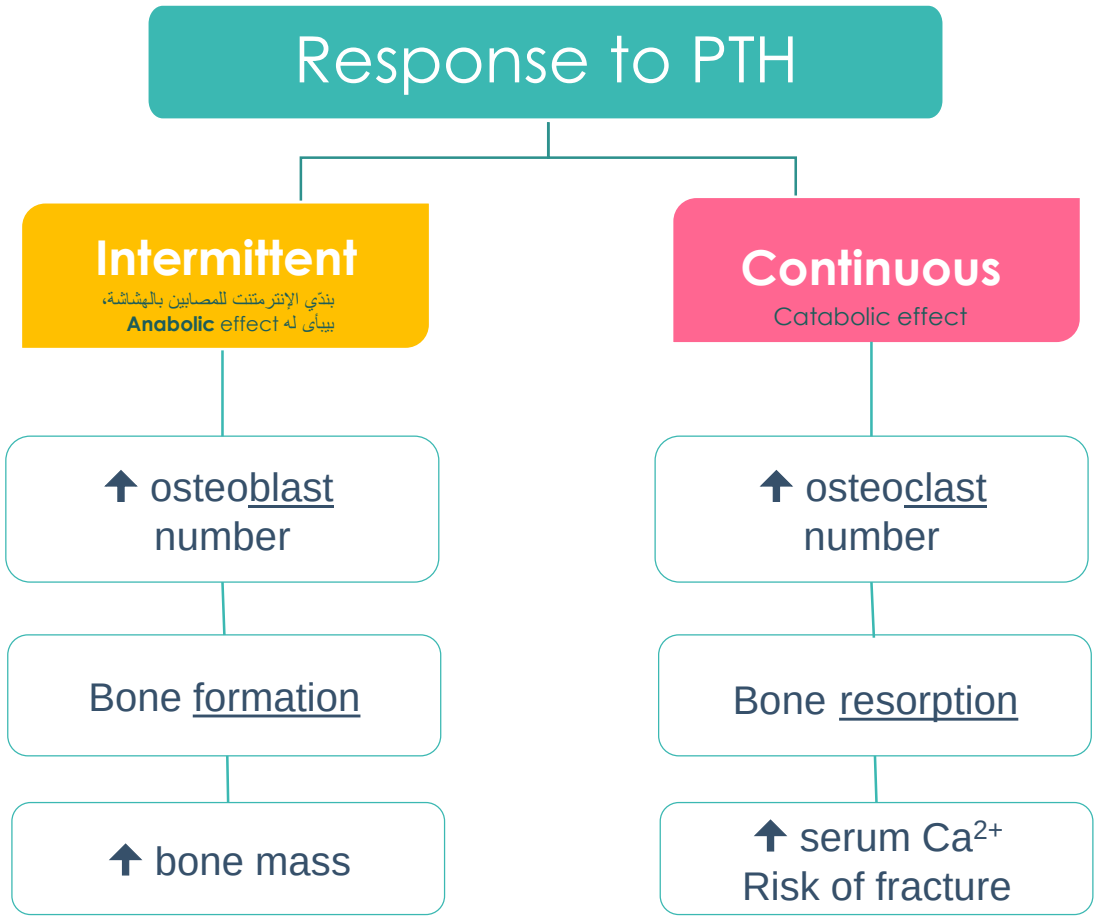
uses

- Treatment of **severe** osteoporosis. (not 1st line treatment)
- **Resistance** cases failed to response to other medications.

Body response

❖ **Response to PTH:** أهم شيء في الباراث: ينعطى intermittent ، وينعطى S.C وهو Anabolic

1. **Daily intermittent** (متقطع) **subcutaneous** administration in the **thigh** (alternate thigh every day) of recombinant human PTH leads to a net **stimulation of bone formation**. المعلومة دي مهمة يا بنات وبأكد عليها! Has an **anabolic** effect
2. **Continuous (chronic) exposure** exposure to **high serum PTH** concentrations (as seen with primary or secondary hyperparathyroidism) results in **bone resorption**.

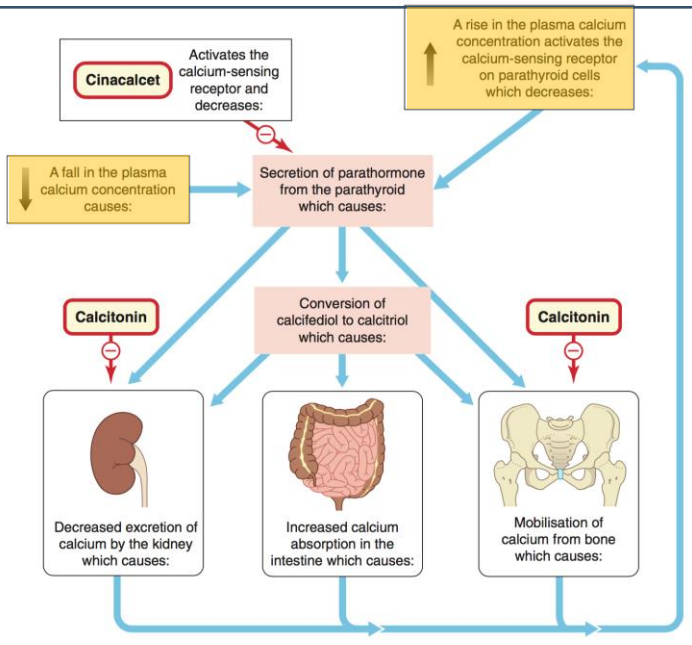


Teriparatide

(PTH analogue)

characteristic	○ Synthetic polypeptide form of PTH. بيبقى كل المعلومات اللي عرفناها في الباراث موقودة في دا الدواء ○ It belongs to a class of **anti-osteoporosis** drugs, the so-called "anabolic" agents.
Uses	○ Good for **postmenopausal** osteoporosis. ○ For treatment of osteoporosis in people have a risk of **getting fracture** → Bc it has anabolic effect. ○ Treatment of **severe osteoporosis**. ○ **Resistance** cases failed to response to other medications.
ROA	○ Once daily **subcutaneous injection** (like PTH)
Body response	❖ **Therapeutic effects of teriparatidedepend upon the pattern of systemic exposure:** زي ما قلنا في الباراث 1. **Once-daily** administration of teriparatide stimulates **new bone formation** by preferential stimulation of osteoblastic activity **over** osteoclastic activity. 2. **Continuous administration** of teriparatide, may be detrimental to the skeleton because bone resorption may be stimulated more than bone formation.
ADRs	○ **Carcinogenic effect** (**osteosarcoma**) → should not be used routinely → the most dangerous side effect. ○ Diarrhea - heart burn – nausea – headache – leg cramps. ○ **Postural hypotension** (orthostatic hypotension) → instruct patient to rise slowly from a sitting/supine position while taking this drug. ○ **Kidney stones** because of elevated serum calcium.
C.I	❖ Should not be used by people with increased risk for **osteosarcoma** (bc of increased osteoclast activity) **including:** • People with **paget's disease** of bone • People who had **radiation treatment involving bones**. • **Children are** not recommended.

Calcitonin is a physiological **antagonist** to PTH with regard to Ca^{2+} homeostasis



Calcitonin

About Calcitonin

- Calcitonin is synthesized and secreted by the parafollicular cells (C cells) of the thyroid gland. It is released when there is a **rise in plasma Ca^{2+} levels**
- While PTH and vitamin D act to increase plasma Ca^{2+}, only calcitonin causes a **decrease in plasma Ca^{2+}**.
- Calcitonin does not appear to be critical for the regulation of calcium homeostasis even if thyroid gland is removed.

Effects of Calcitonin

- Calcitonin protects against development of hypercalcemia caused by a variety of conditions, including **increased calcium absorption** (milk-alkali syndrome) and **decreased calcium excretion** (**thiazide** use).
- The major effect of calcitonin administration is a **rapid fall in Ca^{2+}** caused by:
  - **Bone**: Decrease bone resorption by inhibiting osteoclast activity. (The osteoclast bone cells appear to be a particular target of calcitonin) → **doesn't have anabolic effect**, doesn't favor new bone formation (osteoblast).
  - **Kidney**: Decreases reabsorption of **Ca^{2+} & PO_4** , thus **increasing their excretion**. → drop of plasma Ca^{2+} level

Clinical uses

- Used clinically in treatment of **hypercalcemia** and in certain bone diseases in which sustained reduction of osteoclastic resorption is therapeutically advantageous:
  - **Osteoporosis** (major indication; **alternative to other drugs**).
  - **Hypercalcemia** مهمة أوي (**short-term** "rapid effect" treatment of hypercalcemia of malignancy) e.g. milk-alkali syndrome. It targets osteoclastic activity.
  - **Paget's disease**.
- It has **lower efficacy** compared to other drugs.

Routes of administration

- **S.C., Nasal spray or solution** (**Calcitonin Salmon "Miacalcin"** المستحضر المستخدم) has more affinity towards human calcitonin receptors.

ADRs

- Nausea.
- local inflammation (at the site of injection, if given S.C).
- Flushing of face & hands.
- Nasal irritation.

Vit.D

- Vitamin D is a steroid hormone that is intimately involved in the regulation of plasma calcium levels.
- Its role in calcium metabolism first was recognized in the childhood disease rickets, which is characterized by hypocalcemia and various skeletal abnormalities.

Forms of Vitamin D:

Cholecalciferol (vitamin D3) → skin	Is usually for vitamin D- fortified milk & foods & also available in drug combination products.
Ergocalciferol (vitamin D2) → plants	Is the prescription form of vitamin D & is also used as food additive (milk).

Both forms have equal biological activities

Sources of Vitamin D

D2	D3
Diet as in: - Milk. - Egg yolk. - Fish oils	**Sunshine**: Cholecalciferol (D3) → Generated in the skin from 7-dehydrocholesterol by the action of ultraviolet radiation (sunshine).

❖ Note both D2 and D3 travel to the **liver** and then converted to active from in the kidneys.

Vitamin D Metabolism

- In the **liver**: Transformation of D3 to **Calcifediol** the main storage from of Vit. D in our body (25-hydroxycholecalciferol),(the **inactive** form).
- In the **kidney**: parathyroid hormone stimulates the formation of **active form** of vitamin D calcitriol (1,25-dihydoxycholecalciferol) by **1alpha-hydroxylase**.

Vit.D (cont.)

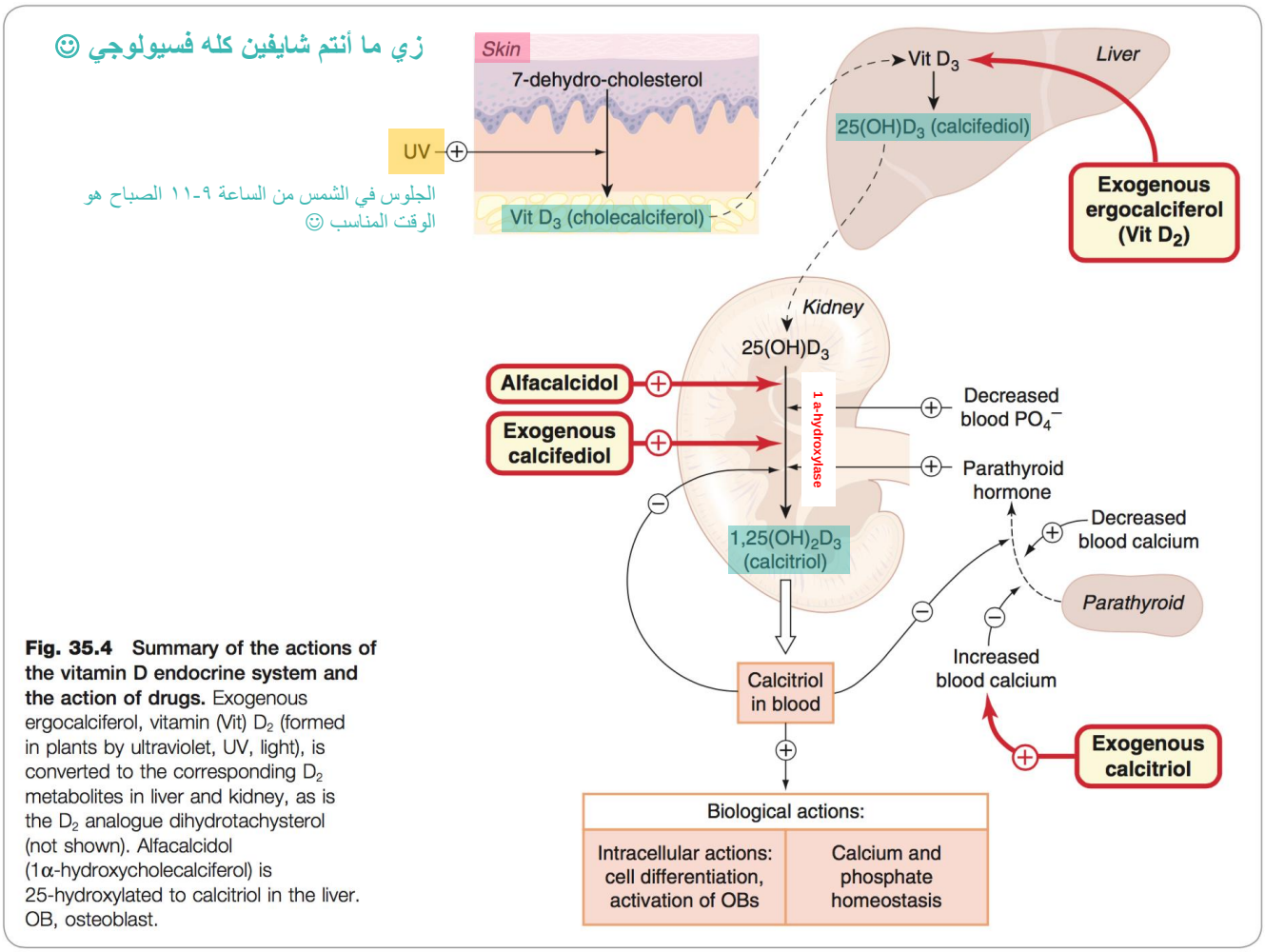


Fig. 35.4 Summary of the actions of the vitamin D endocrine system and the action of drugs. Exogenous ergocalciferol, vitamin (Vit) D_2 (formed in plants by ultraviolet, UV, light), is converted to the corresponding D_2 metabolites in liver and kidney, as is the D_2 analogue dihydrotachysterol (not shown). Alfacalcidol (1α-hydroxycholecalciferol) is 25-hydroxylated to calcitriol in the liver. OB, osteoblast.

Effects of Vitamin D

❖ **Increase plasma Ca^{2+} concentrations by:**
- Increases bone resorption.
- Increases Ca^{2+} absorption from the intestine.
- Increases renal Ca^{2+} reabsorption.
- **Decreases the production of PTH by the parathyroid glands**.

- The overall effect of vitamin D is to **increase plasma Ca^{2+}** concentrations.

↓ of vit.D leads to:	Therapeutic uses of vitamin D:
- Rickets in small children. - Osteomalacia. - Osteoporosis.	- **Rickets & Osteomalacia** - Osteoporosis - **Psoriasis** الصدفية cholecalciferol بيعطوه - **Cancer prevention** (prostate & colorectal)

- Remember that:

- **1,25-dihydroxyvitamin D (calcitriol)** is The **most active** form of vitamin D.
- 25-hydroxyvitamin D (calcidiol, 25-hydroxycholecalciferol): an **inactive** form of vitamin D.
- **1alpha-hydroxylase**: The enzyme that converts the inactive form of Vit.D.

Summary

Drug	Parathyroid hormone PTH		
about	-Released by parathyroid gland. -Low plasma Ca^{++} . -Section is inversely related to Ca^{++} .		
Effect	- Intermittent ↑ osteoblast number & function →↑ bone formation →↑ bone mass & strength. - Continuous: ↑osteoclast →bone resorption→↑ serum Ca^{++} .		
Uses	- Treatment of sever osteoporosis not first choice. - Resistant cases failed to respond to other medications. - Route of Administration is S.C in thigh as daily dose		
Drug	**Teriparatide**	**Vitamin D**	**Calcitonin**
characteristic	-PTH analogue. -Anti-osteoporosis drugs. -Give once daily by subcutaneous injection.	-Vitamin D is a steroid hormone that is intimately involved in the regulation of plasma Ca^{++} levels. -In biological activities Vit D2=Vit D3.	-Synthesized by Para follicular cells of thyroid gland. - ↓in plasma Ca^{++}. -It has lower efficacy compared to other drugs
ROA	S.C	-	S.C, Nasal spray, solution
Effects	-Once daily: Stimulation of osteoblast over osteoclast activity → New bone formation. -Continues bone resorption stimulated more then bone formation → Detrimental to the skeleton.	-↑Bone resorption -↑Ca^{++} absorption from intestine, ↑renal Ca^{++} reabsorption &↓ production of PTH. -All lead to ↑ plasma Ca^{++} concentration.	- Inhibiting osteoclast activity → inhibiting bone resorption - ↓ reabsorption of Ca^{++} & PO_4 by kidney →↑ excretion
Indications	-Postmenopausal osteoporosis. -Patients how have risk to get fracture. -Patients not responding to other drugs.	-Rickets. -Osteomalacia. -Osteoporosis. -Psoriasis. -Cancer prevention for prostate & colorectal.	-Hypercalcemia in case of short term treatment of hypercalcemia of malignancy, Paget's disease -Osteoprosis as alternative to other drugs
ADRs	-Carcinogenic effect (osteosarcoma). -Diarrhea, heart burn, nausea. -Headache, leg cramps, orthostatic hypotension. -↑ serum Ca ++ which may → kidney stones.	-	-Nausea, nasal irritation -Local inflammation at sit flushing of face & hand
C.I	-People how have risk for osteosarcoma like: Paget's disease & radiation treatment involving bone. - Not recommended for children	-	-

SUMMARY Major Drugs Used in Diseases of Bone Mineral Homeostasis

Subclass	Mechanism of Action	Effects	Clinical Applications	Toxicities
VITAMIN D, METABOLITES, ANALOGS				
• Cholecalciferol • Ergocalciferol • Calcitriol • Doxercalciferol • Paricalcitol • Calcipotriene	Regulate gene transcription via the vitamin D receptor	Stimulate intestinal calcium absorption, bone resorption, renal calcium and phosphate reabsorption • decrease parathyroid hormone (PTH) • promote innate immunity • inhibit adaptive immunity	Osteoporosis, osteomalacia, renal failure, malabsorption, psoriasis	Hypercalcemia, hypercalciuria • the vitamin D preparations have much longer half-life than the metabolites and analogs
BISPHOSPHONATES				
• Alendronate • Risedronate • Ibandronate • Pamidronate • Zoledronate	Suppress the activity of osteoclasts in part via inhibition of farnesyl pyrophosphate synthesis	Inhibit bone resorption and secondarily bone formation	Osteoporosis, bone metastases, hypercalcemia	Adynamic bone, possible renal failure, rare osteonecrosis of the jaw, rare subtrochanteric (femur) fractures
HORMONES				
• Teriparatide • Calcitonin	These hormones act via their cognate G protein-coupled receptors	Teriparatide stimulates bone turnover • calcitonin suppresses bone resorption	Both are used in osteoporosis • calcitonin is used for hypercalcemia	Teriparatide may cause hypercalcemia and hypercalciuria
SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMs)				
• Raloxifene	Interacts selectively with estrogen receptors	Inhibits bone resorption without stimulating breast or endometrial hyperplasia	Osteoporosis	Does not prevent hot flashes • increased risk of venous thromboembolism
RANK LIGAND (RANKL) INHIBITOR				
• Denosumab	Monoclonal antibody • binds to RANKL and prevents it from stimulating osteoclast differentiation and function	Blocks bone resorption	Osteoporosis	May increase risk of infections
CALCIUM RECEPTOR AGONIST				
• Cinacalcet	Activates the calcium-sensing receptor	Inhibits PTH secretion	Hyperparathyroidism	Nausea
MINERALS				
• Calcium • Phosphate • Strontium	Multiple physiologic actions through regulation of multiple enzymatic pathways	Strontium suppresses bone resorption and increases bone formation • calcium and phosphate required for bone mineralization	Osteoporosis • osteomalacia • deficiencies in calcium or phosphate	Ectopic calcification

MCQs

1- Which of these two method I better than other in case of PTH?
A- Intermittent
B- Continuous

2- The most serious side affect of teriparatide is?
A- Osteosarcoma
B- Hypotension
C- Diarrhea
D- Headache

3- PTH is released in response of?
A- High serum ca^{2+} level
B- Increased bone mass
C- Low serum Ca^{2+} level

4- The effect of vitamin D ?
A- Decrease bone resorption
B- Decrease Ca^{2+} absorption from the intestine
C- Decrease renal Ca^{2+} reabsorption
D- Decreases the production of PTH by the parathyroid glands

5- Where is the transformation of vit.D3 to Calcifediol happened?
A- Liver
B- Kidney
C- Lung
D- Thyroid gland

6- Bone resorption is accelerated by:
A- Estrogens
B- Parathyroid hormone
C- Bisphosphonates
D- Calcitonin

7- The primary action of parathormone is:
A- To increase intestinal calcium absorption
B- To increase calcium reabsorption in kidney tubules
C- To promote calcium deposition in extraosseus tissues
D- To increase resorption of calcium from bone

8- Which drug is contraindicated in patient with Paget's disease?
A- Calcitonin
B- Toradol
C- Teriparatide
D- Vit.D

Answers: 1-A 2-A 3-C 4-D 5-A 6-B 7-D 8-C

Thank you for checking our team!

Pharmacology 435

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Sources:

1. 435's slides.
2. Pharmacology (Lippincotts Illustrated Reviews Series), chapter 29, 5th edition.
3. Basic & Clinical Pharmacology by Katzung, chapter 42,12th edition.
4. Rang & Dale's pharmacology, chapter 35, 7th edition.