Drug & Indications	MOA	Pharmacokinetics	ADRs & Contraindications	Dosing
1-BISPHOSPHONATES : **Alendronate ➔ 500** **Alendronate ➔ 500** **Risedronate ➔2000** **Zoledronate ➔10000** • **Osteoporosis, secondary to menopause,glucocorticoids, …. etc** • **Paget's Disease** • **Malignancy- associated hypercalcaemia (Malignancy when metastasize to bone)**	-Are structurally similar to pyrophosphate (which is essential for a lot of enzyme functions), thereby inhibiting activation of these enzymes that utilize it. -They are concentrated in bones, bound **to hydroxapatite**.They lead: **1) decrease in osteoclastic** formation/activation **2) increase in osteoclastic** apoptosis (programmed cell death). **3) inhibition of the** cholesterol biosynthetic pathway important for **osteoclast function.**	• **Poorly absorbed (< 10%), food impair absorption more ➔ must be given on an empty stomach or given as infused IV.** • **Half of absorbed drug accumulates in bones, remainder ➔ excreted unchanged in urine.** • **In bone it is retained for months, depending on bone turnover.**	**-GIT irritation; ➔ to avoid give large amount of water** **- Gastro-esophageal reflux ± ulcerations ➔ to avoid give on empty stomach while sitting in upright postion** **- Flue like manifestations upon IV infusion** **- Osteo-necrosis of the jaw [mandible > jaw] more upon long use with IV infusion preparation usually after dental surgical procedures.** **- Atrial fibrillation > women with alendronate & zolidronate** • **Decreased renal function** • **Peptic ulcer / esophageal reflux**	• **Once weekly, or on two consecutive days each month** • **Taken 1st thing am / early morning with glass of water, on empty stomach then nothing taken after for ½ hr.** • **Should be taken in upright position.** • **Separate 4 hrs before giving Ca, Mg, Al containing drugs** • **Newer preparations can be given as 2 hrs IV infusion (or better over a lesser time), monthly in 1st year then every 3 months after.**
2-RANKL Inhibitors (Denosumab) It is a fully human MOA (**monoclonal antibodies**) that mimics the activity of **osteoprotegrin(OPG)**	• **-It binds to RANKL, expressed by osteoblasts ➔ prvents RANKL from interacting with RANK receptor expressed on preosteoclasts ➔ ↓ osteoclastogenesis (no mature osteoclasts).** • **It binds also to mature osteoclast lead to its apoptosis**		• Infections; urinary & respiratory • Eczema & skin rash • Constipation • Cataract • Joint pains **In patients with hypocalcemia (because it is antiresorptive so it will decrease Ca levels in the blood) . Correct Ca & Vit D levels before starting denosumab**	
3- Strontium • Sr^{2+}, is a divalent cation, resembling Ca^{2+} in atomic & ionic properties. • It is orally active as **distrontium.** • Osteoporosis, 2ndry to menopause, glucocorticoids, …. • Malignancy- associated hypercalcaemia	**On Osteoblast;** • Since it is like Ca, it acts as **agonist on Ca Sensing Receptor [CaSP]** ; which is a G-protein coupled receptor that enhances differentiation of preoteoblast to osteoblast ➔↑ bone formation • It **stimulate the expression of OPG (osteoprotogerin) ➔↑RANKL binding** ➔ inhibition of osteo-clustogenesis ➔↓ bone resorption **On Osteoclast;** Acts as agonist **on Ca Sensing Receptor [CaSP]** ➔suppress differentiation of preoteoclast to osteoclast ➔↑ osteoclast apoptosis ➔↓ bone resorption	• **Orally with a modest bioavailability ➔25%** • **Binds partially to plasma proteins and strongly to bones** • **t ½ ➔ 60 hrs** • **Excreted mainly by the kidney**	• GIT irritation; nausea, vomiting, headache, eczema • All resolve in 1st 3 months • **In severe renal disease.** • **In hypersensitivity to it** • **In increased risk of venous thromboembolism** • **In phenylketonuria** • **Food specially containing milk± its** • **Antacids** • **Oral tetracycline & quinolones chelate it** } Precautions 2hrs spacing	

Hormone replacement therapy

Estrogens:

1-In menopausal female we give it:

- If hysterectomy (excision of the uterus)
- If uterus present we give estrogen + progestins . Because estrogen if given alone exogenously it may cause endometrial (uterine) cancer.
- Used : for treatment Menopausal Symptoms
- Elderly men we use androgens:

Estrogen in females & Androgen in males is essential for normal bone remodeling :

-↑ osteoclast apoptosis
-↑ release of growth factors from osteoblasts
-↓ release of inflammatory cytokines causing resorption
-↓ No. & depth of resorption cavities

SERMs (Selective estrogen-receptor modulator)

Raloxifene

- 1st selective estrogen receptor modulator for prevention of osteoporosis
- It has Antiestrogens that exhibits partial agonistic action; acting as an agonist in bone and heart & an antagonist in some female sex organs

Advantages

- ↑ bone density (2%) & ↓ fracture risk (30%)
- No stimulation of breast or endometrial tissue
- No need for progestin in women with uterus
- Decrease LDL

Disadvantages

- ↑ risk of thromboembolic events
- Doesn't treat well Post-menopausal Symptoms
- May ↑ hot flushes
- No effect on HDL

Tibolone

- Synthetic steroid → having estrogen, androgen & progestin properties (because of this balance it doesn't cause thromboembolic risks)
- Can be used without CVS risks.

Summary:

- Osteoporosis is defined as **abnormal loss of bone** predisposing to fractures. (where there is more osteoclastic activity than osteoblastic)
- **In treatment 1- we replace the deficiency of Calcium or Vitamin D by providing them as supplements**
- **Na fluoride** Used to enhance the strength by the formation of **fluorapatite**, and it's **only when the trabecular bone is abnormal in presence of normal cortical bones**

1- BISPHOSPHONATES : Zoledronate has the most potent anti-resorptive activity

MOA : Are structurally similar to pyrophosphate . They prevent bone resorption by inhibiting osteoclast function. It is taken up during osteoclast resorptive activity → blocks steps in cholestrol synthetic pathway within osteoclast → end up by osteoclast apoptosis

Kinetics : Poorly absorbed , food impair absorption more(given on an empty stomach / infused IV) . Half of absorbed drug accumulates in bones, remainder → excreted unchanged in urine. In bone it is retained for months, depending on bone turnover.

Indications: Osteoporosis, 2ndry to menopause, glucocorticoids, …. Etc. Paget's Disease . Malignancy- associated hypercalcaemia

Dosing : Once weekly, or on two each month. Taken 1st thing am / early morning with glass of water, on empty stomach then nothing taken after for ½ hr. Should be taken in upright position . Separate 4 hrs before giving Ca, Mg, Al containing drugs

ADRs : GIT irritation . Gastro-esophageal reflux ± ulcerations . Flue like manifestations upon IV infusion. Osteo-necrosis of the jaw [mandible > jaw] more upon long use with IV infusion preparation usually after dental surgical procedures. It is due to activation of matrix metalloproteinase that cause lysis . Atrial fibrillation occur more in women who use alendronate & zolidronate

Contraindications : Decreased renal function and in peptic ulcer / esophageal reflux.

2-RANKL Inhibitors (Denosumab)

- **MOA :** It binds to RANKL, expressed by osteoblasts →↓ osteoclastogenesis (no mature osteoclasts). It binds also to mature osteoclast enhance its apoptosis . So net effect → ↓ bone resorption.

Administration : Subcutaneous every 6 month

Contraindications : In patients with hypocalcemia (Correct Ca & Vit D levels before starting denosumab)

ADRs : infections; urinary & respiratory. Eczema & skin rash. Constipation. Cataract. Joint pains

3-Strontium : is a divalent cation, resembling Ca^{2+} in atomic & ionic properties.

Mechanism : 1st drug to possess " dual action " On Osteoblast; Since it is like Ca, it acts as agonist on Ca Sensing Receptor [CaSP] ; that enhances differentiation of preoteoblast to osteoblast (↑ bone formation). Also, It stimulate the expression of OPG (osteoprotogerin) →↑RANKL binding → -ve of osteo-clustogenesis (↓ bone resorption). And On Osteoclast; Acts as agonist on Ca Sensing Receptor [CaSP] →suppress differentiation of preoteoclast to osteoclast →↑ osteoclast apoptosis (↓ bone resorption)

Indications : Osteoporosis, 2ndry to menopause, glucocorticoids, …., and Malignancy- associated hypercalcaemia

Contraindications : In severe renal disease. In hypersensitivity to it . In increased risk of venous thromboembolism . In phenylketonuria, Food specially containing milk± its products and Antacids Oral tetracycline & quinolones chelate it

ADRs : GIT irritation; nausea, vomiting, headache, eczema (All resolve in 1st 3 months)

- Estrogen in females & Androgen in males is essential for normal bone remodeling .

- Estrogens : In under menopausal female we give it: If hysterectomy, and if If uterus present we give estrogen + progestins.
- **SERMs: Raloxifene :** 1st selective estrogen R modulator for prevention of osteoporosis
- Mechanism : Antiestrogens that exhibits partial agonistic action; acting as an agonist in bone and heart & an antagonist in some female sex organs .
- **Tibolone : Synthetic steroid** → estrogen, androgen & progestin properties . Can be used without CVS risks