Pharmacological use in Osteoporosis Prevention and Treatment

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Osteoporosis Risk Factors

Factors	Effects
Age-Related	Reduction in absorption of calcium
	Rise in parathyroid hormone levels
	Decline in calcitonin
Nutritional	Low calcium intake
	High alcohol
	High caffeine
	High sodium
	High animal Protein
Gender and Genetic	Women more than men
	Familial prevalence
	High concorance in monozygotic twins
Lifestyle	Cigarette use Living indoors with poor exposure to sun Low physical activity

Consequences of osteoporosis	
Physical	**Social and psychological**
Fractures	Sleep disorders
Reduced physical performance	Quality of life deterioration
Difficulty performing daily activities	Depression
Chronic pain	Social isolation
Upper back kyphosis – "dowager's hump"	Deterioration of economic and financial standing
Gastrointestinal disorders: bloating, pain, difficulty in passing stools, sense of fullness	Disability
Loss of height	

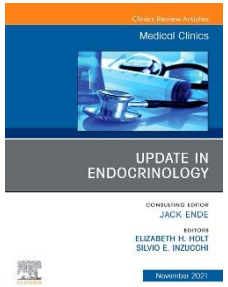
Review > Med Clin North Am. 2021 Nov;105(6):1117-1134. doi: 10.1016/j.mcna.2021.05.016. Epub 2021 Sep 8.

Update on Osteoporosis Screening and Management

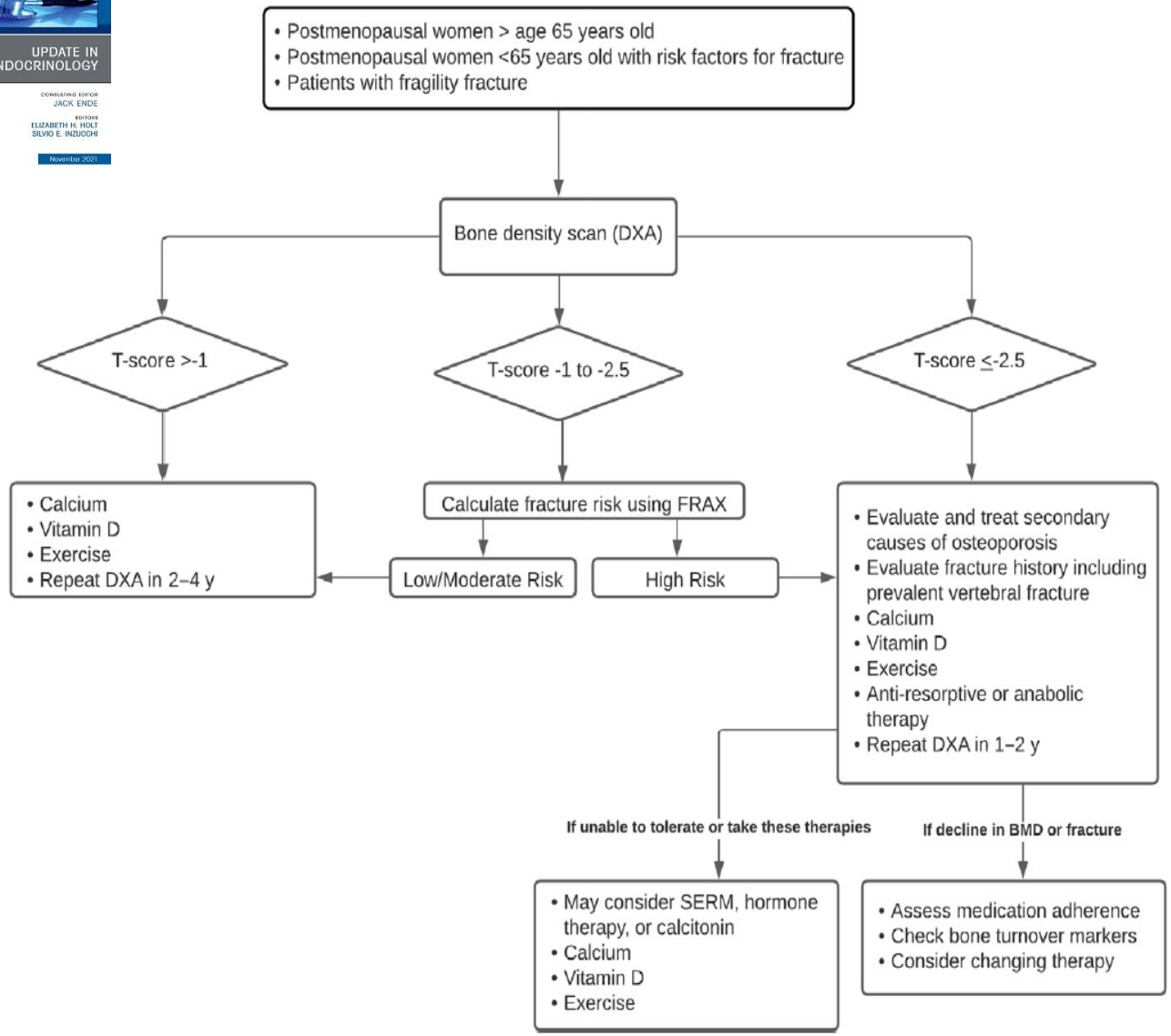
Anika K Anam [1], Karl Insogna [2]

Affiliations + expand

PMID: 34688418 DOI: 10.1016/j.mcna.2021.05.016



Suggested algorithm for diagnosis and management of postmenopausal osteoporosis.



Of note, a high FRAX score should not be the sole determinant for drug treatment

Current Treatment Plans and Approaches in Osteoporosis

non-pharmacological management

can be quite important in preventing OP or promoting fracture healing in OP patients.

- *Adequate calcium and vitamin D intake*
- *weight-bearing exercise*
- *smoking cessation*
- *limitation of alcohol/caffeine consumption*
- *fall-prevention techniques*

Current Treatment Plans and Approaches in Osteoporosis

pharmacological interventions and screenings

- *Anti-resorptive agents*
  (i.e., Bisphosphonates, Estrogen agonist/ antagonists [EAAs], Estrogens, Calcitonin, Denosumab)
  decrease bone resorption by inhibiting osteoclast activity

- *Anabolic agents*
  (i.e., Teriparatide , Romosozumab , Blosozumab)
  increase bone formation by promoting osteoblast activity

- *Besides these pharmacological agents there are other bio-molecules which enhance fracture healing through improvement in biological environment and biomechanical functioning*

Review > J Intern Med. 2019 Apr;285(4):381-394. doi: 10.1111/joim.12873. Epub 2019 Jan 18.

Treating osteoporosis to prevent fractures: current concepts and future developments

Mattias Lorentzon [1] [2]

Affiliations + expand

PMID: 30657216 DOI: 10.1111/joim.12873

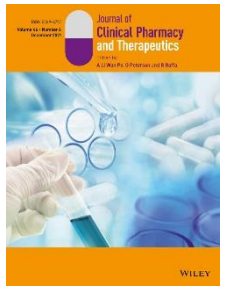
Anti-resorptive drugs

- *Anti-resorptive drugs, especially, bisphosphonates, are currently the treatment of choice in most developing countries. However, they do have limitations and adverse effects.*
- *Bisphosphonates and the RANKL inhibitor denosumab*
- *increase bone mineral density (BMD)*
- *reduce the risk of vertebral (by 40–70%), nonvertebral (by 25–40%) and hip fractures (by 40–53%) in postmenopausal women with osteoporosis.*
- *Due to the risk of rare side-effects, the use of bisphosphonates has been limited to up to 10 years with oral bisphosphonates and 6 years with intravenous zoledronic acid*

P T. 2018 Feb;43(2):92-104.

Osteoporosis: A Review of Treatment Options

Kristie N Tu, Janette D Lie, Chew King Victoria Wan, Madison Cameron, Alaina G Austel, Jenny K Nguyen, Kevin Van, Diana Hyun



- *Bisphosphonates remain the first-line and most cost-effective treatment option for osteoporosis, but there is increasing concern about their long-term safety*
- *screening is important based on age, gender, and other risk factors*

Dose Recommendations for Bisphosphonates

Bisphosphonate	Prophylactic Dose	Treatment Dose	CrCl Recommendation
Alendronate	5 mg PO once daily or 35 mg PO once weekly	10 mg PO once daily or 70 mg PO once weekly	≥ 35 mL/min
Risedronate (IR)	5 mg PO once daily or 35 mg once weekly	5 mg PO once daily or 35 mg PO once weekly or 150 mg PO once monthly	≥ 30 mL/min
Zoledronic acid	5 mg IV every 2 years	5 mg IV once yearly	≥ 35 mL/min
Ibandronate	2.5 mg PO once daily or 150 mg PO once monthly	2.5 mg PO once daily or 150 mg PO once monthly or 3 mg IV every 3 months	≥ 30 mL/min

CrCl = creatinine clearance; IR = immediate release; IV = intravenous; PO = orally.

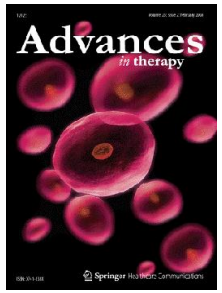
Food and Drug Administration-Approved Pharmacological Interventions for Osteoporosis Treatment and Prevention

Class/Medication	Dose	Route of Administration	Major Action	Type of Fracture Reduction	FDA Indication
Bisphosphonate					
Alendronate	10 mg daily/70 mg weekly	Oral	Anti-resorptive	Vertebral, nonvertebral, hip	Treatment and prevention
Risedronate	5 mg daily/35 mg weekly/150 mg monthly	Oral	Anti-resorptive	Vertebral, nonvertebral, hip	Treatment and prevention
Ibandronate	2.5 mg daily/150 mg monthly/3 mg every three months	Oral/intravenous	Anti-resorptive	Vertebral	Treatment and prevention
Zoledronic acid	5 mg yearly	Intravenous	Anti-resorptive	Vertebral, nonvertebral, hip	Treatment and prevention
RANK Ligand inhibitor					
Denosumab	60 mg every six months	Subcutaneous	Anti-resorptive	Vertebral, nonvertebral, hip	Treatment
Selective estrogen receptor modulators					
Raloxifene	60 mg daily	Oral	Anti-resorptive	Vertebral	Treatment and prevention
Parathyroid hormone analogs					
Teriparatide	20 ug daily	Subcutaneous	Osteoanabolic	Vertebral, non-vertebral	Treatment
Abaloparatide	80 ug daily	Subcutaneous	Osteoanabolic	Vertebral, non-vertebral	Treatment
Sclerostin inhibitor					
Romosozumab	210 mg monthly	Subcutaneous	Osteoanabolic/ anti-resorptive	Vertebral	Treatment

Review > Adv Ther. 2021 Nov 11. doi: 10.1007/s12325-021-01936-y. Online ahead of print.

Denosumab in the Treatment of Osteoporosis: 10 Years Later: A Narrative Review

David L Kendler [1], Felicia Cosman [2], Robert Kees Stad [3], Serge Ferrari [4]



Denosumab

- *Denosumab can be offered as an alternative initial treatment to postmenopausal women with osteoporosis at high risk for fractures*

- *It reduces osteoclastogenesis, induces osteoclast apoptosis, decreases bone resorption, increases BMD,*
- *and reduces fracture risk*

- *Denosumab increases lumbar spine BMD by 9% and total hip BMD by 4%.*

- *denosumab has a favorable benefit/risk profile and is a versatile agent for preventing osteoporotic fractures in the short and long term.*

- *Adverse effects: rates of osteonecrosis of the jaw (ONJ) and atypical femoral fracture (AFF) were very low*

- *Adequate calcium and vitamin D levels should be ensured before initiating denosumab*

Menopausal Hormone Therapy—Estrogen

- *Estrogen therapy is suggested for women under 60 years of age or less than 10 years past menopause, who have vasomotor or climacteric symptoms associated with menopause, and those in whom bisphosphonates or denosumab are not appropriate*

- *potential risks associated with hormonal therapy :*
  myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombophlebitis

- *especially when combined with a progestin, non-estrogen treatments should first be considered for treatment and prevention of osteoporosis*

- *In the Women's Health Initiative, 5 years of combined estrogen and progestin therapy (Prempro) reduced the risk of clinical vertebral fractures and hip fractures by 34% and other osteoporotic fractures by 23%.*

Review > J Intern Med. 2019 Apr;285(4):381-394. doi: 10.1111/joim.12873. Epub 2019 Jan 18.

Treating osteoporosis to prevent fractures: current concepts and future developments

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Anabolic agents

- *Anabolic therapy with teriparatide was demonstrated to be superior to the bisphosphonate risedronate in preventing vertebral and clinical fractures in postmenopausal women with vertebral fracture*
- *Treatment with the sclerostin antibody romosozumab increases BMD more profoundly and rapidly than alendronate and is also superior to alendronate in reducing the risk of vertebral and nonvertebral fracture in postmenopausal women with osteoporosis*
- *For patients with severe osteoporosis and high fracture risk, bisphosphonates alone are unlikely to be able to provide long-term protection against fracture and restore BMD.*
- *For those patients, sequential treatment, starting with a bone-building drug (e.g. teriparatide), followed by an antiresorptive, will likely provide better longterm fracture prevention and should be the golden standard of future osteoporosis treatment.*

Summary of fracture risk reduction of pharmacologic therapies approved for postmenopausal osteoporosis

Drug	Vertebral Fracture	Hip Fracture	Nonvertebral Fracture
Alendronate	✓	✓	✓
Risedronate	✓	✓	✓
Ibandronate	✓	-	✓[a]
Zoledronic acid	✓	✓	✓
Denosumab	✓	✓	✓
Teriparatide	✓	-	✓
Abaloparatide	✓	-	✓
Romosozumab	✓	✓	✓
Estrogen	✓	✓	✓
Raloxifene	✓	-	-
Bazedoxifene	✓	-	-
Bazedoxifene and conjugated estrogen	-	-	-
Calcitonin	✓	-	-

[a] Effect shown in a post hoc analysis.

Randomized Controlled Trial > N Engl J Med. 2018 Dec 20;379(25):2407-2416.
doi: 10.1056/NEJMoa1808082. Epub 2018 Oct 1.

Fracture Prevention with Zoledronate in Older Women with Osteopenia

Ian R Reid [1], Anne M Horne [1], Borislav Mihov [1], Angela Stewart [1], Elizabeth Garratt [1], Sumwai Wong [1], Katy R Wiessing [1], Mark J Bolland [1], Sonja Bastin [1], Gregory D Gamble [1]

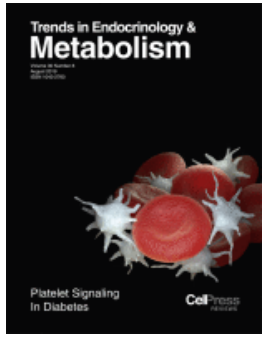
Primary fracture prevention by targeting osteopenic women

- *In a recent 6-year study ….. 2000 osteopenic women, 65 years and older*
- *iv.zoledronic once every 18 months, which was less frequently administered than in previous trials, was able to increase BMD and reduce the risk of fragility fractures*

Review > Trends Endocrinol Metab. 2021 Nov;32(11):846-861. doi: 10.1016/j.tem.2021.07.011. Epub 2021 Sep 1.

Terpenoid treatment in osteoporosis: this is where we have come in research

Daniele Bellavia [1], Fabio Caradonna [2], Eufrosina Dimarco [2], Viviana Costa [3], Valeria Carina [3], Angela De Luca [3], Lavinia Raimondi [3], Carla Gentile [2], Riccardo Alessandro [4], Milena Fini [3], Gianluca Giavaresi [3]



- *Terpenoids act by promoting bone deposition and inhibiting bone resorption.*
- *Terpenoids reduce oxidative stress, determining bone deposition and reducing resorption, through regulation of bone tissue cells.*
- *They are potentially more suitable for long-term use compared with traditional therapeutics*

Review > Front Pharmacol. 2021 Jul 22;12:717065. doi: 10.3389/fphar.2021.717065.
eCollection 2021.

Recent Progresses in the Treatment of Osteoporosis

Shan-Shan Li [1], Shi-Hao He [1], Peng-Yu Xie [1], Wei Li [1], Xin-Xin Zhang [1], Tian-Fang Li [1], Dai-Feng Li [2] [3]

Great endeavors have been made to find next generation drugs with maximal efficacy and minimal toxicity,

improved understanding of the role of different signaling pathways and their crosstalk in the pathogenesis of osteoporosis may help achieve this goal.

In-depth understanding of molecular events in the pathogenesis of osteoporosis including epigenetic regulation of Wnt pathway may facilitate the development of new drugs with better efficacy and less side effects.

potential side effects and the factors underlying the treatment gap

Review > J Clin Med. 2021 Jul 5;10(13):3002. doi: 10.3390/jcm10133002.

The Treatment Gap in Osteoporosis

Nazia Ayub [1], Malak Faraj [2], Sam Ghatan [3], Joannes A A Reijers [4], Nicola Napoli [2 5], Ling Oei [3 6]

Affiliations + expand

PMID: 34279485 PMCID: PMC8268346 DOI: 10.3390/jcm10133002

concerns about rare side effects of the medications (such as osteonecrosis of the jaw), current comorbidities, and inadequate long-term efficacy of anti-resorptive drugs have led to an increase in the number of untreated patients, referred to as an osteoporosis treatment gap

Although these side effects are very rare and not associated with all osteoporosis drugs, patient concerns about these risks are expanding to all osteoporosis drugs.

The Growing Gap in Treatment Options:

- *Rare Side Effects and Growing Treatment Gap*
- *Underestimation of the Fracture Risk and Growing Treatment Gap*

Osteoporos Int. 2018 Jul;29(7):1609-1616. doi: 10.1007/s00198-018-4524-7. Epub 2018 Apr 27.

The relation of low levels of bone mineral density with coronary artery calcium and mortality

N Ahmadi [1 2], S S Mao [3], F Hajsadeghi [4 3], B Arnold [5], S Kiramijyan [3], Y Gao [3], F Flores [3], S Azen [6], M Budoff [3]

Atherosclerosis. 2020 May;301:1-7. doi: 10.1016/j.atherosclerosis.2020.03.021. Epub 2020 Apr 7.

Association between the cumulative exposure to bisphosphonates and hospitalization for atherosclerotic cardiovascular events: A population-based study

Manuela Casula [1], Elena Olmastroni [2], Federica Galimberti [2], Elena Tragni [2], Giovanni Corrao [3], Lorenza Scotti [4], Alberico L Catapano [5]

Bisphosphonate Use, Mortality, and Vascular Calcification

- *Atherosclerosis and osteoporosis share common pathophysiological pathways.*
- *Evidence of cardiovascular implications of bisphosphonate treatment is conflicting.*
- *Cumulative bisphosphonate use results in up to 25% reduction of cardiovascular events.*
- *Bisphosphonates could be considered in the prevention of cardiovascular events*
- *it could provide further justification for the intervention of osteoporotic patients and even patients with moderately compromised BMD with high cardiovascular risk with bisphosphonates.*

nature › nature reviews endocrinology › review articles › article

Review Article | Published: 14 April 2020

Pathogenesis of glucocorticoid-induced osteoporosis and options for treatment

Pojchong Chotiyarnwong & Eugene V. McCloskey

- *Glucocorticoid-induced osteoporosis is the most common cause of secondary osteoporosis and is an iatrogenic disease; the main pathogenesis in the long term is a reduction in bone formation.*
- *Fracture risk is correlated with the dose and duration of glucocorticoid administration, and seems to decrease rapidly on discontinuation; the underlying disease requiring glucocorticoid therapy often contributes to bone loss.*
- *Evaluation of fracture risk, using tools such as FRAX, is recommended in all patients treated with glucocorticoids, preferably around the time of treatment initiation.*
- *Non-pharmacological management (such as nutrition and exercise) should be advocated in all patients receiving long-term glucocorticoid treatment.*
- *Using the minimally effective dose and duration of glucocorticoids with steroid-sparing drugs should be considered where possible.*
- *Pharmacological anti-osteoporotic treatment is recommended in patients at high risk of fracture; anti-resorptives are the primary option but anabolic therapy might also be considered.*

help in narrowing the treatment gap

Review > J Clin Med. 2021 Jul 5;10(13):3002. doi: 10.3390/jcm10133002.

The Treatment Gap in Osteoporosis

Nazia Ayub [1], Malak Faraj [2], Sam Ghatan [3], Joannes A A Reijers [4], Nicola Napoli [2 5], Ling Oei [3 6]

Affiliations + expand

PMID: 34279485 PMCID: PMC8268346 DOI: 10.3390/jcm10133002

- *increased awareness of newly-developed drugs that lack these side effects among patients and doctors*
- *routinely following up and reevaluating patients, such as through fracture liaison services*
- *identification of patients in high-risk groups such as the aforementioned glucocorticoid-induced osteoporosis.*
- *screening for atypical femoral fractures using extended femur scans by DXA to monitor patients on bisphosphonates and denosumab*
- *harmacogenomic markers will also aid in identifying patients at increased risk of atypical femur fractures, which will probably help in narrowing the treatment gap*

Take Home Message

As each elderly patient needs unique interventions due to co-morbidities hence which treatment plan is the best treatment for the healing of fractures in osteoporotic elderly patients is still debatable.

Case finding strategies, such as fracture risk-based screening in primary care using the fracture risk assessment tool (FRAX) and Fracture Liaison Services, have proved effective in increasing treatment rates and reducing fracture rates

In patients with high or very high risk for fracture, sequential or combined therapies may be considered with the initial drugs being anabolic agents.

- *All postmenopausal women and men aged 50 and older should be evaluated for risk of osteoporosis.*
- *Evaluation for osteoporosis should include a detailed history, physical exam, and laboratory tests to assess for secondary causes of bone loss and mineral metabolism.*
- *Osteoporosis treatment should be individualized to the patient*
- *Bisphosphonates or denosumab can be offered as initial treatments.*
- *Anabolic therapy with teriparatide, abaloparatide, or romosozumab is recommended in postmenopausal women with osteoporosis and at very high risk for fracture, especially those with severe fragility fractures or multiple vertebral fractures.*

Thanks