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MEDICAL MANAGEMENT OF OSTEOPOROSIS: CONTEMPORARY STRATEGIES, THERAPEUTIC SEQUENCING AND FUTURE DIRECTIONS

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ABSTRACT

Background: Osteoporosis is a chronic skeletal disorder associated with impaired bone strength and an increased risk of fragility fractures. Despite the availability of effective pharmacological therapies, osteoporosis remains substantially underdiagnosed and undertreated, and recurrent fractures continue to impose a significant clinical and socioeconomic burden. Contemporary management increasingly emphasizes individualized treatment based on fracture risk, treatment history, comorbidities and the anticipated duration of therapy. This review summarizes current pharmacological approaches to osteoporosis, with particular emphasis on antiresorptive and anabolic therapies, therapeutic sequencing, combination strategies, treatment monitoring, emerging therapeutic targets and the role of Fracture Liaison Services (FLS).

Main content: Bisphosphonates remain an important first-line treatment for many patients at high fracture risk, while denosumab provides potent and sustained antiresorptive activity but requires careful planning when treatment is discontinued because of rebound bone turnover and vertebral fracture risk. Anabolic therapies, including teriparatide and romosozumab, provide an opportunity for rapid improvement in bone formation and are particularly relevant to patients at very high fracture risk. Increasing evidence indicates that the sequence of osteoporosis medications influences the magnitude and persistence of skeletal benefit. In particular, anabolic therapy followed by antiresorptive treatment can consolidate gains in bone mineral density and fracture protection. Transition strategies are especially important following denosumab therapy. Combination anabolic-antiresorptive treatment may have a role in selected patients with severe skeletal fragility. Bone turnover markers such as P1NP and CTX can complement BMD and clinical assessment during treatment monitoring. Emerging approaches targeting sclerostin, DKK-1, cathepsin K and regulatory RNA molecules may further expand therapeutic options. FLS programs provide a coordinated framework for identifying fragility fractures, evaluating secondary causes, assessing fracture and fall risk, initiating appropriate therapy and improving long-term adherence.

Conclusion: Modern osteoporosis care should move beyond a medication-centered approach toward individualized, long-term fracture prevention. Appropriate selection and sequencing of anabolic and antiresorptive therapies, systematic monitoring, attention to fall prevention and coordinated multidisciplinary care are essential for optimizing outcomes. Future advances in molecularly targeted therapies and structured FLS pathways may further improve the prevention of recurrent fractures and preservation of functional independence.

Keywords: Osteoporosis; Fragility fracture; Antiresorptive therapy; Anabolic therapy; Bisphosphonates; Denosumab; Teriparatide; Romosozumab; Sequential therapy; Fracture Liaison Service.

INTRODUCTION

Osteoporosis is a systemic skeletal disorder characterized by reduced bone strength and deterioration of bone quality, resulting in increased susceptibility to fragility fractures. The clinical consequences extend beyond the fracture itself and include persistent pain, functional limitation, loss of independence, reduced quality of life, and increased morbidity and mortality. Prevention and treatment therefore require a comprehensive strategy rather than reliance on pharmacological intervention alone. Adequate nutritional intake, particularly sufficient protein, calcium and vitamin D, together with regular weight-bearing and resistance exercise, are fundamental components of osteoporosis care. Measures such as smoking cessation, moderation or avoidance of excessive alcohol consumption, optimization of general health, and appropriate management of comorbidities are equally important. In patients who sustain significant fractures, surgical management may be required. However, one of the most important and frequently overlooked components of fracture prevention is assessment and reduction of fall risk.

The therapeutic landscape of osteoporosis has evolved considerably over recent decades. Treatment has progressed from conventional antiresorptive agents to potent bone-forming therapies, with increasing recognition that the sequence in which medications are prescribed can substantially influence the magnitude and durability of skeletal benefit. In addition, multidisciplinary models such as Fracture Liaison Services (FLS) have emerged as effective strategies for identifying patients with fragility fractures and improving secondary fracture prevention.

This review discusses currently available pharmacological therapies, biomarkers used in treatment monitoring, principles of sequential and combination treatment, emerging therapeutic approaches, and the role of FLS in comprehensive osteoporosis care. Much of the strongest clinical evidence has historically been generated in postmenopausal women; consequently, extrapolation of these findings to older men and other high-risk populations should be undertaken with appropriate clinical judgment.

Pharmacological treatment has demonstrated substantial efficacy in reducing the risk of subsequent fractures. Depending on the agent, patient population and fracture site, reductions of approximately 70% in vertebral fractures, 50% in hip fractures and 20–30% in other nonvertebral fractures have been reported.^[1] Broadly, osteoporosis medications can be divided into antiresorptive agents, which primarily reduce bone loss, and anabolic or bone-forming therapies, which stimulate new bone formation. The availability of multiple agents has made individualized treatment and therapeutic sequencing increasingly important.

Assessment and Monitoring of Osteoporosis:

Imaging techniques used for the diagnosis and assessment of osteoporosis, including conventional radiography, dual-energy X-ray absorptiometry (DXA), vertebral fracture assessment, quantitative imaging techniques and emerging artificial intelligence-based approaches, are discussed separately in another article in the present issue.

Bone turnover markers: Bone turnover markers (BTMs) provide biochemical information regarding the dynamic processes of bone formation and resorption. Unlike bone mineral density (BMD), which changes relatively slowly, BTMs can respond within a shorter period to alterations in skeletal remodeling. They therefore serve as complementary tools rather than replacements for BMD and clinical fracture-risk assessment.

The most widely used markers include procollagen type 1 N-terminal propeptide (P1NP) as an indicator of bone formation and C-terminal telopeptide of type I collagen (CTX) as a marker of bone resorption. In selected clinical situations, serial measurement may assist in evaluating treatment response and adherence, identifying inadequate suppression or stimulation of bone turnover, planning treatment transitions, and determining the need for further antiresorptive therapy after discontinuation of certain medications.^[2] Their potential applications in clinical practice are summarized in [Table 1].

Table 1: Utility of BTMs in clinical practice

S. no.	Indication	Remarks
1	Diagnosis of Osteoporosis	• Mean BTMs are higher in the osteoporotic cohort as compared to controls. However, the use of BTM has not been clinically useful in diagnosing osteoporosis in individual patients. • Very high BTM levels (>3 SD) should prompt the clinician to evaluate for secondary causes of osteoporosis, like hyperparathyroidism, thyrotoxicosis, multiple myeloma, or Cushing's syndrome. • Population studies have shown that increased BTM values around menopause are associated with increased risk of fractures later. However, these relationships are not strong enough in individual patients for BTMs to be used to predict bone loss or fractures.
2	Predicting fractures or bone loss	• Anti-resorptive treatment leads to significant reduction in bone resorption markers, and with time, smaller reductions in bone formation markers. • Anabolic therapies cause major increases in bone formation markers, followed by smaller increments in bone resorption markers.
3	Monitoring osteoporosis therapy	• An adequate response to plasma CTX after 3 months of initiation of therapy is target level <300 ng/L, with an absolute decrease of >10 ng/L from baseline. ^[3] • An adequate response to plasma P1NP after 6 months of initiation of therapy is target level <35 µg/L, with an absolute decrease of >10 µg/L from baseline. ^[3] • A lack of adequate response can also be seen in patients with diabetes mellitus, suboptimal calcium and vitamin D supplementation, reduced gut absorption of the medications, or having an underlying secondary cause for osteoporosis. • Unavailable for use in patients with renal failure.
4	Confirm adherence to oral BP therapies	• A significant increase in P1NP >10 µg/L at 1 month or more after the initiation of treatment confirms the effectiveness of treatment. ^[3]
5	Confirming adherence to teriparatide therapy	• Oral alendronate and IV zoledronic acid therapies may be discontinued after 3 and 3 years of therapy, respectively, provided that there are no new incident fractures and the BMD values are stable (drug holiday). • An increase in the BTMs above the treatment target may be used to guide reinstating the BP therapy after the "drug holiday". • Similarly, BTMs have been used to monitor the effect of treatment effects following zoledronic acid infusion to determine the timing of the next infusion.
6	Monitoring the effect of BP treatment effects	• Cessation of denosumab therapy leads to a rebound increase in the BTMs above the baseline by 8–10 months of the last injection. It is thus recommended that discontinuation of denosumab should be followed by treatment with a potent BP, and the BTMs can be used to monitor the effectiveness of this therapy.
7	Therapy after denosumab	

BTM = bone turnover marker; CTX = C-terminal telopeptide; P1NP = procollagen type-1 intact N-terminal propeptide; SD = standard deviation

Emerging molecular biomarkers: The biology of bone remodelling is regulated by a complex network of genetic and epigenetic mechanisms. MicroRNAs (miRNAs) and long non-coding RNAs influence osteoblast and osteoclast differentiation, cellular signalling and skeletal adaptation to mechanical stimuli.

Among the molecules investigated, miRNA-103a has attracted attention because of its inhibitory effect on osteoblast differentiation and its increased expression during mechanical unloading and immobility.^[3] Experimental studies using animal models and cell-based systems have suggested that inhibition of miRNA-103a with antagomir-103a may attenuate or reverse bone loss associated with reduced mechanical loading.^[4]

These findings raise the possibility that non-coding RNA molecules could eventually have a dual role as biomarkers of skeletal health and therapeutic targets. However, most evidence in this field remains preclinical, and translation into routine clinical practice will require further validation.

Pharmacological Management of Osteoporosis

Currently available therapies: The modern era of pharmacological osteoporosis treatment began with the recognition that estrogen could prevent postmenopausal bone loss. Subsequently, bisphosphonates and other antiresorptive therapies became established components of clinical practice. Over time, concerns regarding safety, limited efficacy at certain fracture sites or the availability of more effective alternatives have resulted in declining use of several older agents, including calcitonin, calcitriol and strontium ranelate in many clinical settings.

Current treatment options, their usual dosing schedules, important adverse effects and contraindications are summarized in [Table 2].

Table 2: Current anti-osteoporosis drugs available in India.

Class	Drug	Usual dose	Precautions	Significant adverse reactions	Contraindications
Oral BP	Alendronate	70mg weekly	The tablet has to be taken empty stomach, with adequate water, and the patient has to refrain from eating or lying down for at least 30 min after consumption of the tablet.	Transient hypocalcemia; GI: abdominal pain, dyspepsia, nausea, esophagephalinitis, reflux, esophageal ulcers, gastritis; Muscle cramps, bone pains.	Hypersensitivity; Uncorrected hypocalcemia; Esophageal stricture or Achalasia; Inability to stand/sit upright for 30 min; CrCl <35 mL/min.
	Risedronate	35mg weekly			
	Ibandronate	150mg monthly			
IV BP	Zoledronic acid	5mg once every 12 months	Muculocutaneous pain and flu-like symptoms may be prevented by normalization of serum 25-OH-D before infusion.	Hypocalcemia; Nausea; Arthralgia; Flu-like symptoms; AFF; ONJ	Hypersensitivity; Uncorrected hypocalcemia; CrCl <35 mL/min.
RANKL antibody	Denosumab	60mg sc once every 6 months	To correct hypocalcemia and hypovitaminosis D before therapy initiation; To replace with another therapy if Denosumab discontinuation is contemplated.	Hypocalcemia; ENT and GI infections; Peripheral edema; AFF; ONJ	Hypersensitivity; Uncorrected hypocalcemia; No dose adjustment is needed in renal failure, though the prevalence and severity of hypocalcemia are increased in renal failure.
PTH analogue	Teriparatide	20 µg sc daily	The cumulative duration of therapy generally does not exceed 24 months.	Hypocalcemia; Hyperparathyroidism; Musculoskeletal pains;	Hypersensitivity; Hypocalcemia; Skeletal metastases; Osteonecrosis; eGFR <30 mL/minute/1.73 m ² ; use only in very high-risk risk-selective patients with utmost caution.
Sclerostin inhibitor	Romosozumab	210mg sc monthly	Cumulative duration of therapy not to exceed 12 months; Following a course of Romosozumab, switch to anti-resorptive therapy.	Arthralgia; Local injection reaction; ONJ; Blackbox Warning: This may increase the risk of MI, stroke, and cardiovascular death, and should not be initiated in patients who have had an MI or stroke within the previous year. Discontinue use if MI or stroke occurs during therapy.	Hypersensitivity; Uncorrected Hypocalcemia; High risk of cardiovascular disease and stroke. No dose adjustment is needed in renal failure, though eGFR <30 mL/min/1.73 m ² or receiving dialysis, monitor closely for hypocalcemia

All patients on anti-osteoporotic drugs should receive supplemental calcium and vitamin D.
 25OHD = 25-hydroxy vitamin D, AFF = atypical femur fractures, BP = bisphosphonates, CrCl = creatinine clearance, eGFR = estimated glomerular filtration rate, ENT = ear nose throat, GI = gastrointestinal, IV = intravenous, MI = myocardial infarction, ONJ = osteonecrosis of jaw, PTH = parathyroid hormone; RANKL = receptor activator of nuclear factor kappa-B ligand, sc = subcutaneous.

The choice of treatment should be individualized according to baseline fracture risk, previous fractures, BMD, age, renal function, comorbidities, previous osteoporosis therapy, treatment adherence, cost and patient preference.

Bisphosphonates: Bisphosphonates remain an important first-line pharmacological option for many patients with osteoporosis. Commonly used agents include alendronate, risedronate, ibandronate and intravenous zoledronic acid.

Alendronate, risedronate and zoledronic acid have demonstrated clinically meaningful reductions in vertebral, hip and nonvertebral fractures. Evidence for reduction of hip and other nonvertebral fractures with ibandronate is less convincing.^[5,6] Although many pivotal fracture trials used daily administration schedules, weekly or monthly regimens are

frequently preferred in clinical practice because of improved convenience and, for oral agents, potentially better tolerability.

Before initiating bisphosphonate treatment, correctable contributors to poor skeletal health should be addressed. These include inadequate vitamin D status, insufficient calcium intake and poor dental health. Patients receiving intravenous zoledronic acid may experience an acute-phase reaction characterized by transient fever, myalgia, fatigue or flu-like symptoms. Administration of an appropriate antipyretic or analgesic around the time of infusion may reduce these symptoms.

Transient reductions in serum calcium can occur following zoledronic acid administration. Clinically important hypocalcaemia is uncommon in patients treated for osteoporosis but becomes more relevant in individuals receiving intensive intravenous bisphosphonate therapy for malignancy.^[7] Vitamin D deficiency, renal dysfunction, hypomagnesaemia and concomitant medications that influence calcium handling may increase the risk.^[8,9]

Long-term bisphosphonate therapy and atypical femoral fractures: Prolonged suppression of bone remodelling has been associated with atypical femoral fractures (AFF), particularly after several years of bisphosphonate exposure. Additional risk factors may include glucocorticoid exposure, femoral geometry and certain ethnic backgrounds.^[10–13] The absolute incidence remains low, with estimates of approximately 0.2% after more than five years of treatment.^[14]

Patients presenting with an atypical femoral fracture should undergo careful evaluation of the opposite femur because bilateral or sequential involvement may occur. Persistent thigh or groin pain in a patient receiving long-term bisphosphonate therapy should also prompt appropriate imaging.

Osteonecrosis of the jaw: Medication-related osteonecrosis of the jaw (MRONJ) is another recognized complication of antiresorptive therapy. The underlying mechanisms are likely multifactorial and may include suppression of bone turnover, local tissue toxicity, altered immune responses and infection.^[15–17]

The risk is considerably influenced by the clinical setting and cumulative exposure. Factors associated with increased risk include active malignancy, cancer treatment, invasive dental procedures, poor oral hygiene, intravenous bisphosphonate administration, head and neck radiotherapy, diabetes, tobacco exposure, excessive alcohol consumption and anemia.^[18]

Good oral hygiene and appropriate dental assessment are therefore important components of long-term osteoporosis management.

Bisphosphonate treatment duration and drug holidays: One of the advantages of bisphosphonates is their persistence within bone and their residual anti-fracture effect after treatment is temporarily discontinued. In appropriately selected patients who have completed several years of therapy and are no

longer at very high fracture risk, a bisphosphonate holiday may therefore be considered.

Extension data from the HORIZON study demonstrated continued skeletal protection following an initial three-year course of annual zoledronic acid.^[19] Longer treatment produced additional BMD benefits and fewer morphometric vertebral fractures in selected patients, but prolonged exposure must be balanced against rare adverse events.

A treatment holiday should therefore not be regarded as an automatic step after a fixed duration of therapy. Patients with persistent high fracture risk—particularly those with previous vertebral or hip fractures, very low BMD or fractures occurring during treatment—may benefit from continued therapy or an alternative pharmacological strategy.

Denosumab: Denosumab is a potent antiresorptive monoclonal antibody that acts by inhibiting the RANK–RANK ligand pathway, a key regulator of osteoclast differentiation and activity. By reducing osteoclast-mediated bone resorption, denosumab produces substantial increases in bone mass and improves bone strength.

Long-term clinical studies have demonstrated reductions in vertebral, hip, nonvertebral and wrist fractures in postmenopausal women, with benefits maintained during prolonged treatment.^[20,21]

Patients should receive appropriate calcium and vitamin D supplementation, and those at risk for mineral abnormalities should undergo relevant biochemical monitoring. Particular caution is required in individuals with advanced chronic kidney disease, in whom severe hypocalcaemia can occur. In such patients, the distinction between osteoporosis and other forms of renal bone disease is especially important before treatment is initiated.^[22,23]

Dental health should be optimized, and patients should maintain good oral hygiene throughout therapy, particularly when additional risk factors for MRONJ are present.

Discontinuation of denosumab: An important characteristic of denosumab is the rapid reversal of its antiresorptive effect after treatment interruption. Bone turnover can increase markedly after the effect of the drug wanes, accompanied by loss of BMD and an increased risk of multiple vertebral fractures.^[24]

Consequently, denosumab should not simply be stopped without a subsequent antiresorptive strategy. Patients should be informed about the importance of maintaining scheduled injections. If discontinuation becomes necessary, an appropriate transition to another antiresorptive agent should be planned to reduce rebound bone loss and vertebral fracture risk.

Teriparatide: Teriparatide is a recombinant form of the biologically active N-terminal portion of parathyroid hormone. When administered intermittently, it preferentially stimulates osteoblast activity and promotes new bone formation.

Its skeletal effects include increased bone formation, improvement in BMD and enhancement of bone strength. Clinical trials have demonstrated a reduction in vertebral and other osteoporosis-related

fractures in postmenopausal women.^[25,26] Teriparatide is also used in selected men with osteoporosis and in glucocorticoid-associated osteoporosis.

Hypercalcemia is an important contraindication or precaution. Historically, treatment has generally been limited to approximately 24 months because of the evidence base and regulatory considerations. The greatest fracture-prevention benefit has been demonstrated during prolonged treatment courses approaching this duration.^[26]

Importantly, the skeletal gains achieved with teriparatide should be consolidated with an antiresorptive agent after completion of anabolic therapy. Without subsequent antiresorptive treatment, some of the BMD benefit may be lost.

Longer exposure may occasionally be considered in individuals who remain at very high fracture risk, but this should be based on current regulatory guidance and individualized assessment. Evidence supporting routine re-treatment with teriparatide after a previous course remains limited.

Romosozumab: Romosozumab is a humanized monoclonal antibody directed against sclerostin and represents an important advance in anabolic osteoporosis treatment. By inhibiting sclerostin, romosozumab enhances Wnt signaling and stimulates osteoblast-mediated bone formation. It also produces an antiresorptive effect, making it a distinctive therapy with both bone-forming and bone-resorption-suppressing actions.

The FRAME trial demonstrated substantial increases in BMD and reductions in vertebral and clinical fracture risk when romosozumab was followed by denosumab.^[28] The ARCH trial similarly demonstrated superior BMD improvement and fracture-risk reduction with an initial year of romosozumab followed by alendronate compared with alendronate alone.^[29]

Romosozumab is particularly relevant for individuals with very high fracture risk, such as patients with severe osteoporosis, recent major osteoporotic fractures or multiple fractures.

The usual regimen is 210 mg administered subcutaneously once monthly for a maximum treatment period of 12 months, after which antiresorptive therapy should be initiated to maintain the skeletal gains.

Because of concerns regarding cardiovascular safety, romosozumab should be avoided in patients with a recent myocardial infarction or stroke, and cardiovascular risk should be carefully assessed before treatment. Hypocalcemia and vitamin D deficiency should be corrected before initiation.

Why Therapeutic Sequencing Matters: The major bone-forming therapies are administered for relatively defined treatment periods, whereas osteoporosis itself is a chronic condition requiring long-term fracture-risk management. Consequently, treatment cannot simply end when a finite anabolic course is completed.

The concept of sequential therapy has therefore become central to contemporary osteoporosis management.^[30]

The order in which drugs are used can influence BMD response, bone turnover and long-term fracture protection. Treatment history should consequently be considered whenever a change in therapy is planned.

Sequential Treatment Strategies

Antiresorptive therapy followed by anabolic treatment: Bisphosphonates and denosumab are commonly used as initial treatments. However, previous antiresorptive exposure can influence the response to subsequent anabolic therapy.

Patients previously treated with alendronate may demonstrate a slower or attenuated BTM and BMD response after initiation of teriparatide.^[31] Some studies have reported a reduction in hip BMD during the initial months of teriparatide therapy following previous alendronate treatment.^[32]

The situation may be more complex after denosumab. Transitioning directly from denosumab to teriparatide has been associated with transient decreases in BMD, particularly at the hip and spine.^[33] Although this has not clearly translated into an increased fracture rate in clinical studies, the period warrants careful monitoring.

Similarly, romosozumab produces smaller BMD gains in patients previously exposed to potent antiresorptive therapy than in treatment-naïve individuals.^[34] Among women previously treated with bisphosphonates, romosozumab has demonstrated more favorable hip BMD outcomes than teriparatide over 12 months.^[35]

Nevertheless, previous treatment should not automatically exclude patients with severe or progressive osteoporosis from receiving anabolic therapy. Individuals who continue to experience fractures or substantial bone loss despite antiresorptive treatment may still derive meaningful benefit from an anabolic approach.

When a patient requires anabolic treatment after denosumab, abrupt conversion to teriparatide should generally be avoided. Continuing antiresorptive protection while introducing anabolic therapy may be considered in selected high-risk situations.

Anabolic therapy followed by antiresorptive therapy The reverse sequence—anabolic therapy followed by an antiresorptive agent—is particularly important because bone gains obtained with teriparatide or romosozumab can diminish after discontinuation.

Following teriparatide with raloxifene has been associated with maintenance of lumbar spine BMD and continued improvement at the hip, whereas alendronate after teriparatide can preserve and further improve BMD at the hip, femoral neck and lumbar spine.^[36]

Data from the DATA-Switch study demonstrated substantial skeletal benefits when denosumab followed teriparatide, including improvements in areal and volumetric BMD, cortical parameters,

trabecular bone score and finite-element measures of bone strength.^[33,37,38]

Similarly, patients receiving romosozumab followed by denosumab or alendronate have demonstrated sustained fracture protection and retention of BMD gains.^[28,29] Studies have also suggested that zoledronic acid can preserve a significant proportion of the BMD improvement achieved during romosozumab therapy.^[39]

Thus, an anabolic course should generally be viewed as the first phase of a longer treatment strategy rather than the endpoint of therapy.

Switching between antiresorptive therapies:

Although the increasing availability of anabolic medications has reduced the need for repeated switching between antiresorptive agents, such transitions remain relevant in everyday practice.

Reasons for changing therapy may include inadequate BMD response, adverse effects, adherence difficulties, cost considerations, patient preference or the need to consolidate the skeletal benefit achieved with denosumab.

Switching from alendronate to denosumab has been associated with greater BMD improvement than continuing alendronate in appropriate patients.^[40] Denosumab has also produced greater suppression of bone remodeling and greater BMD gains than zoledronic acid following previous alendronate treatment.^[41]

Conversely, transition from denosumab to a bisphosphonate requires special attention because the antiresorptive effect of denosumab is rapidly reversible.

Studies examining zoledronic acid after denosumab have demonstrated variable preservation of BMD.^[43,44] Some patients retain a substantial proportion of their previous gains, whereas others experience clinically meaningful BMD decline. Consequently, a single standardized approach may not be appropriate for every patient.

Where denosumab discontinuation is planned, the subsequent bisphosphonate strategy should consider the duration of denosumab exposure, baseline fracture risk, BMD, bone turnover markers and the availability of biochemical monitoring.

CTX measurement may assist in assessing the adequacy of suppression after transition and determining whether additional antiresorptive treatment is required.

The major principles of commonly used sequential regimens are summarized in [Table 3].

Table 3. Sequential therapies for Osteoporosis.

S. no.	Initial therapy	Follow-up therapy	Effect on spine BMD	Effect on hip BMD	Effect on fracture prevention	References
1.	Alendronate	Teriparatide	Benefit	No benefit or loss > 6 months	N/A	Miller <i>et al.</i> ^[50] Eslinger <i>et al.</i> ^[5] and Cosman <i>et al.</i> ^[5]
2.	Denosumab	Teriparatide	Benefit (after transient loss < 6 months)	Loss > 18 months	N/A	Leder <i>et al.</i> ^[50]
3.	Alendronate	Teriparatide	No benefit	Loss > 18 months	Loss of cortical BMD and hip strength > 18 months	Langdahl <i>et al.</i> ^[50]
		Romosozumab	Benefit	Benefit	Cortical BMD and hip strength benefit	
4.	Teriparatide/PTH	Alendronate	Benefit	Benefit	N/A	Eastell <i>et al.</i> ^[50] and Reid <i>et al.</i> ^[5]
5.	Teriparatide	Denosumab	Benefit	Benefit	N/A	Leder <i>et al.</i> ^[50]
6.	Romosozumab	Denosumab	N/A	N/A	VF and NVF risk reduction	Cosman <i>et al.</i> ^[50]
7.	Romosozumab	Alendronate	N/A	N/A	VF and NVF risk reduction	Saag <i>et al.</i> ^[50]
8.	Alendronate	Denosumab	Benefit	Benefit	N/A	Kendler <i>et al.</i> ^[50]

BMD = bone mineral density, N/A = not available, NVF = nonvertebral fractures, VF = vertebral fractures

Combination Pharmacotherapy: The simultaneous use of two antiresorptive drugs generally provides little additional clinical benefit and is not routinely recommended. In contrast, combining an anabolic agent with an antiresorptive drug has been investigated as a strategy to maximize skeletal gains in patients with very severe osteoporosis.

Studies involving women previously treated with alendronate or raloxifene found that adding teriparatide could produce greater BMD improvements than simply switching to teriparatide.^[45]

Combination treatment with zoledronic acid and teriparatide has also been evaluated. Lumbar spine BMD gains were comparable between combination treatment and teriparatide alone, whereas hip BMD responses favored the combination over teriparatide alone.^[46]

More compelling data have emerged from studies combining teriparatide and denosumab. Over 24 months, combined treatment resulted in greater improvements in areal and volumetric BMD, cortical thickness and finite-element measures compared with either treatment alone.^[38,47,48]

The DATA-HD study further explored the effect of higher-dose teriparatide in combination with denosumab and demonstrated greater BMD gains at the spine and hip compared with the conventional teriparatide dose.^[49]

The biological rationale is particularly interesting: denosumab can suppress the secondary increase in bone resorption associated with anabolic therapy while allowing the anabolic stimulus to continue. This effect is less complete with bisphosphonates.

Despite these promising findings, combination treatment is not routinely necessary for most patients. Its role is primarily in carefully selected individuals with very high fracture risk, severe skeletal fragility or other circumstances in which rapid and substantial increases in bone strength are clinically desirable.

The comparative effects of combination strategies are summarized in [Table 4].

Table 4: Combination therapies compared to single/sequential therapies for osteoporosis

S. no.	BMD improvement in combination therapies versus single/sequential therapies	References
At spine		
1.	[Alendronate + teriparatide] > [alendronate → teriparatide]	Cosman <i>et al.</i> ^[50]
2.	[Raloxifene + teriparatide] > [raloxifene → teriparatide]	Cosman <i>et al.</i> ^[50]
3.	[Alendronate + PTH] = [alendronate] OR [PTH]	Black <i>et al.</i> ^[50]
4.	[Zoledronic acid + teriparatide] > [teriparatide] > [zoledronic acid]	Cosman <i>et al.</i> ^[50]
5.	[Denosumab + teriparatide] > [denosumab] OR [teriparatide]	Leder <i>et al.</i> ^[50] Tsai <i>et al.</i> ^[50] and Tsai <i>et al.</i> ^[50]
At hip		
1.	[Alendronate + teriparatide] > [alendronate → teriparatide]	Cosman <i>et al.</i> ^[50]
2.	[Raloxifene + teriparatide] > [raloxifene → teriparatide]	Cosman <i>et al.</i> ^[50]
3.	[Alendronate + PTH] = [alendronate] OR [PTH]	Black <i>et al.</i> ^[50]
4.	[Zoledronic acid + teriparatide] > [zoledronic acid] > [teriparatide]	Cosman <i>et al.</i> ^[50]
5.	[Denosumab + teriparatide] > [denosumab] OR [teriparatide]	Leder <i>et al.</i> ^[50] Tsai <i>et al.</i> ^[50] and Tsai <i>et al.</i> ^[50]

PTH = parathyroid hormone

Emerging Therapies and Future Directions: The therapeutic pipeline for osteoporosis continues to expand, with several approaches targeting different components of bone remodeling.^[51]

Sclerostin and DKK-1 inhibition: Romosozumab has established the clinical value of targeting sclerostin. Other sclerostin inhibitors, including blosozumab, have undergone clinical development.

DKK-1 represents another potential target within the Wnt signaling pathway. Experimental work has suggested that inhibition of sclerostin may result in compensatory increases in DKK-1, potentially contributing to the eventual attenuation of the anabolic response.

A therapeutic strategy capable of simultaneously inhibiting sclerostin and DKK-1 could therefore theoretically produce more sustained stimulation of bone formation. Preclinical studies in rodents and non-human primates have provided evidence of synergistic effects of combined pathway inhibition, including enhanced bone formation and repair.^[52]

RNA-based approaches: The discovery of regulatory miRNAs has created another potential avenue for osteoporosis therapy. Experimental inhibition of miRNA-103a has demonstrated anabolic effects in models of skeletal unloading.^[4] Similarly, antagomir-214 has shown bone-forming effects in preclinical studies, apparently through mechanisms that may operate independently of conventional osteoblast–osteoclast coupling.^[53]

Although these approaches remain experimental, they illustrate the potential for future osteoporosis therapies to act at the molecular and genetic level rather than solely through conventional systemic pathways.

Abaloparatide: Abaloparatide is a synthetic analog of parathyroid hormone-related peptide that activates the PTH1 receptor and stimulates osteoblast activity. It is an anabolic treatment option for postmenopausal women and men at increased fracture risk.^[54,55]

The usual dose is 80 µg administered subcutaneously once daily. As with other anabolic therapies, treatment is generally limited to a defined duration, after which antiresorptive therapy should be used to maintain the skeletal benefit.^[55]

Cathepsin K inhibition: Cathepsin K inhibitors represent a mechanistically distinct approach to antiresorptive treatment. Cathepsin K is an enzyme involved in the degradation of bone matrix by osteoclasts. Inhibition can suppress osteoclastic bone resorption while potentially preserving osteoclast viability.

Odanacatib progressed through extensive clinical development and demonstrated anti-fracture efficacy. However, its development was discontinued because of an unexpected increase in cerebrovascular events.^[56]

Although this particular agent did not reach clinical practice, the concept remains scientifically important. Future cathepsin K-directed therapies may potentially separate the beneficial suppression of bone resorption from the coupled reduction in bone

formation observed with some conventional antiresorptive treatments.

Fracture Liaison Services: The effectiveness of osteoporosis treatment depends not only on the availability of medications but also on identifying appropriate patients, initiating therapy and maintaining adherence.

Despite the growing burden of osteoporosis, awareness and treatment rates remain suboptimal in India. Surveys have suggested that osteoporosis awareness is low, a substantial proportion of individuals with fragility fractures are not evaluated or treated for the underlying skeletal disorder, and long-term treatment adherence remains inadequate.^[57]

A Fracture Liaison Service (FLS) provides a structured system for identifying patients who have sustained fragility fractures and ensuring that they receive systematic assessment and secondary fracture prevention.

In India, FLS initiatives have been established at several major institutions, including Postgraduate Institute of Medical Education and Research, Chandigarh; P. D. Hinduja Hospital and Medical Research Centre, Mumbai; and Maulana Azad Medical College, New Delhi, under the Indian Society for Bone and Mineral Research.^[58]

The essential components of an FLS include:

- * identification of patients with fragility fractures;
- * coordinated multidisciplinary referral;
- * evaluation for previously unrecognized vertebral fractures;
- * BMD assessment using DXA;
- * calculation of fracture probability using tools such as FRAX;
- * investigation for secondary causes of osteoporosis;
- * assessment of nutritional status;
- * evaluation of fall risk;
- * review of medications and comorbidities;
- * individualized selection of pharmacological therapy;
- * patient education and adherence support; and
- * longitudinal follow-up.

A structured pathway such as this can transform fracture care from an isolated episode of treatment into a long-term fracture-prevention program.^[59]

The precise organization of an FLS should be adapted to the resources, patient population and clinical infrastructure of each institution.

Practical Approach to Medical Management

The expanding therapeutic armamentarium makes individualized treatment increasingly important. A practical approach can be summarized as follows:

1. Identify fracture risk: Patients with fragility fractures, particularly hip or vertebral fractures, should be considered at high or very high risk even when BMD alone does not meet conventional diagnostic thresholds.

2. Look for secondary causes: Before commencing long-term pharmacological treatment, appropriate investigations should be performed to identify potentially reversible contributors to bone loss.

3. Optimize the foundation of treatment: Adequate calcium and vitamin D intake, sufficient dietary protein, weight-bearing and resistance exercise, smoking cessation, avoidance of excessive alcohol and fall-prevention strategies should accompany pharmacological treatment.

4. Select treatment according to fracture risk: Patients at conventional high risk may be appropriately treated with an antiresorptive agent. Individuals with very high fracture risk, multiple or recent fractures, severe osteoporosis or fractures despite therapy may be candidates for an anabolic-first strategy.

5. Plan the treatment sequence from the beginning: When an anabolic agent is selected, the subsequent antiresorptive treatment should already be considered. Similarly, denosumab should never be discontinued without planning subsequent antiresorptive protection.

6. Monitor response: Clinical events, adherence, BMD and, when appropriate, BTMs should be used together to evaluate treatment effectiveness.

7. Reassess periodically: Fracture occurrence, change in BMD, new risk factors, adverse effects, treatment duration and patient preferences should determine whether therapy should be continued, changed or temporarily interrupted.

CONCLUSION

Osteoporosis should be regarded as a chronic systemic disease requiring sustained attention rather than as a disorder treated only after a fracture has occurred. Contemporary management combines lifestyle optimization, identification of secondary causes, fall prevention and appropriately selected pharmacological therapy.

The expansion of the therapeutic armamentarium has shifted the focus from simply choosing an osteoporosis medication to determining which treatment should be used, in whom, for how long and what should follow it. Sequential treatment has consequently become an essential component of modern osteoporosis care. In patients with very high fracture risk, an anabolic-first strategy followed by antiresorptive maintenance may provide substantial skeletal benefit, while conventional antiresorptive therapy remains appropriate for many patients with high fracture risk.

Combination therapy has a potential role in selected patients with severe skeletal fragility, although it should not be considered routine treatment. Similarly, bisphosphonate holidays may be appropriate for carefully selected patients whose fracture risk has fallen after several years of therapy, whereas individuals who remain at very high risk may require continued treatment.

The future of osteoporosis management is likely to include therapies directed at increasingly specific molecular pathways, including Wnt signaling, sclerostin, DKK-1, cathepsin K and regulatory RNA

molecules. However, technological and pharmacological advances will have limited population-level impact unless patients with fragility fractures are consistently identified and treated.

FLS programs provide an effective framework for achieving this goal by integrating fracture identification, diagnostic evaluation, secondary-cause assessment, treatment selection, fall prevention and long-term follow-up.

Ultimately, successful osteoporosis management should aim not merely to increase BMD but to prevent the next fracture, preserve independence and maintain quality of life. A coordinated, multidisciplinary and patient-centered approach offers the greatest opportunity to achieve these objectives.

Clinical Pearls

* Osteoporosis is a chronic disease requiring long-term fracture-risk management, not simply short-term treatment after diagnosis.

* Anabolic therapy followed by antiresorptive therapy is an important strategy for patients at very high fracture risk.

* Bisphosphonate treatment can be followed by a drug holiday in appropriately selected patients whose fracture risk has substantially decreased.

* Denosumab should not be stopped abruptly; an appropriate antiresorptive transition strategy is essential.

* Combination anabolic–antiresorptive therapy may be considered in carefully selected patients with severe osteoporosis, rather than being used routinely.

* Treatment duration and drug selection should be individualized after discussing benefits, limitations, adverse effects, cost and patient preferences.

* Evaluation for secondary causes of osteoporosis should precede pharmacological treatment whenever clinically appropriate.

* Calcium, vitamin D, adequate protein intake, resistance exercise and fall prevention remain fundamental components of therapy.

* A fragility fracture should trigger evaluation for osteoporosis and consideration of secondary fracture prevention through an FLS or an equivalent coordinated care pathway.

* The ultimate objective of osteoporosis treatment is fracture prevention and preservation of function and independence, rather than improvement in BMD alone.

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