COMPASS Therapeutic Notes On The Management Of Osteoporosis

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Glossary of terms	
NOGG	National Osteoporosis Guideline Group
BMI	Body Mass Index
WHO	World Health Organisation
IOF	International Osteoporosis Foundation
Kyphosis	Abnormal curvature of the thoracic vertebrae (upper back)
UVB	Ultraviolet B light
RCT	Randomised Control Trial
EMA	European Medicines Agency
MHRA	Medicines and Healthcare Products Regulatory Agency
Osteoblasts	Cells which form bone by deposition of protein matrix materials and mineralisation
Osteoclasts	Cells which act to resorb bone by breaking up the matrix

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Introduction, Background and Diagnosis

What is osteoporosis?

Osteoporosis is a chronic disease with late clinical consequences.[28] WHO defined osteoporosis in 1994 as a 'progressive systemic skeletal disease characterised by low bone mass and structural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture'.[2] The more recent 2001 National Institutes of Health (NIH) definition takes into account that bone strength is dependant, not just on bone density, but also on bone quality: 'a skeletal disorder characterized by compromised bone strength, which predisposes an individual to an increased risk of fracture.'[169]

What is the prevalence of osteoporosis?

It is estimated that almost 3 million people in the UK have osteoporosis, with Northern Ireland accounting for 72,000 of this. In Northern Ireland, the combined cost of hospital and social care for patients with a hip fracture alone is £65million per year.[28] Age is a significant risk factor: in women the prevalence is approximately 2% at 50 years of age to almost 50% at 80 years of age.[8,28] As the longevity of the population increases, so will the incidence of osteoporosis and fragility fracture.[18]

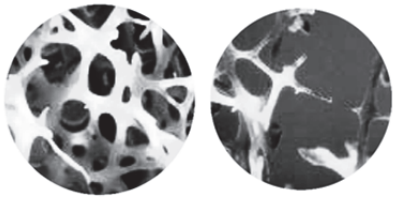
Bone resorption and remodelling

Bone is a dynamic tissue; it is continually remodelling throughout life. This maintains circulating calcium homeostasis and repairs tissue damage (microcracks) that impair bone quality.[128] The process involves resorption of microscopic amounts of bone by osteoclasts (over a period of 2 to 3 weeks), followed by bone formation at the same site by osteoblasts (over a period of months); full mineralisation of the matrix requires even longer periods (years).[129] 10% of adult skeleton is remodelled each year.

Osteoporotic bone [28]

Osteoporosis means "porous bone". The density and quality of bone is reduced. Osteoporotic bones are therefore more brittle and prone to fracture.[121] This is illustrated in **FIGURE ONE**.

FIGURE ONE: Matrix diagrams of normal and osteoporotic bone



Normal Osteoporosis

What causes osteoporosis?

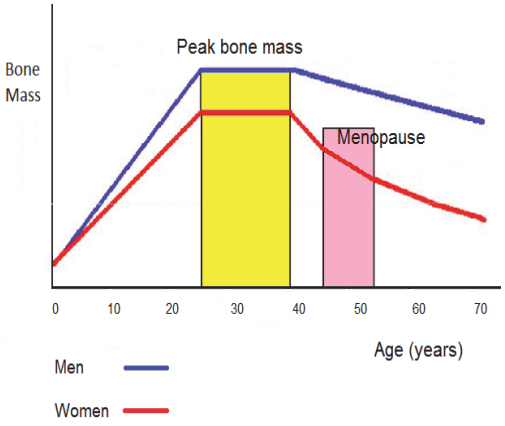
Osteoporosis is caused by an imbalance in the normal process of bone remodelling – breakdown of bone (by osteoclasts) is not sufficiently matched by new bone formation (by osteoblasts).[1] The age when

osteoporosis becomes apparent depends on peak bone mass and the rate at which bone is lost.[1]

Changes in bone mass

Peak bone mass is when bones are at their most dense. This occurs in the 20s to 30s. After skeletal maturity, bone mass begins to decrease with age. Women experience a phase of accelerated bone loss for approximately 3 years after the menopause. Afterwards this returns to the same rate as in men, i.e. 1% per year.[27]

GRAPH ONE: Changes in Bone Mass with Age
(Adapted from Compston JE, Clinical Endocrinology, 1990)[57]



Determinants of bone loss

After peak bone mass, the rate at which bone is lost depends on a number of factors, including:

- Genetic factors (50-85%)[67]
- Physical activity[6]
- Body mass[1]
- Hormonal status (reduced oestrogen or testosterone; hyperparathyroidism; reduced insulin-like growth factors)[1]
- Nutrition (calcium and vitamin D during life and in utero).[1]

Bone Mineral Density (BMD)

Bone mineral density (BMD) is a measure of the mineral content of bone. It is mostly calcium, but also comprises potassium, manganese, magnesium, strontium, selenium, and other minerals.[1]

How is osteoporosis diagnosed?

Osteoporosis is diagnosed either by measurement of BMD or based on the history of a non-traumatic fracture.[64] A diagnosis of osteoporosis is confirmed by dual energy X-ray absorptiometry (DXA).[1]

What are Dual-energy X-ray Absorptiometry (DXA) scans?

DXA is the most commonly used technique to measure BMD.[27] Two low dose X-rays are directed to the area of interest. These X-rays are absorbed to different extents by bone and soft tissue, allowing the density of bone to be calculated (g/cm^2).

From what site are measurements taken?

The femoral neck (hip) or spine are the preferred areas for measuring BMD, as per World Health Organisation (WHO).[1,5,27,62]

What results are obtained by DXA?

Results of a DXA scan are reported as T-scores and Z-scores.

T-scores: the difference (in standard deviations [SDs]) between the person's measurement and the reference standard for a healthy *young* adult, matched for gender and ethnic group.[167]

Z-scores: the comparison of the individual's BMD with an individual of the *same age* and gender.[27,167]

$$\text{T-score} = \frac{\text{Measured BMD} - \text{Young adult mean BMD}}{\text{Young adult population SD}}$$

$$\text{Z-score} = \frac{\text{Measured BMD} - \text{Age-matched mean BMD}}{\text{Age-matched population SD}}$$

Interpretation of DXA results

T-scores are used to assist in the diagnosis of osteoporosis using the WHO criteria as shown in **TABLE ONE**. BMD decreases with age, therefore an older person may have an average Z-score even if their bone density is low. The Z-score is therefore not as useful as the T-score in calculating fracture risk and making decisions about treatment.[1] Z-scores may however indicate secondary causes of osteoporosis.[1,167]

TABLE ONE: T-scores and WHO classifications [2]

T-score (SD)	Classification
≥ −1	Normal
−1 to −2.5	Osteopenia
≤ −2.5	Osteoporosis
≤ −2.5 plus one or more osteoporotic fragility fractures	Established (or severe) osteoporosis

What is osteopenia?

Osteopenia is a category of low BMD. It is useful for fracture risk assessment and for epidemiological studies, but it is not itself a disease.[3]

What are the symptoms of osteoporosis?

Osteoporosis itself is asymptomatic, and often remains undiagnosed until a fracture occurs.[1] Osteoporosis has been termed the 'silent epidemic' since there are no associated symptoms or warning signs prior to fracture.[28]

What is a fragility fracture?

A fragility fracture is a low-trauma fracture, i.e. mechanical forces that would not ordinarily result in fracture.[1,18] WHO has quantified this as forces equivalent to a fall from a standing height or less.[6,18] They are the clinically relevant outcome of osteoporosis.

Where do fragility fractures occur?

Skeleton is 80% cortical (dense) bone and 20% trabecular (marrow) bone. Osteoporotic fractures typically occur where there is significant trabecular bone. The most common sites of fragility fractures are:

- Spine (vertebrae)
- Hip (proximal femur)
- Wrist (distal radius).

They also occur in the arm (humerus), pelvis, ribs, and other bones. Fractures of the hands and feet (e.g. metacarpal and metatarsal fractures) are not generally regarded as osteoporotic fragility fractures.[1]

What is the prognosis following a fragility fracture?

Fragility fractures are associated with increased morbidity and mortality. Nearly 25% of people will die within one year of sustaining a hip fracture. Half will be left incapacitated and many fail to regain their previous level of independence.[64] People who have had a fragility fracture often report chronic pain and a reduced quality of life.[1,7,8]

Particular problems with fractures of the vertebrae

Fragility fractures of the vertebrae can be difficult to diagnose as they do not necessarily cause symptoms: around 50 to 70% are clinically silent and do not come to clinical attention.[8,9] Vertebral fractures can cause back pain, loss of height and kyphosis (abnormal curvature). Severe kyphosis can lead to breathing difficulties, gastrointestinal problems, difficulties in bending/reaching, and other activities of daily living.[8] If there is kyphosis, loss of height (more than 2 inches), or unexplained back pain, consider lateral X-ray of the spine to detect wedge and crush fractures.[1]

Causes of non-osteoporotic fragility fractures

Consider the following in differential diagnosis:

- Bone cancer — most commonly metastatic (e.g. breast cancer and prostate cancer)
- Multiple myeloma
- Other bone condition, e.g. osteomalacia and Paget's disease of bone.
- Previous trauma (if the person has one or more vertebral fractures).

Investigations for assessing underlying causes of fragility fractures:

Clinical assessment may indicate one or more of the following investigations:

- Lateral X-rays of the lumbar and thoracic spine — consider when there is spinal pain, loss of height, or kyphosis.[1]
- Full blood count and erythrocyte sedimentation rate.[1]
- Liver and renal function tests.[1]
- Bone function tests (serum calcium, phosphate, and alkaline phosphatase; 24-hour urinary calcium).[1]
- Serum vitamin D and parathyroid hormone (PTH) to assess for hyperparathyroidism.[1]
- Thyroid function tests.[1]
- Coeliac disease serology — if there is marked unexplained osteoporosis or clinical suspicion of coeliac disease.[1]
- Serum immunoglobulins and paraproteins, urinary Bence-Jones proteins — to assess for multiple myeloma, if there is a vertebral fracture.[1]
- Prostate specific antigen (PSA) to assess for prostate cancer in men with bone pain.[1]
- For hypogonadism:
    - In men: testosterone (on a 9:00 am specimen), SHBG (sex hormone-binding globulin), FSH (follicle stimulating hormone), and LH (luteinizing hormone).
    - In women: FSH (follicle stimulating hormone).[1]

TABLE TWO: Causes of secondary osteoporosis

Glucocorticoids (long-term use)[1]
Inflammatory bowel disease[1]
Coeliac disease (due to malabsorption)[1]
Drugs, e.g. aromatase inhibitors, progestogen only contraceptives, (e.g. medroxyprogesterone)[1], proton pump inhibitors[122], heparin, anticonvulsants, barbiturates, ciclosporin, tacrolimus, gonadotrophin-releasing hormone agonists, lithium and thiazolidinediones.[1] See below for further details *
Prolonged immobility[1]
Endocrine disorders, e.g. Type 1 diabetes, hyperthyroidism, hyperparathyroidism, and hypogonadal states[1]
Rheumatic and autoimmune conditions (Rheumatoid arthritis, ankylosing spondylitis, and systemic lupus erythematosus)[1]
Chronic liver disease[1]
COPD[1]
Haematological disorders[1]
Organ transplantation[1]
Neurological conditions, e.g. Parkinson's disease[1]
Genetic conditions, e.g. cystic fibrosis, Gaucher's disease, hemochromatosis, osteogenesis imperfect.[1]

Drugs and risk of osteoporosis*

Aromatase inhibitors (such as anastrozole, letrozole and exemestane) lower circulating oestrogen levels and they may cause a reduction in BMD with a possible subsequent increased risk of fracture. Women with osteoporosis or at risk of osteoporosis should have their BMD formally assessed at the commencement of treatment and at regular intervals thereafter. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored.
NB – this does not apply to treatment with tamoxifen.[61]

Medroxyprogesterone (Depo-Provera®)[1] reduces serum oestrogen levels and is associated with significant loss of BMD due to the effect of oestrogen deficiency on the bone remodelling system. Bone loss is greater with increasing duration of use, however BMD appears to increase after drug is discontinued and ovarian oestrogen production increases. In women of all ages, careful re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue use for more than 2 years.[170]

Proton pump inhibitors especially if used in high doses and over long durations (>1 year), may increase the risk of fracture, predominantly in the elderly or in presence of other recognised risk factors.[122] The MHRA Drug Safety Update April 2012 reported on two meta-analyses that suggested the risk of fracture is increased by 10–40% above baseline. The primary studies in these analyses have varied in the extent to which they have adjusted for other potential risk factors for fracture, and use of calcium or vitamin D.[171] Patients should have an adequate intake of vitamin D and calcium[122]

Risk Assessment of Fragility Fracture

Should routine screening of the population be carried out?

It is not recommended to routinely screen everyone for osteoporosis.[1] Instead, fracture risk should be assessed opportunistically when patients present to a healthcare professional for other reasons.[18]

What about screening for those at higher risk?

People at a high risk, particularly those with a fragility fracture, should be screened for the detection of osteoporosis, and treatment initiated to prevent further fragility fractures.[1]

Risk factors for fragility fracture

Reduced bone density is a major risk factor for fragility fracture. However, factors other than BMD scores are important and must be considered. Factors that can affect the risk of fragility fracture are shown in **TABLE THREE**.

TABLE THREE: Risk factors for fragility fractures

Risk factor	Reason
Female gender	Women are at greater risk than men[1]
Age	Risk increases with increasing age, and is at least partly independent of bone mineral density.
Bone mineral density (BMD)	The lower the BMD the higher the risk[1]
Previous osteoporotic fragility fracture	The greater the number of previous fractures the greater the risk[1,64]
Parental history of hip fracture	50-85% genetic link. Biggest risk factor [67]
Alcohol intake	The risk increases proportionally with the amount of alcohol consumed. NICE use a threshold of 4 units a day; NOGG and FRAX® use a threshold of 3 units a day[1]. Alcohol is one of the biggest risk factors in men.[64]
Rheumatoid arthritis (RA)	RA itself poses a risk, in addition to patients having a low BMD and receiving treatment with glucocorticoids.[1]
Body Mass Index (BMI)	The lower the BMI, the greater the risk. NICE use a threshold of 22 kg/m^2; the NOGG guidance uses a threshold of 19 kg/m^2
Smoking	Specified in the NOGG guidance, but not by NICE: the effect of smoking is large enough to warrant inclusion in FRAX®, and to support recommendations to quit smoking. However, it is not large enough to be included in decision rules such as those used in the NICE guidance.[1]
Glucocorticoids (used systemically over the long term)	This is taken into account in the NOGG guidance, but not in the NICE guidance (the scope of which excluded women using systemic glucocorticoids).[1]
Falls	An increased risk of falls is an important risk factor for fracture.[1]

Some risk factors act independently of BMD to increase fracture risk whereas others increase fracture risk through their association with low BMD – as indicated in **TABLE FOUR**.[59]

TABLE FOUR: NICE Clinical indicators of fracture risk

Independent of BMD	Indicators of low BMD
● Parental history of hip fracture. ● Alcohol intake of 3 to 4 units or more per day ● Rheumatoid arthritis.[1]	● Body mass index less than 22 kg/m^2 (NOGG recommends a threshold of 19 kg/m^2). ● Conditions such as ankylosing spondylitis, Crohn's disease. ● Rheumatoid arthritis ● Untreated hypogonadism in men and women ● Prolonged immobility ● Organ transplantation ● Type I diabetes ● Hyperthyroidism ● Chronic liver disease ● Chronic obstructive pulmonary disease [1,59]

When to use a DXA scan?

BMD should not be used routinely to assess fracture risk without prior assessment using a risk assessment tool.[18] NICE and NOGG guidance differ slightly on when a DXA scan should be used. This guidance is summarised below:

TABLE FIVE: NICE AND NOGG ADVICE IN RELATION TO DXA SCANNING

According to NICE

NICE does not stipulate when exactly to offer a DXA scan. However it does imply the following:

Women with a fragility fracture:
DXA scan is required to confirm osteoporosis (unless patient is over 75 years or clinician considers DXA scan to be clinically inappropriate or unfeasible).

Women without a fragility fracture:
DXA scan is required to confirm osteoporosis in the following age groups:

- ≥70 years with one independent clinical risk factor for fracture or one indicator of low BMD.
- 65 to 69 years who have one independent clinical risk factor for fracture.
- < 65 years who have one independent clinical risk factor for fracture and at least one indicator of low BMD.[1]

NB – in women aged 75 years or older it may sometimes be clinically inappropriate or unfeasible to organise a DXA scan, in which case the woman must have two or more independent clinical risk factors for fracture, or two or more indicators of low BMD before treatment can be started.
NICE guidance on osteoporotic fragility fractures applies only to postmenopausal women with osteoporosis.[1]

According to NOGG

These thresholds are for guidance only and the final decision to assess BMD or to initiate therapeutic

intervention lies with the individual clinician.

Women with a fragility fracture:
DXA is not required to confirm osteoporosis.[1]
(NOGG guidelines always recommend treatment)[1]

Men with a fragility fracture:
DXA scan is required to confirm osteoporosis.[1]

People without a fragility fracture:
Use the online FRAX® calculator to assess whether a DXA scan should be done.[1]

Osteoporosis in men

30% to 60% of osteoporosis in men is secondary to another underlying condition. The most common secondary causes are:

- Glucocorticoid use or hypercortisolism (i.e. Cushing syndrome or disease)
- Excessive alcohol use
- Hypogonadism
- Vitamin D deficiency/low calcium intake
- Smoking
- Family history of fracture. [64]

Therefore osteoporosis in men requires thorough investigation. All men at risk of osteoporosis or fracture should obtain a DXA scan for screening, i.e. men ≥70 years and men aged 50 to 69 with additional risk factors for osteoporosis.[64] Consideration should be given to referring men to specialist centres.

Other uses of bone densitometry

BMD measurement may also be useful for monitoring of treatment, determination of the extent of bone loss and assessment of suitability for certain treatments.[56]

Who should be screened?

Guidelines surrounding management of osteoporosis are not clear cut. Clinical decision is therefore required in many cases. Identifying who will benefit from preventative treatment for osteoporosis is imprecise. A number of risk assessment tools are available to predict fracture incidence over a period of time, and may be used to help decision-making.

Fracture risk assessment tools

FRAX® and QFracture® are both validated for use in the UK.[18] FRAX® can be accessed at: www.shef.ac.uk/FRAX. QFracture® can be accessed at http://qfracture.org.
Both tools estimate absolute risk of fracture as the predicted risk of major osteoporotic or hip fracture over 10 years, expressed as a percentage.[18] Above the upper age limits defined by the tools, people are considered to be at high risk of fragility fracture.[18]
They are intended for people not currently on treatment for osteoporosis.[19]

Which risk assessment tool to use?

It is not clear whether these tools are equally accurate and whether choice of tool should depend on circumstances.[18] FRAX® can be used for people aged between 40 and 90 years, either with or without BMD values.[18] QFracture® can be used for people aged 30 to 84 years; BMD values cannot be incorporated into the risk algorithm.[18]

Limitations of the assessment tools

These tools may not include all risk factors (e.g. living in care home, other medicines that affect bone metabolism), or may lack details of some risk factors (e.g. amount of alcohol consumed). The thresholds of these tools are also subject to some debate.[104]
These tools may *underestimate* fracture risk in circumstances including in people with:

- A history of multiple fractures
- Previous vertebral fracture(s)
- A high alcohol intake
- Taking high-dose systemic glucocorticoids (more than 7.5 mg prednisolone or equivalent per day for ≥3 months)
- Causes of secondary osteoporosis.[18]

Who to assess for risk of fragility fracture?

Consider using a risk assessment tool in the following:

- All women ≥65 years and all men ≥75 years.
- Women < 65 years and men <75 years with risk factors.
- People < 50 years with **major** risk factors, e.g. current or frequent recent use of oral or systemic glucocorticoids, untreated premature menopause or previous fragility fracture.[18]

FRAX®

Following the assessment of fracture risk using the FRAX® tool in the absence of BMD, the patient may be classified to be at low, intermediate or high risk. Intervention thresholds are depicted by the lines between the green and red areas. The intervention threshold at each age is set at a risk equivalent to that associated with a prior fracture and, therefore rises with age.[56]

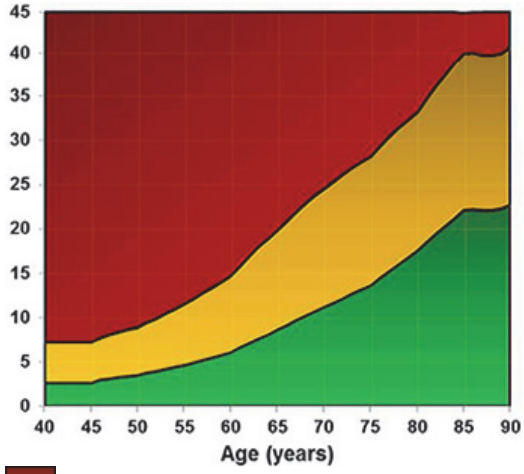
FRAX®: Assessment with/without BMD?

In the absence of BMD, clinical risk factors may be used to assess risk, making calculation of fracture risk possible at the time of consultation.[18] However, refinement of a patient's 10-year fracture risk may be required in those at medium risk.[18]
Currently, there are no studies that have evaluated whether the addition of BMD to FRAX® improves the accuracy of the predicted fracture risk.[18]

When to refer to secondary care?

- For people who do not meet the eligibility criteria in guidelines, but for whom drug treatment seems clinically indicated.[1]
- For people who are not able to use any of the drugs used in primary care to prevent osteoporotic fragility fractures.[1]
- For people with secondary osteoporosis.[1]
- For men with osteoporosis, especially younger men and those with severe disease.[1]

FIGURE ONE: Assessment without BMD 10 year probability of major osteoporotic fracture (%) (Taken from NOGG Guidance)



Low risk

BMD measurement by DXA is not recommended. The person can be reassured, offered lifestyle advice, and followed up after a minimum of 2 years (depending on their risk). Recalculate risk if risk factors change.[1,18,19,56]

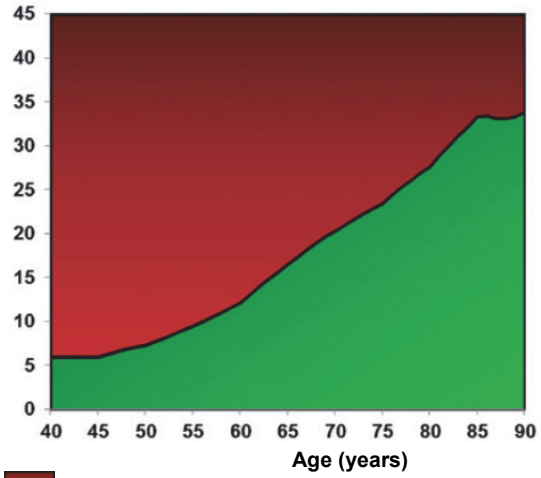
Medium risk

Measure BMD using DXA and recalculate the fracture risk to determine whether an individual's risk lies above or below the intervention threshold – see **FIGURE ONE**.[18,19,56]

High risk

People with probabilities above the intervention threshold should be considered for treatment.[56] NOGG guidance suggests that treatment without measuring BMD could be appropriate.
NICE guidance suggests that BMD be measured.[18,19] If measurement of BMD is not required prior to treatment initiation, a baseline BMD measurement may be considered to facilitate assessment of response to treatment.[1]

FIGURE TWO: Assessment with BMD 10 year probability of major osteoporotic fracture (%) (Taken from NOGG Guidance)



Lifestyle, Calcium & Vitamin D

What lifestyle advice should be offered?

Modifiable risk factors should be addressed.[104]
All people at risk of osteoporosis should be advised of the following:

- Diet – a balanced diet containing foods rich in calcium and vitamin D. Also ensure an adequate protein intake (as low protein intake has been associated with increased bone loss).[1,126]
- Exercise – regular, weight-bearing and tailored to the individual – will help to improve muscle strength, and reduce pain and stiffness. Walking, especially outdoors to increase exposure to sunlight (and so increasing vitamin D production) is a good option.[1,27]
- Stop smoking (for smokers)[1]
- Limit alcohol consumption[1]
- Falls – identify and modify factors that increase the risk of falling[1]

Preventing falls

Among the elderly, the greatest risk of fracture comes from falls, not osteoporosis.[54] Therefore preventing falls in susceptible people may be more important than treating a low BMD. Patients should be provided with appropriate walking aids if required.[27]
There are many factors that increase the risk of a fall which should be considered including:

- Adverse effects of medicines that impair alertness and balance [1]
- Hazards in the home, e.g. scatter mats, slippery floors, obstacles, insufficient lighting, and loose or absent handrails[1,27,53]
- Poor eye sight [1]
- Cardiovascular disease [1]
- Neurological disorders [1]

NB – not all fragility fractures are caused by falls: hip and vertebral fragility fractures may occur spontaneously or during routine activities, e.g. bending or lifting.[35]

Hip protectors

Hip protectors are plastic shields or foam pads that are worn under clothing to absorb impact during a fall.[24] They have been shown to reduce the incidence of hip fracture in residents of nursing homes.

Vitamin D and falls

In addition to its role in fracture reduction, vitamin D insufficiency has been found to be associated with

increased risk of a fall.[112] Supplementation has been found to reduce the risk of falls, likely through improved musculoskeletal function.[112-115]

What is the evidence for calcium and vitamin D in reducing risk of fracture?

Supplementation with calcium and vitamin D alone has been shown to reduce fracture rates in housebound elderly patients without previous fracture. Evidence in other patient groups is lacking.[104]

Calcium

The role of calcium

Calcium requirements increase with age, especially after the menopause. This is due to reduced intestinal absorption of calcium and increased renal calcium loss. The primary factor influencing the amount of calcium absorbed is the amount of calcium ingested.

Recommended daily intake

The average adult should aim for an intake of approximately 1000mg – 1200 mg of calcium per day (with those aged over 50 years aiming for 1200mg).[1] An average daily intake of 1000 mg of calcium can usually be met through food intake.

Who should take calcium supplements?

Most people should be able to obtain sufficient calcium from their food, without the need for calcium supplements. As a rough guide, if a person is consuming three or more servings of calcium-rich foods per day, then calcium supplementation may not be needed.

Elderly patients, living either at home or in care homes, may be at risk of calcium deficiency through poor diet.[64] Therefore calcium supplementation may be considered in this group, once assessing intake of calcium through diet.

A low calcium and/or vitamin D intake can be a common secondary cause of osteoporosis in men.[64] Therefore some men may benefit from calcium supplements.

Sources of calcium

Examples of foods containing relatively high amounts of calcium are shown in **TABLE SIX**.

TABLE SIX: Calcium-containing food [17,174]

Food	Portion	Calcium content (mg)
Milk (skimmed, semi-skimmed, whole)	200mL	240
Soya milk (plain)	200mL	26
Soya milk + calcium	200mL	180
Fruit yoghurt	125g	170
Hard cheese e.g. Cheddar, Edam	30g	225
Softer cheese e.g. Brie	30g	80
Milk chocolate	50g	110
White bread	4 x 30 g slices	200
Wholemeal bread	4 x 30 g slices	120
Baked beans	150g	80
Concentrated orange juice (unsweetened)	200mL	70
Porridge with milk	1 bowl	216
Figs (ready to eat)	30g	70
Pizza with cheese and tomato	9-10" (410g)	873
Whitebait, fried	80g portion	688

Caution: Calcium and renal impairment

Excessive calcium intake (> 2500 mg daily) should be avoided in people with impaired renal function.[1] However, in people with normal renal function, calcium intake of up to 2500 mg daily does not promote hypercalciuria or stone formation.[1]

Compliance issues

There are compliance issues with combination calcium/vitamin D products. There may be increased compliance with single agent vitamin D (due to a smaller tablet size). Supplementation with single agent vitamin D should be considered in people receiving sufficient calcium from food sources.

Cardiovascular disease and calcium and vitamin D supplements?

Recent observational studies have raised concerns about a possible association between calcium supplements and risk of cardiovascular events. The Heart Journal reported findings of the EPIC-Heidelberg study (2012), that increasing calcium intake from diet might not confer significant cardiovascular benefits, while calcium supplements might actually increase risk of myocardial infarction and should be taken with caution. However, there are limitations to the data and no change to prescribing practice is currently recommended.[58,168] That said, with the introduction of licensed vitamin D preparations, many clinicians are now moving away from the use of combined calcium and vitamin D preparations in favour of single agent vitamin D preparations (in patients who are calcium replete).

Vitamin D

The role of vitamin D

Vitamin D has two roles in bone health: it counter-regulates parathyroid hormone (a promoter of bone loss), and stimulates intestinal and renal calcium absorption.[64]

Sources of vitamin D

The main source of vitamin D is exposure of the skin to the sun.[1] Relatively few foods contain vitamin D, therefore it is generally not possible to meet the vitamin D requirement from diet alone. Diet, on average, provides 2 to 4 micrograms (80IU to 160IU) of vitamin D daily.[1] Oily fish (e.g. salmon, mackerel and sardines), eggs, meat, fortified breakfast cereals, soya products, dairy products, and low-fat spreads contain higher amounts of vitamin D.

Vitamin D conversions

Vitamin D may be expressed as either international units (IU) or micrograms.
One microgram is equivalent to 40 international units, i.e. 10 micrograms of vitamin D = 400 IU.

How long to spend in the sun?

The amount of vitamin D produced by the skin on exposure to the sun depends on skin type, the time of year and the time of day.[36] From April to October, short daily periods (10 to 15 minutes) of sun exposure without sunscreen are sufficient for most people to make enough vitamin D. Approximately 10,000 to

20,000 IU of vitamin D are produced within 30 minutes of exposure to sunlight in the summer.[125] The larger the area of skin that is exposed to sunlight, the more chance there is of making vitamin D before starting to burn. People with darker skin will need to spend longer in the sun to produce the same amount of vitamin D. In the winter months, vitamin D is obtained from body stores and food sources.[36]

Should vitamin D levels be routinely measured?

No, it is not recommended to routinely screen for vitamin D deficiency. This includes both the normal population and those in high risk groups.

Who should take vitamin D supplements?

The Department of Health issued guidance on at risk groups in 2010 – see 'Chief Medical Officer Advice'.

Chief Medical Officer Advice

The Department of Health has advised that the following patient groups take daily vitamin D supplements:

- All pregnant and breastfeeding women
- All babies and young children from six months to five years of age
- People aged ≥65 years
- People who are not exposed to much sun, e.g. those who cover their skin, or who are housebound or confined indoors for long periods
- People who have darker skin, e.g. those of African Caribbean and South Asian origin.[124]

People who are receiving drug treatment for osteoporosis (unless confident that the patient is receiving an adequate dietary intake) should receive vitamin D supplement (+/- calcium).[1,7,8] Pharmacological treatments for osteoporosis have been shown to reduce the risk of vertebral fracture when given with calcium and vitamin D supplements.[59] For people with osteoporosis, the recommended daily dose of vitamin D is 20 micrograms (800IU).

Prescribing Points with Calcium and/or Vitamin D products

►Some preparations contain soya (or soya bean) oil and are therefore unsuitable for people who are allergic to peanuts or soya.

► Oral vitamin D_3, i.e. colecalciferol, is the vitamin D of choice (rather than vitamin D_2 – ergocalciferol).[105]

► For conditions other than osteoporosis, consider prescribing Fultium D3® and Desunin® for patients requiring higher doses, e.g. 20,000IU, rather than ordering in expensive unlicensed specials.

► Adverse effects are generally related to the calcium content. They are mainly gastrointestinal disturbance — such as constipation, flatulence, nausea, gastric pain, and diarrhoea. Hypercalciuria (and rarely hypercalcaemia) may occur with long-term high doses. Colecalciferol supplements have been reported to cause occasional skin rashes.

Fultium D3® and Desunin® are *licensed* vitamin D (colecalciferol) products and are indicated as an adjunct to specific therapy for osteoporosis, at a dose of 800IU (20 micrograms) daily. These products should be prescribed in preference to a supplement where appropriate. [172,173]

Pharmacological Management of Osteoporosis

The two main classes of drugs used to treat osteoporosis are:

1. **Antiresorptive agents** (agents that block bone resorption by inhibiting the activity of osteoclasts). These include bisphosphonates, denosumab, raloxifene, and calcitonin.
2. **Anabolic agents** (agents that stimulate bone formation by acting primarily on osteoblasts). These include parathyroid hormone and teriparatide.

GRAPH TWO: Prescribing of agents to manage osteoporosis in Northern Ireland in 2012/2013

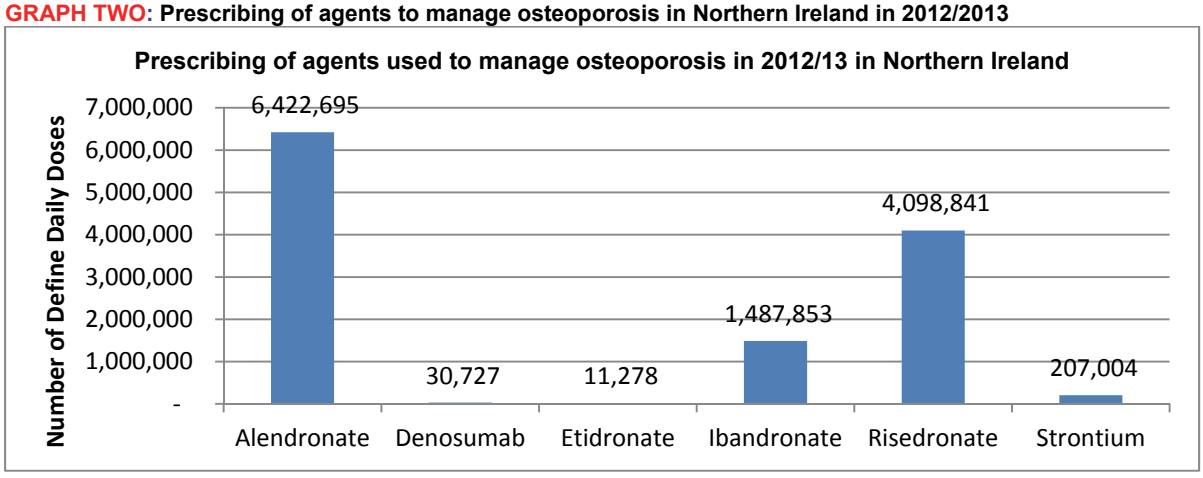


TABLE SEVEN: Cost of osteoporosis treatments for one year [51,52]

Drug	Preparation	Administration frequency	Cost (£)
Alendronate	Generic 10mg tablets	Daily	17.40
	Generic 70mg tablets	Weekly	10.92
	Fosamax® 10mg tablets	Daily	277.44
	Fosamax® 70mg tablets	Weekly	273.60
	Generic 70mg/100mL oral solution	Weekly	273.60
Risedronate	Generic 5mg tablets	Daily	160.32
	Generic 35mg tablets	Weekly	14.40
	Actonel® 5mg tablets	Daily	215.88
	Actonel Once a Week®	Weekly	229.44
Ibandronate	Bonviva® 150mg tablets	Monthly	220.80
Disodium etidronate	Didronel PMO®	Daily	79.56
Denosumab	Prolia® 60mg injection	6 monthly	366.00
Strontium ranelate	Protelos® 2g sachets	Daily	307.20
Teriparatide	Forsteo® injection	Daily	3262.56
Raloxifene	Evista® 60mg tablets	Daily	238.36
Zoledronate	Aclasta® IV infusion	Yearly	253.38

Bisphosphonates

Mechanism of action of bisphosphonates

Bisphosphonates are adsorbed onto hydroxyapatite crystals in bone. In doing so they decrease osteoclast-mediated bone resorption, and therefore reduce the rate of bone turnover.[1,51,64]

Bioavailability of bisphosphonates

Bisphosphonates are minimally absorbed following oral administration –1 to 5% of the administered dose.[1,64] Therefore, for optimal absorption, bisphosphonates must be taken on an empty stomach.

How effective are bisphosphonates?

Alendronate, risedronate and etidronate have been shown to reduce the risk of vertebral fracture (when given with calcium and vitamin D supplements). Alendronate and risedronate have been shown to also reduce the risk of non-vertebral fractures, in some cases specifically at the hip.[59]

SIGN guidance summarised several RCTs on numbers needed to treat (NNT) with bisphosphonates for both primary and secondary prevention of fractures, see **TABLE EIGHT**.[17]

TABLE EIGHT: Summary of RCTs evaluating the effectiveness of drug therapies in reducing fracture incidence in postmenopausal women[17]

Fracture	Therapy	BMD	NNT
Women with multiple vertebral fractures, but no DXA scan			
Vertebral fractures	Risedronate	-	10 to 20
Non-vertebral fracture	Risedronate	-	32
Women with low BMD established by axial DXA, and with at least one vertebral fracture			
Vertebral fracture	Alendronate	Femoral neck T=< -1.6	15
Hip fracture	Alendronate	Femoral neck T=< -1.6	90
Women with low BMD determined by axial DXA, with or without previous non-vertebral fracture			
Vertebral fracture	Alendronate	Femoral neck T=< -1.6	60
Vertebral fracture	Alendronate	Femoral neck T=< -2.5	35
Hip fracture	Alendronate	Femoral neck T=< -2.5	81
Non-vertebral fracture	Alendronate	Femoral neck T=< -2.5	54
Hip fracture	Risedronate	Femoral neck T=< -2.7	78
Non-vertebral fracture	Risedronate	Femoral neck T=< -2.7	43

E.g. in the last RCT: out of 43 patients with a low BMD (defined as T-score ≥2.7 in this study) who receive prophylactic therapy with risedronate, 1 patient will not develop a non-vertebral fracture.

Which oral bisphosphonate to choose?

Four oral bisphosphonates are currently marketed for the treatment of osteoporosis[1]:

- Alendronate (10 mg once daily or 70 mg once weekly)
- Risedronate (5 mg once daily or 35 mg once weekly)
- Ibandronate (150 mg once monthly)
- Etidronate (400 mg daily for 14 days, by elemental calcium, 500 mg daily for 11 weeks, as part of a 90-day cyclical regimen)

Oral alendronate or risedronate are both considered first line choices in Northern Ireland.[37] NICE recommend generic alendronate as first-line bisphosphonate of choice. However, since publication of the NICE Technology Appraisals, generic risedronate has become available, making it a cost effective option.[49]

Monthly oral ibandronate is an alternative option for younger patients who have predominantly spinal osteoporosis (no data is available for hip fracture).[135]

Intravenous bisphosphonate options

Two intravenous bisphosphonates are currently marketed for the treatment of osteoporosis:

- Zoledronic acid (Aclasta®) – 5mg once-yearly
- Ibandronic acid (Bonviva®) – 3mg every 3 months [51]

Both are listed as a **RED** medicine in the Red / Amber list in Northern Ireland for the treatment of osteoporosis.[39]

Intravenous administration ensures that treatment is correctly delivered and avoids the stringent administration instructions required for oral bisphosphonates. A single infusion of zoledronic acid appears to ensure efficacy for at least 1 year and probably longer. The practicability and acceptability of annual intravenous therapy in large numbers of patients remains to be tested.[134]

Bisphosphonate intolerance

NICE defines intolerance as persistent upper GI disturbance that is sufficiently severe to warrant discontinuation of treatment, where instructions for administration have been followed correctly.

Patients should not have their bisphosphonate discontinued without good reason. In cases of intolerance, a trial of another agent should be tried.

It may be worth changing the calcium/vitamin D supplement to establish if this is the cause of the GI disturbance.[104]

Studies have shown that oesophageal reactions may be less common with risedronate.[130-132] Indeed, risedronate may be preferable in those patients that have a history of (recent) proven peptic ulcer disease, active GORD, or who develop significant GI side effects on alendronate.[7,133,135]

Adherence issues with bisphosphonates

Long term adherence to osteoporosis treatment is poor.[3] A significant decline after the first year of treatment is often seen.[8] Therefore patients should be encouraged to continue taking their bisphosphonate.[1]

A reminder that bisphosphonate treatment is long term, for the prevention of fragility fracture, should be reinforced.[1]

Attempts to improve adherence include the development of weekly, monthly, three-monthly and annual bisphosphonates and injectable formulations.[166]

Daily or weekly alendronate/risedronate?

In trials lasting 2 years, the same effect on BMD was seen and both were equally well tolerated.[29-33]

For alendronate and risedronate, the weekly formulations are commonly prescribed (despite differences in licensed indications).[1]

Administration issues

There are complicated administration protocols that must be adhered to with bisphosphonates – see Administration Points. Patients who are unable to comply with these protocols are unlikely to be suitable candidates for bisphosphonate therapy.[17]

Administration Points with bisphosphonates

► Take on an empty stomach (as absorption is affected by food, drink, and other drugs)[1]

► The tablet must be swallowed whole and taken with a glass of plain water (at least 200 mL). It must not be sucked or chewed.

► Take while in an upright position, and do not lie down for 30 to 60 minutes (depending on the bisphosphonate – see SPCs).[1]

► Bisphosphonates must not be taken at bedtime or before getting up in the morning.[1]

► When to take:

- Alendronate – at least 30 minutes before the first food, other medicinal product, or drink (other than plain water) of the day.
- Risedronate – at least 30 minutes before the first food, other medicinal product, or drink (other than plain water) of the day
- Ibandronate – after an overnight fast (of at least 6 hours) and 1 hour before the first food, other medicinal product, or drink (other than plain water) of the day
- Etidronate – at the midpoint of a 4-hour fast[1]

► For once-weekly and once-monthly preparations, they should be taken on the same day each week or month respectively.[1]

How to manage missed doses of bisphosphonates?

For once-weekly preparations:

Take the missed tablet on the day that it is remembered. Continue taking one tablet once a week, on the day the tablet is normally taken. Do not take more than two tablets on the same day.[1]

For once-monthly preparations:

If the next scheduled dose is more than 7 days away, the missed tablet should be taken on the morning after it is remembered. The person should then continue taking one tablet once a month on their originally scheduled date.

If the next scheduled dose is within the next 7 days, ignore the missed dose and continue taking one tablet once a month as originally scheduled. The person should not take two tablets within the same week.[1]

What follow up is required on bisphosphonates?

Follow up 2 to 3 months after starting treatment.[1]

Consider repeating BMD measurement with DXA scan at 2 years and 5 years after treatment initiation.[1] (T-scores are unlikely to change significantly over shorter intervals).[1] It is not necessary to measure BMD if the result is unlikely to affect management decisions.[1] If the new BMD is below the pre-treatment level, assess adherence and consider alternative treatment.[1]

Are bone turnover markers helpful?

Measuring bone turnover markers to assess response to treatment is sometimes used in secondary care; it is not recommended for routine primary care.[1]

What if a patient develops a fracture while taking treatment?

A fracture does not necessarily indicate treatment failure.[1]Treatment *reduces*, but does not eliminate, the risk of fracture. Indeed, if the person has been taking treatment for at least a year, it may already have prevented one or more fractures.

Adherence issues should be addressed and/or consideration given to an alternative drug.[1]

NICE defines an unsatisfactory response as when a patient has another fragility fracture despite adhering fully to treatment for one year and there is evidence of a decline in BMD to below pre-treatment baseline.[18] An alternative treatment should then be considered.[1]

Prescribing Points with oral bisphosphonates

►Before starting treatment, calcium, phosphate, alkaline phosphatase and renal function should be checked[135]

► Advise patients that if they experience any signs or symptoms of possible oesophageal reaction (e.g. dysphagia, pain on swallowing, retrosternal pain, or new/worsened heartburn) to stop taking the bisphosphonate and seek medical advice.[1]

► Advise patients that if they experience any signs or symptoms of possible atypical stress fracture (e.g. thigh, hip or groin pain) to seek medical advice.

► The patient's diet should contain sufficient calcium; if not, a calcium supplement, 500 mg/day, should be given in the evening.

► Pharmacokinetics: plasma half-life is one hour, however they remain in bone for much longer. Bisphosphonates are bound to the bone and their elimination half-life may be up to 10 years.

► Bisphosphonates remain in the bone for many years, raising concerns that maternal bone stores could be mobilised during pregnancy.[60] Therefore bisphosphonates are unsuitable for women who are pregnant or considering a family after treatment.

► Regular dental check-ups are advised. Patients should be told to inform their dentist that they are taking a bisphosphonate, particularly if they are going to undertake invasive dental procedures.[1]

►The need to continue bisphosphonate treatment for osteoporosis should be re-evaluated periodically based on the benefits and potential risks of therapy for the individual patient, particularly after 5 or more years of use.[23] Treatment should generally not exceed 10 years. A proper indication is needed, otherwise the benefit-risk ratio may not be advantageous.[1,28,18,117,135,136]

► Caution with concomitant use with a NSAID as both are associated with gastrointestinal irritation.[43,44]

► Adverse effects: flu-like symptoms, hypocalcaemia, impaired fracture healing, inflammatory eye disorders[80]

► Contraindications: hypocalcaemia, pregnancy or breastfeeding, severe renal impairment, any abnormalities of the oesophagus or other conditions which could delay oesophageal emptying (e.g. stricture, Barrett's oesophagus, or achalasia; inability to stand or sit upright for 30-60mins).

See SPCs for full details.[1]

Renal impairment and bisphosphonates

Clearance is 80% renal and 20% bone. Caution is therefore required in renal impairment:

- Alendronate – avoid if eGFR <35mL/min[43]
- Risedronate – avoid if eGFR < 30mL/min[44]
- Ibandronate – avoid if eGFR < 30mL/min [55]

Avoid in patients receiving dialysis.

Safety issues with bisphosphonates

Bisphosphonates have been associated with several serious adverse effects, which have warranted MHRA safety alerts – see summaries in 'MHRA warnings with bisphosphonates' box.

What is bisphosphonate-related osteonecrosis of the jaw (BRONJ)?

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is defined as exposed bone in the maxillofacial region for more than eight weeks in the absence of radiotherapy but in the presence of bisphosphonate use.[120]

What is the incidence of BRONJ?

The incidence is thought to be (at worst) 'rare' (occurring in ≥ 1/10,000 to< 1/1,000).[21]

A national study on avascular necrosis of the jaw, (including BRONJ) estimated the incidence of BRONJ in the UK population (62 million people) to be in the region of 620 (508-793) cases a year.[21]

What are the risk factors for BRONJ?

A history of trauma (extractions), dental surgery and dental infection appear to precipitate BRONJ.

With intravenous bisphosphonate administration, the extent and duration of exposure to bisphosphonates seems to correlate with the risk. The cumulative risk from long-term oral bisphosphonates is unknown.[21]

Other risk factors for developing BRONJ include steroid treatment, immunosuppression (e.g. methotrexate), co-morbidity such as rheumatoid arthritis, smoking and poor periodontal health.[21]

Is withholding bisphosphonate prior to dental treatment helpful?

Briefly withholding bisphosphonate treatment before dental surgery is unlikely to be of benefit due to the prolonged effect of bisphosphonates.[80]

MHRA warnings with bisphosphonates

Jaw Osteonecrosis (November 2009)

Osteonecrosis of the jaw may be a particular risk for people with cancer who are receiving intravenous bisphosphonates. Poor oral hygiene should be managed (with advice or dental referral), and specialist advice obtained if major dento-alveolar surgery is planned.[1]

Atypical fractures (June 2011)[46]

Bisphosphonates might increase the risks of fracture of the shaft of the femur.[1] Any increase in the risk of atypical subtrochanteric fractures is more than offset by the decreased risk of fracture of the hip and other sites.[1]

Oesophageal cancer

The risk of oesophageal cancer is low, and does not outweigh the benefits of treatment.[1,47]

Atrial fibrillation (July 2008)

Clinical trial results have suggested an increased risk of atrial fibrillation for zoledronic acid (Aclasta®), pamidronic acid, and possibly for alendronic acid. The balance of risks and benefits for bisphosphonates remains favourable

What are atypical stress fractures?

Atypical stress fractures occur in relatively unusual locations for osteoporotic fragility fractures, often in the middle or upper third of the femur (thigh bone).[28] They often occur spontaneously, after little or no force. In many cases there is a history of pain at the site of fracture for a few weeks or months. In some cases the fractures affected both sides and were often slow to heal.[28,119]

A possible link between bisphosphonates and atypical stress fractures?

Bisphosphonates slow down the rate at which bone is destroyed and replaced, by reducing the activity of osteoclast cells that break down bone. Although this is a useful process to prevent bone loss and fractures, there are concerns that over a prolonged period of time, this may result in bones becoming 'older' and more brittle.[28,119]

What is the risk of atypical stress fracture?

They have been a small number of reports of atypical stress fractures in patients treated with alendronate for osteoporosis. In most cases, patients had been taking alendronate for three years or more.[28] At present it is uncertain whether these fractures are directly related to treatment with alendronate, but an association has not been excluded. [28] Atypical fractures are considered a class effect of the bisphosphonates.

Overall, the absolute risk of developing an atypical stress fracture with bisphosphonate therapy is thought to be much lower than the number of osteoporotic fractures that bisphosphonate therapy prevents. However, discontinuation of bisphosphonate therapy should be considered if a patient develops an atypical fracture while on treatment, based on an assessment of risk and benefits of bisphosphonates for the individual.

What are the risk factors for atypical fractures?

Reports of atypical stress fractures have been mainly in patients on long-term therapy. Duration of bisphosphonate use is therefore considered an important risk factor.[80,109] Additional risk factors include treatment with glucocorticoid or proton-pump inhibitors.[108-110]

Duration of bisphosphonate treatment?

The optimum duration of bisphosphonate therapy has not been established. Concerns about rare but serious side effects of long-term treatment, together with limited evidence that bisphosphonates actually prevent fractures after 4 to 5 years of treatment, has led to a cautious approach.

The need to continue bisphosphonate treatment for osteoporosis should be re-evaluated periodically, based on the benefits and potential risks of therapy for the individual patient, particularly after 5 or more years of use.[23] Treatment should generally not exceed 10 years. A proper indication is needed, otherwise the benefit-risk ratio may not be advantageous.[1,28,18,117,135,136]

How soon after stopping treatment are benefits lost?

At treatment discontinuation, bone loss resumes. The rate of bone loss varies across the drugs. Bone markers remain suppressed but return to pre-treatment levels over time. If alendronate is stopped, its benefits on BMD reduce over a period of 3 to 5 years. Whether this equates to fracture protection is unknown. However, an abrupt increase in fracture risk has not been reported.[1,87,104,118]

Discontinuation of risedronate therapy after 2 years in young postmenopausal women has been shown to result in significant bone loss at both spine and hip during the first year after treatment is stopped.[161] The effects of stopping therapy in older women or after longer treatment intervals are not known. Discontinuation of oestrogen therapies, raloxifene and teriparatide are associated with immediate and substantial decreases in BMD.[145,162,163]

TABLE NINE: Risks for fragility fractures in patients receiving treatment

Low risk of fragility fracture	Higher risk of fragility fracture
● Cause(s) of secondary osteoporosis has been removed ● T-score has improved to >-2.5[1] ● BMD currently above the threshold for treatment, or has substantially improved during treatment ● No previous fracture ● No fragility fracture within last 12–24 months ● Low risk of falls ● Younger than 70 years of age, (as treatment could potentially be required at a future point)[1]	● A major risk factor (e.g. rheumatoid arthritis) remains ● T-score ≤-3.5 ● No improvement of T-score on treatment ● Previous fracture ● High risk of falls[1]

What about 'drug holidays'?

Given the concerns over long-term treatment with bisphosphonates, some clinicians have advocated a 'drug holiday', i.e. stopping treatment for a year or two and re-assessing the need for further treatment (with the original or an alternative drug).[8,64,104] This is supported by the theory that bisphosphonates continue to exert anti-resorptive effects for an unknown period of time after discontinuation of treatment. However, this is reliant on prior good concordance with treatment.[104] There is currently no evidence from trials to support drug holidays. [8,64,104]

When to consider a drug holiday?

People at a relatively lower risk for fragility fractures are potential candidates for drug holidays. However, for people at higher risk, the benefits of continuing therapy probably far outweigh the risk of harm. [8,64,104] See **TABLE NINE**.

Follow up if bisphosphonate is discontinued:

Consider obtaining specialist advice.[1]

The nitrogen containing bisphosphonates (alendronate, risedronate and ibandronate) have a long half-life in bone. Alendronate appears to have the longest half-life and may remain in bone for years. There is presently insufficient evidence to give clear definitive directions regarding drug holidays. However, if considering a drug holiday, local practice tends to be a two year break with a repeat DXA scan after two years.

Neither FRAX® nor QFracture® has been validated in patients who have received treatment. Therefore the predictive power of these tools to assess fracture risk in such circumstances is unknown.[18] However these assessment tools may be worth considering in re-assessing risk of fracture within 2 to 3 years after discontinuation.[80]

Other drug therapies

Denosumab

What is denosumab licensed for?

Denosumab (Prolia®) is licensed for the treatment of osteoporosis in postmenopausal women at increased risk of fractures.[40]

Mechanism of action

Denosumab is a monoclonal antibody. It blocks Rank Ligand (a substance involved in bone development) that stimulates the activity of osteoclasts.[28] By inhibiting osteoclast formation this thereby decreases bone resorption.[51]

Pharmacokinetics of denosumab

Denosumab has very different pharmacokinetics from bisphosphonates. Denosumab concentrations peak in the first 1 to 3 weeks after administration, decline over 4 to 5 months, with minimal levels at the end of its dosing interval (6 months). [64]

When to consider denosumab?

Denosumab may be considered as a treatment option after an appropriate therapeutic trial of at least two generic bisphosphonates.
Denosumab may be considered both for primary and secondary prevention of osteoporotic fractures in postmenopausal women.

For primary prevention, patients should comply with particular combinations of BMD, age, and independent risk factors for fracture (see **TABLE FOUR**, p4), as indicated in the full NICE technology appraisal (www.nice.org.uk/TA204), as summarised in **TABLE TEN.**

TABLE TEN: Combination of risk factors for denosumab treatment in relation to T-score

Age (years)	Number of independent risk factors		
	0	1	2
65-69	a	-4.5	-4
70-74	-4.5	-4	-3.5
≥75	-4	-4	-3
(a) treatment with denosumab not recommended			

For secondary prevention, denosumab is recommended as a treatment option only in postmenopausal women at increased risk of fractures who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments.[12]

Red/amber status

Denosumab is listed as an **AMBER** medicine on the Interface Pharmacy Red Amber list in Northern Ireland.[39] The first dose of denosumab should be given in secondary care. A Shared Care Guideline (SCG) is available to assist transfer of care to primary care: http://www.ipnsm.hscni.net/library/DenosumabSCGNov12.pdf.[38]

Atypical stress fractures

Atypical femoral fractures have been reported rarely in patients with postmenopausal osteoporosis receiving long-term (≥2.5 years) treatment with denosumab 60 mg (Prolia®) in a clinical trial.[50]

Prescribing Points with denosumab

► Administration: 60 mg every 6 months by subcutaneous injection.[51]
► Monitoring is not routinely required – see SCG.[38]
► May cause hypocalcaemia (fatal cases reported).[51] Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Patients with severe renal impairment (eGFR < 30 mL/min) or receiving dialysis are at greater risk of developing hypocalcaemia. Clinical monitoring of calcium levels is recommended for patients predisposed to hypocalcaemia.[40]
► Renal failure is not a contraindication to using denosumab.[1] However, there is an increased risk of hypocalcaemia if eGFR < 30 mL/min—monitor plasma-calcium concentration[51]
► Consider dental check-up and carry out invasive procedures before initiating treatment.[51]
► Patients may develop skin infections (predominantly cellulitis) leading to hospitalisation. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.[40]
► Denosumab has a half-life of 26 days. It is cleared from the body in most patients after 6 months.[40] It may therefore be considered in preference to bisphosphonates in women considering a family after treatment.
► Side effects include: diarrhoea, constipation, dyspnoea, urinary tract infection, upper respiratory tract infection, pain in extremity, sciatica, hypophosphataemia, cataracts, rash, sweating, diverticulitis and ear infection.[51]

MHRA warnings with denosumab (Prolia®)[50]

Full details can be found on the MHRA website (http://www.mhra.gov.uk)

Atypical femoral fracture with long-term use (February 2013)

During denosumab treatment, patients presenting with new or unusual thigh, hip or groin pain should be evaluated for an incomplete femoral fracture. Discontinuation of denosumab therapy should be considered if an atypical femur fracture is suspected, while the patient is evaluated.

Raloxifene

Mechanism of action

A selective estrogen receptor modulator (SERM). Raloxifene mimics the action of oestrogen, giving protection to bones, while simultaneously blocking the effect of oestrogen on other organs, such as the uterus and breast.[28]

When to consider raloxifene?

Raloxifene may be considered for *secondary* prevention of osteoporotic fracture as an alternative for women in whom alendronate, risedronate or etidronate are contra-indicated or not tolerated and who comply with particular combinations of BMD, age, and independent risk factors for fracture, as indicated in NICE guidance www.nice.org.uk/TA161 and summarised in **TABLE ELEVEN**.[7]

NB: Raloxifene is not recommended for *primary* prevention of osteoporotic fractures in post-menopausal women.[8]

Does raloxifene have any effect on menopausal vasomotor symptoms?

Raloxifene does not relieve menopausal vasomotor symptoms and may make them worse in some women.[1,27]

Evidence for raloxifene?

Raloxifene has been shown to reduce the risk of spine (but not other) fracture, and may reduce the risk of breast cancer. [27]

TABLE ELEVEN: Combination of risk factors for raloxifene treatment in relation to T-score

Age (years)	Number of independent risk factors		
	0	1	2
50-54	a	-3.5	-3.5
55-59	-4	-3.5	-3.5
60-64	-4	-3.5	-3.5
65-69	-4	-3.5	-3
70-74	-3	-3	-2.5
≥75	-3	-2.5	-2.5
(a) treatment with raloxifene not recommended			

Prescribing Points with raloxifene

► Dose: 60 mg/day continuously[27]
► It may be taken with food[27]
► A sufficient intake of calcium is recommended[27]
► It may increase the risk of deep vein thrombosis.[27] Therefore it is contraindicated in people with an active or past history of venous thromboembolic events (VTE), including deep vein thrombosis, pulmonary embolism and retinal vein thrombosis.

Strontium ranelate

What is strontium ranelate?

Strontium is an alkaline metal similar to calcium and naturally present in trace amounts in bone.[148] Strontium ranelate is composed of two atoms of strontium combined with a carrier molecule, ranelic acid.

What is strontium ranelate licensed for?

Strontium ranelate (Protelos®) is licensed for the treatment of osteoporosis in postmenopausal women to reduce the risk of vertebral and hip fractures and for the treatment of osteoporosis in adult men at increased risk of fracture.[41]

Mechanism of action

Strontium ranelate differs from other treatments because of its two-fold action. It increases bone formation and reduces bone resorption. These two actions lead to a rebalance of bone turnover in favour of bone formation. [28,51,148,149]

Red/amber status

Strontium does *not* appear on the Red/Amber list in Northern Ireland.[39] However it should only be initiated by a physician with experience in the treatment of osteoporosis.[41]

When to consider strontium ranelate?

Strontium ranelate is currently recommended as an alternative for women in whom alendronate, risedronate or editronate are contra-indicated or not tolerated and who comply with particular combinations of BMD, age, and independent risk factors for fracture (see **TABLE FOUR**, p4), as summarised in **TABLES TWELVE and THIRTEEN**.[51]

Updated cautions with strontium ranelate

Recent MHRA cautions may limit the use of strontium is some patient groups – see MHRA warning box. Strontium ranelate should not be used in patients with: ischaemic heart disease, peripheral arterial disease; cerebrovascular disease; a history of these conditions; or in patients with uncontrolled hypertension. Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with strontium ranelate after careful consideration.[45]

TABLE TWELVE: Combination of risk factors for strontium treatment in relation to T-score – Primary prevention

Age (years)	Number of independent risk factors		
	0	1	2
65-69	a	-4.5	-4
70-74	-4.5	-4	-3.5
≥75	-4	-4	-3
(a) treatment with strontium not recommended			

TABLE THIRTEEN: Combination of risk factors for strontium treatment in relation to T-score – Secondary prevention

Age (years)	Number of independent risk factors		
	0	1	2
50-54	a	-3.5	-3.5
55-59	-4	-3.5	-3.5
60-64	-4	-3.5	-3.5
65-69	-4	-3.5	-3
70-74	-3	-3	-2.5
≥75	-3	-2.5	-2.5
(a) treatment with strontium not recommended			

Prescribing Points with strontium ranelate

► The contents of one sachet should be taken in a glass of water and drank immediately[41]
► Avoid food for 2 hours before and after taking the granules[51]
► Do not use a DXA scan to assess BMD after strontium has been started as strontium in bone affects BMD measurements.[1]
► Renal impairment: avoid if eGFR < than 30 mL/min[51]
► Strontium should not be used in patients with established, current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.[41]
► Strontium should not be used in patients with uncontrolled hypertension.[41]
► Strontium should not be used in patients with temporary or permanent immobilisation e.g. due to post-surgical recovery or prolonged bed rest.[41]
► Intolerance of strontium ranelate is defined as persistent nausea or diarrhoea, either of which warrants discontinuation of treatment.[7]

MHRA warnings with strontium ranelate

Risk of serious cardiac disorders (April 2013)
A review of available safety data for strontium raised concerns about the cardiovascular safety of strontium, beyond the already recognised risk of venous thromboembolism. An analysis of RCT data has

identified an increased risk of serious cardiac disorders, including myocardial infarction. The EMA is to evaluate the benefits and risks of strontium in the coming months. In the meantime, in order to help minimise these risks, updated advice from the MHRA is available at: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON266148 [45]

Strontium ranelate (Protelos): should not be used in patients with current or previous venous thromboembolism (VTE) or temporary or permanent immobilisation because of risk of VTE. Rare serious skin reactions may occur within the first weeks of treatment (May 2012)
Strontium ranelate (Protelos) is known to increase the risk of venous thromboembolic events (VTE) and should not be used in patients with current or previous VTE, including deep vein thrombosis and pulmonary embolism, or in patients with temporary or permanent immobilisation (e.g. post-surgical recovery or prolonged bed rest). The need for continued treatment with strontium ranelate should also be re-evaluated in patients over 80 years who have been diagnosed at risk of VTE. [24]

Risk of severe allergic reactions (December 2007)
Severe allergic reactions, including drug rash with eosinophilia and systemic symptoms (DRESS), have been reported. DRESS starts with rash, fever, swollen glands, and increased white cell count, and it can affect the liver, kidneys and lungs; DRESS can also be fatal. Patients should be advised to stop taking strontium ranelate and consult their doctor immediately if skin rash develops. Treatment with strontium ranelate should not be restarted.[51,127]

Teriparatide and parathyroid hormone

Two forms of recombinant human parathyroid hormone are available: teriparatide (Forsteo®) (a fragment of parathyroid hormone containing 34 amino acids) and the intact 84 amino acid form, Preotact®.

What is teriparatide licensed for?
Teriparatide (Forsteo®) is licensed for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture. It is also licensed for the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture.[42]

Mechanism of action
Administering parathyroid hormone or teriparatide might seem counterintuitive as endogenous parathyroid hormone increases serum calcium, (partially by increasing bone resorption) and chronically elevated parathyroid hormone will deplete bone stores. However, intermittent exposure activates osteoblasts more than osteoclasts. Therefore teriparatide has a net effect of stimulating new bone formation, leading to increased BMD.
Teriparatide is an anabolic treatment option for osteoporosis and results in significant improvement of BMD and reduction in the incidence of vertebral and non-vertebral fracture.[28,64] Bone loss will occur after discontinuation.[145,146]

Red/amber status?
Both parathyroid hormone (Preotact®) and teriparatide (Forsteo®) are listed as **RED** medicines on the Interface Pharmacy Red Amber list in Northern Ireland for osteoporosis.[39]

When to consider teriparatide?
Teriparatide is not for primary prevention of osteoporotic fractures. It may be considered for secondary prevention of osteoporotic fractures as an alternative for women in whom alendronate, risedronate, editronate, or strontium ranelate are contra-indicated or not tolerated, or where treatment with alendronate, risedronate or editronate has been unsatisfactory (indicated by another fragility fracture and a decline in BMD despite treatment for 1 year) and who comply with particular combinations of BMD, age, and number of fractures, as indicated in the NICE guidance www.nice.org.uk/TA161.

Calcitonin
Calcitonin is no longer recommended for the treatment of postmenopausal osteoporosis as the benefits are outweighed by the risk of malignancy associated with long-term use.[51]

Oestrogen therapies (HRT and Tibolone)

Mechanism of action of HRT
HRT replaces oestrogen (and sometimes progesterone) in women. HRT is an effective treatment for menopausal symptoms that also offers protection against fractures at both hip and spine.[28,51]

When to consider Hormone Replacement Therapy?
Hormone replacement therapy (HRT) is an option where other therapies are contra-indicated, cannot be tolerated, or if there is a lack of response. HRT should not be considered first-line therapy for long-term prevention of osteoporosis in women over 50 years of age.
In women using HRT for relief of menopausal symptoms it is accepted that the HRT benefit normally exceeds risk irrespective of the potential bone effect, which will be an additional benefit.[28,51]
For postmenopausal women under the age of 60, who do not have risk factors for breast cancer, heart disease, stroke or venous thromboembolism, the risks associated with HRT are low. HRT is of most benefit for the prophylaxis of postmenopausal osteoporosis if started early in menopause and continued for up to 5 years.
However, the majority of women who are affected by osteoporosis are over the age of 60. HRT is therefore not considered a suitable treatment for osteoporosis in this group.[28,51]

Mechanism of action of tibolone?
Tibolone is metabolised into three compounds which all contribute to the pharmacological effects of tibolone. Two of these metabolites have oestrogen-like activity, whereas the third metabolite has progestogenic and androgenic-like activities. Tibolone substitutes for the loss of oestrogen production in postmenopausal women, and alleviates menopausal symptoms.
Tibolone (Livial®) prevents bone loss following menopause or oophorectomy and reduces the risk of fracture.[153,154]

When to consider tibolone?

Tibolone is licensed for the prevention of osteoporosis in postmenopausal women at high risk of fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.[152]

Risk of stroke and breast cancer with tibolone and HRT

In younger women, the risk profile of tibolone is broadly similar to that for conventional combined HRT. For women older than about 60 years, the risks associated with tibolone start to outweigh the benefits because of the increased risk of stroke. See MHRA caution warning box.

MHRA Drug Safety Updates with tibolone

Increased risk of breast cancer recurrence (February 2009)
Tibolone increases the risk of breast cancer recurrence in women with a history of breast cancer. Tibolone should not be used in women with known or suspected breast cancer, or in those with a history of breast cancer.

Increased risk of stroke (September 2007)
Increased risk of stroke in older women should be taken into account in prescribing decisions.

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COMPASS THERAPEUTIC NOTES ASSESSMENT
Management of Osteoporosis

COMPASS Therapeutic Notes are circulated to GPs, nurses, pharmacists and others in Northern Ireland. Each issue is compiled following the review of approximately 250 papers, journal articles, guidelines and standards documents. They are written in question and answer format, with summary points and recommendations on each topic. They reflect local, national and international guidelines and standards on current best clinical practice. Each issue is reviewed and updated every three years.
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Successful completion of these assessment questions equates with **2 hours** Continuing Professional Development time. Circle your answer TRUE (T) or FALSE (F) for each question. When completed please post this form to the relevant address shown overleaf. Alternatively, you can submit your answers online:

- **Doctors and nurses** should submit their answers at: **www.medicinesni.com**
- **Pharmacists** should submit their answers at: **www.nicpld.org**

1	**In relation to background and diagnosis of osteoporosis:**			
	a	Density and quality of bone are both reduced in osteoporosis	T	F
	b	Women experience reduced bone loss for approximately 3 years after the menopause	T	F
	c	Genetics factors are the main determinant of bone loss	T	F
	d	A T-score of -2 confirms the diagnosis of osteoporosis	T	F
2	**In relation to risk assessment of fragility fracture:**			
	a	People at high risk should be screened for the detection of osteoporosis	T	F
	b	Alcohol is one of the biggest risk factors in men	T	F
	c	A risk assessment tool such as FRAX® or QFracture® should be used to assess fracture risk before using a DXA scan	T	F
	d	FRAX® or QFracture® are intended for people currently on treatment	T	F
3	**In relation to lifestyle, calcium and vitamin D:**			
	a	All elderly people should receive a calcium and vitamin D supplement	T	F
	b	Supplementation with calcium and vitamin D has been shown to reduce fracture risk in all patient groups	T	F
	c	Patients on pharmacological treatments for osteoporosis do not need to receive calcium or vitamin D supplements	T	F
	d	Vitamin D levels should be measured in at risk patient groups	T	F
4	**In relation to bisphosphonates:**			
	a	Bisphosphonates are almost completely absorbed following oral administration	T	F
	b	Bisphosphonates may be used in patients with severe renal impairment	T	F
	c	Atypical fractures usually occur soon after initiation of treatment	T	F
	d	Bisphosphonates may be considered in women who are contemplating having a family	T	F
5	**In relation to other therapies:**			
	a	Denosumab should be used only in patients with a fragility fracture	T	F
	b	Strontium ranelate should not be used in patients with ischaemic heart disease, peripheral arterial disease; cerebrovascular disease; a history of these conditions; or in patients with uncontrolled hypertension.	T	F
	c	Hormone Replacement Therapy should be considered in women over 60 years of age as a suitable treatment for osteoporosis	T	F
	d	Teriparatide may be used for both primary and secondary prevention	T	F