Osteoporosis and fracture risk: a practical guide for management in the neurology clinic

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# Abstract

Many people with neurological disorders are at high risk of osteoporosis and fragility fractures. Such fractures are a leading cause of disability and premature mortality. There are a variety of underlying mechanisms, including reduction in bone mineral density from biomechanical factors (e.g. reduced muscle strength), inflammation and/or medications such as glucocorticoids, together with increased risk of falls. Neurologists are well-placed to initiate measures to protect bone health. In this review article, we address the epidemiological associations between bone health, fracture risk and different neurological disorders; and elucidate the potential underlying mechanisms. We set out overarching principles for the management of bone health in the context of neurological disorders, together with guidance for specific diseases.

# Key words

osteoporosis; epidemiology; neurological disease; fracture

# Key points

1. People with neurological disorders often have increased risk of fragility fractures.
2. Personalised fracture risk may be calculated using the FRAX® calculator.
3. Intervention thresholds are age-specific and inform the need for bone density scanning and treatment.
4. All suitable patients with high fracture risk should be offered lifestyle advice plus calcium and vitamin D supplementation.
5. Oral bisphosphonates are considered for initial treatment where swallowing is intact.
6. When oral bisphosphonates are not appropriate, parenteral antiresorptives are an alternative.
7. For patients at very high fracture risk, referral to an osteoporosis clinic is recommended for consideration of anabolic therapy.

# Further reading

1. **NOGG guidelines:** Gregson CL, Armstrong DJ, Bowden J, Cooper C, Edwards J, Gittoes NJL, Harvey N, Kanis J, Leyland S, Low R, McCloskey E, Moss K, Parker J, Paskins Z, Poole K, Reid DM, Stone M, Thomson J, Vine N, Compston J. UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos. 2022 Apr 5;17(1):58. 1
2. **FRAX®:** Schini M, Johansson H, Harvey NC, Lorentzon M, Kanis JA, McCloskey EV. An overview of the use of the fracture risk assessment tool (FRAX) in osteoporosis. J Endocrinol Invest. 2024 Mar;47(3):501-511.2

# Introduction

Neurological disorders have a substantial impact on disability, mobility, quality of life and are associated with an increased risk of fragility fractures 3, often as a consequence of falls (the incidence of falls is reported to be 2-4 times higher in patients with neurological disorders) 4, 5. Falls are particularly a feature of certain common neurological disorders, such as Parkinson’s disease 6and peripheral neuropathy 7.

Osteoporosis is defined as: ‘A systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture’ 8. This conceptual definition was followed by the World Health Organization’s operational definition, originally for epidemiological use, based on bone mineral density (BMD) from dual-energy x-ray absorptiometry (DXA). Thus a BMD which is 2.5 or more standard deviations below the mean value of young healthy woman (i.e. a T-score of -2.5 or below) constitutes osteoporosis 9. The site scanned may be the proximal femur or lumbar spine, with the femoral neck the reference site 10. The distal forearm may be used if other sites are not appropriate. Osteoporosis is more common in patients with long-term neurological conditions, while sudden neurological events such as stroke and spinal cord injury can cause rapid bone loss 11. Osteoporosis and the associated fracture risk is often underestimated in neurological disease 12.

This review outlines neurology practice essentials on the diagnosis and management of osteoporosis in patients with common neurological disorders.

# Determinants of increased fracture risk in neurological disorders

There are a wide range of underlying mechanisms, which can be broadly considered as factors related to:

* osteoporosis risk, falls risk, or both.
* neurological disease, or its treatment.

*Physical mobility:* Disuse and immobilisation result in reduced mechanical strain, inhibiting osteoblast-mediated bone formation while accelerating bone resorption. In stroke patients, low levels of mobility on the paretic side results in regional bone loss, whereas the effect on the non-paretic side may be variable dependent upon the overall amount of weight-bearing exercise and mobility 13. With many neurological conditions balance issues, reduced mobility, leg weakness and fatigue result in increased risk of falls. These factors may interact, for example in multiple sclerosis; the risk of falls is greatest at intermediate levels of disability, and reduces as activity levels and overall mobility decline 14-17.

*Vitamin D:* Low levels of vitamin D are common in the UK and worldwide 1819, although biochemical and musculoskeletal consequences of vitamin D deficiency are rare outside of particular high risk groups such as those who have pigmented skin and/or are covered in the UK20. Many neurological disorders are particularly associated with vitamin D deficiency including multiple sclerosis 21, Parkinson’s disease 22, Alzheimer’s disease 23. The association may be due to a general effect of immobility on sun exposure and eating habits. Whilst vitamin D supplementation has not been shown to reduce fracture risk in the general population, profound deficiency may lead to osteomalacia, with increased risk of insufficiency fractures, and reduced response to anti-osteoporosis medications 20, 24.

*Antiseizure medication (ASM):* A possible mechanism for cytochrome inducing ASMs is the hepatic induction of the cytochrome P450 enzyme system leading to catabolism of vitamin D 25, 26. Cumulative exposure to ASMs, duration of therapy, use of multidrug regime, and gender are additional risk factors that need to be considered 27, 28. Data on the effect of specific ASMs on BMD and bone markers remain conflicting. Phenytoin has been associated with secondary hyperparathyroidism and increased bone remodelling 29. Lamotrigine, sodium valproate and carbamazepine appear less implicated 29. However, in other studies, these ASMs had a negative effect on vitamin D levels in adults with epilepsy and data on the changes in BMD are conflicting in regard to carbamazepine and sodium valproate 27, 30-33. Levetiracetam was shown not to decrease BMD in a recent meta-analysis 34, 35.

*Anticoagulants*: Warfarin, in a number of small studies, was associated with an increased risk of vertebral and hip fractures but these findings remain conflicting 36-39. Direct oral anticoagulants (DOACs) are associated with a significantly lower risk of fractures compared to warfarin; this may be attributable to the effect of warfarin on Vitamin K 40. NOACs might be preferable in patients with high fracture risk, where appropriate to use, but it should be noted that the evidence of the negative effect of warfarin on bone remains sparse 40.

*Glucocorticoids:* A seminal meta-analysis published over two decades ago clearly demonstrated increased fracture risk occurring rapidly within 3-6 months after initiating glucocorticoid treatment, persisting during the treatment period and decreasing within months after cessation 41. The increase in fracture risk is observed for vertebral and nonvertebral fractures, is partially independent of BMD, is dose dependent, but present even for low doses less than 5 mg per day 42. Evidence is very limited with regard to high-dose methylprednisolone pulses. Comparable BMD measurements were found on patients receiving regular high dose methylprednisolone pulses compared to those receiving pulses on relapses only; sample size was small 43. Although unrelated to osteoporosis it is worth noting here the need to counsel patients regarding the risk of avascular necrosis, which is a leading cause of litigation in neurology. 44

*Antidepressants:* These are associated with increased fracture risk, either via a direct effect on bone health or falls, or both. Serotonin receptors are presents on bone cells. Evidence suggests that tricyclic antidepressant use is associated with a greater risk to falls initially and less of an impact on BMD, whereas selective serotonin reuptake inhibitors potentially have a longer term impact on bone health 45, 46.

*Proton pump inhibitors (PPIs)* These have been associated with fracture risk, and although the causal associations have not been directly ascertained in human clinical studies, epidemiological associations and laboratory investigations suggest that they should be used carefully in patients with high fracture risk 47, 48. The balance of risk should be carefully considered, since glucocorticoids also increase the risk of gastrointestinal bleeding and many neurologists would consider co-prescription of a PPI. Recent guidance in Practical Neurology outlined risk factors for gastrointestinal bleeding and it would be prudent to recommend that medication reviews are in place to ensure that PPIs are stopped when they are no longer required 49.

# Fracture risk assessment in the neurology clinic

## From BMD to absolute fracture probability

Whilst osteoporosis has a definition based on BMD, as described above, BMD alone identifies only a modest proportion of individuals who go on to experience a fragility fracture. The reason for this is that the proportion of the population with a BMD T-score of -2.5 or below is small. However, there are far more people above this threshold but still with a negative T-score, each of which are individually at lower risk than those with T-score below -2.5, but, as a population, contribute far more fractures. For this reason, BMD (and so densitometrically defined osteoporosis) is now viewed as one of several risk factors for fracture rather than an indication for treatment 50. The approach to clinical assessment therefore now focuses on the ascertainment of an individual's absolute risk of fracture, based on clinical risk factors and incorporating BMD where this is available.

The most widely used tool to calculate an individual’s risk of fracture is FRAX®, which estimates an individual's 10-year-probability of hip fracture or major osteoporotic fracture (hip, forearm, proximal humerus, vertebra), based on readily obtainable clinical risk factors 51. BMD can be included if available. The model integrates the risk of fracture with risk of death over a 10-year time horizon. In patients with life expectancy of less than 10 years, it provides an estimate of their lifetime risk of fracture. It was derived using 9 international cohorts and has been designed to be implementable globally, currently available in models calibrated to 85 regions internationally. It can be accessed online via <https://www.fraxplus.org/>. It was formally validated on a similar number of international cohorts and has been further validated in numerous studies since 52. FRAX is currently implemented in over 100 guidelines globally53.

FRAX® is the preferred tool for predicting fracture risk in the general population, and forms the basis of intervention thresholds in the UK National Osteoporosis Guideline Group (NOGG) recommendations 1. NICE guidance also considers the QFracture tool, which was developed and validated purely on single UK primary care data sets. Unlike FRAX®, QFracture does not include BMD as an input variable, and cannot be directly linked to intervention thresholds, substantially limiting its use 52,54-56.

## Overview of the approach to risk assessment

In the neurology clinic, if individual risk factors (outlined in **Table 1**) suggest the need for formal bone health assessment, the first step is to complete a risk assessment using FRAX®, incorporating BMD obtained from a DXA scan if available. We recommend that published NOGG recommendations be used to guide further action 57. When the FRAX score is completed via the fraxplus.org website, the result can be automatically transferred to the NOGG nomogram. **Figure 1** summarises the management from risk assessment to treatment and long-term considerations.

NOGG has set age-specific thresholds for intervention, which level off from age 70 years upwards. The FRAX® probability threshold for intervention at any age is equivalent to the 10-year fracture probability for a woman at that age conferred by having had a prior fracture, with an average body mass index, and other risk factors set to “no”, with BMD not considered. The premise for this threshold is that the majority of guidelines recommend treatment of older individuals if they have had a prior fragility fracture. The same thresholds are used for women and men on the basis of equity and health economic justification1. The NOGG nomogram contains three elements if BMD is not included (**Figure 2**). The green zone suggests reassurance and optimisation of lifestyle factors, the amber zone suggests obtaining a BMD measurement to refine the risk estimate, and the red zone suggests treatment is recommended. The red treatment zone is further subdivided into “high risk” and “very high risk”, the latter indicating that assessment by a specialist might well be warranted . After BMD is included in the FRAX® calculation, the NOGG recommendations then become low risk, high risk or very high risk.

A brief clinical examination to assess thoracic kyphosis and the patient's ability to correct it is important; a thoracic kyphosis may result from muscle weakness, degenerative disc disease, or vertebral fractures.

## When to measure BMD and other investigations

DXA should be performed on all patients who may be at increased risk of fragility fracture, particularly when indicated through the NOGG algorithm. This means those with intermediate, high, or very high risk on the nomogram.

Where local capabilities allow “Vertebral Fracture Assessment” by DXA, which is a lateral radiographic view of the spine, this should be requested also. The VFA approach permits detection of occult vertebral fractures, only a third of which ordinarily come to clinical attention, but which are major risk factors for future fracture if present 58.

Prior to any intervention it is also appropriate to measure baseline renal, liver, and thyroid function, as well as serum levels of calcium, phosphate and vitamin D. Investigations to exclude secondary causes of osteoporosis should also be considered, particularly if a fracture is sustained on osteoporosis treatment (**Table 2**).

## Specific considerations in risk evaluation beyond FRAX®

FRAX® permits risk assessment based on a modest number of clinical risk factors, together with BMD if available. Importantly, the FRAX® probability arising and subsequent recommendations do not remove the need for individualised clinical assessment and decision making. In the neurology clinic, there will be further risk factors which should be considered. For some of these, strategies have been delineated with which to incorporate the additional risk associated with them. Where a clinical judgement has been made to modify the FRAX probability, the result can be manually viewed on the NOGG nomogram (nogg.org.uk/manual-data-entry).

### Glucocorticoids

**Table 3** documents multipliers that can be used to modify FRAX® probability to account for the dose of oral prednisolone (once the glucocorticoids box is ticked). The following individuals treated with glucocorticoids should be considered for anti-osteoporosis medication, regardless of FRAX probability.

* Anyone with a prior fragility fracture.
* Women aged ≥ 70 years.
* Post-menopausal women, and men aged ≥ 50 years, prescribed high doses of glucocorticoids, i.e., ≥ 7.5 mg/day of prednisolone or equivalent for over a 3 month duration.

Since bone loss occurs early after starting glucocorticoids, it is important that anti-osteoporosis medication is started at the commencement of glucocorticoid therapy, where there is likely to be a commitment to at least 3 months glucocorticoid medication.

### Other medications

As outlined above, other medication used in neurology may be associated with increased fracture risk. However, this risk is not quantified in a way that can be incorporated directly into risk assessment. It is recommended that the presence of these medications is considered in the overall clinical view of risk. Where appropriate these drugs may be minimised, but that of course needs careful assessment of the primary indication.

### Specific neurological conditions

Again, this risk has not been quantified in a way that can be numerically incorporated into fracture risk assessment. Elderly women with Parkinson’s Disease are at increased fracture risk2, 59; it is suggested that selecting the "rheumatoid arthritis" input in FRAX® may be a reasonable option to capture excess fracture risk associated with Parkinson’s Disease and other neurological diseases, independent of BMD. The approach of selecting the “rheumatoid arthritis” has been recommended for type 2 diabetes also; this option reasonably proxies diabetes effects on fracture risk 60. Importantly, the secondary osteoporosis channel in FRAX only contributes to the risk estimate in the absence of a BMD measure.

### Number of falls

Prior falls increase subsequent fracture risk. FRAX does not account for the presence or absence and number of falls when assessing fracture risk. Simple arithmetic procedures to adjust major osteoporotic fracture and hip fracture risk predictions from FRAX are available ( in a simple rule of thumb, for MOF FRAX adjustments, multiply by 1.2, 1.3 and 1.7 when there is history of 1, 2, or 3 falls respectively; for hip fracture probabilities, the multipliers would be 1.2, 1.5,and 2.0, respectively) 61.

*FRAXplus®* is a new tool which allows modification of FRAX® probability to account for additional risk factors, such as the recency and site of a prior fracture, and dose of glucocorticoids, number of falls amongst several others. The various multipliers have been documented and can be used manually, but FRAXplus® provides an automated approach, at the time of writing, on a pay for credit basis 2.

## Premenopausal women and men below 50 years

Age is a major determinant of absolute fracture probability. Thus, although a T-score of -3 will relatively increase a person’s risk of fracture at a young age compared with a person of the same age with normal BMD, the absolute fracture probability will still be low. However, a T-score of -3 at the age of 25 years is likely to translate into a substantial lifetime risk of fracture. The approach to managing bone health in younger individuals is therefore more complex, and should be addressed on a case-by-case basis, with input from the metabolic bone clinic if appropriate. Although there is no convincing evidence that anti-osteoporosis medications may cause harm to the foetus in pregnancy, these drugs may be generally avoided, and when used in premenopausal women, appropriate contraceptive advice should be given. Historically in the UK, we have often held off specific anti-osteoporosis treatments in younger patients, unless there has been a fragility fracture. Minimisation of fracture risk is achieved through optimal treatment of the disease, ideally with steroid-sparing agents. Expected remaining life span is also an important consideration.

The clinical assessment should be a two-way dialogue with the patient, incorporating all these various considerations. Several scenarios may play out: in young patients with very high fracture risk but limited lifespan and (if female) no aspirations for pregnancy, then anti-osteoporosis treatment now may prevent a painful and unpleasant fracture event in the coming few years. Alternatively in the context of very high lifetime fracture risk, but modest immediate 10-year risk (because of young age), judicious use of anti-osteoporosis medications may well be helpful in order to address fracture risk lifelong. Anabolic (bone building) agents may be considered in younger individuals with very low bone mineral density, with a view to mitigating high lifetime risk of fracture, even in the absence of a prior fracture event. For those with very severe life limiting diseases, with majorly impaired mobility, the benefits of fracture risk reduction may simply not be realised. Specific aspects of medications are discussed below.

# Management (Figure 2)

Whilst there is a dearth of evidence for the use of anti-osteoporosis medications in specific neurological conditions, there is no reason to suppose that this absence of evidence denotes evidence of lack of effect. Thus, appropriate non-pharmacological and pharmacological management should be undertaken to reduce fracture risk based on clinical judgement, informed by the available evidence.

## Non-pharmacological approaches

*Exercise and physical activity:* Research supports the benefit of exercise on falls reduction and bone health in neurology patients, with more robust evidence in stroke patients. In stroke patients, weight-bearing exercises enhance mobility, paretic muscle strength, and maintain femoral BMD, while balance and aerobic strengthening exercise increases tibial bone content and cortical thickness. 62, 63. Quick recovery and higher motor function within the first 6 months of a moderate stroke was associated with less bone loss 64. Although exercises may improve functional status, this is not shown to be linked to reduced fracture risk in stroke patients 65. Facility-based training is more beneficial than community or home-based training for reducing falls, improving balance and gait function in early diagnosed Parkinson’s Disease and multiple sclerosis patients 66-69 Tai chi and yoga improve postural stability in Parkinson’s Disease patients 70. In the general population, a recent meta-analysis favoured exercise for its positive effect on the risk of major osteoporotic fractures, while specifically high intensity training significantly improved lumbar spine BMD 71, 72. Combining low- to moderate-impact weight-bearing exercises with progressive resistance and/or agility training is most effective for enhancing hip and spine BMD, preventing bone loss, and improving functional ability in older adults 73. However, the variability in study designs and exercise characteristics prevents reliable recommendations for exercise protocols to reduce fractures in neurology patients.

*Diet and lifestyle:* Patients at increased risk of fracture, in general, should aim for a daily calcium intake of around 500-1000mg per day and sufficient dietary protein 74. A daily dose of at least 800-1000 IU cholecalciferol is recommended 74. Although any beneficial effect on fracture risk is likely to be minimal in the absence of overt nutritional deficiency, these approaches reduce the risk of such deficiency and are the backdrop to which the majority of anti-osteoporosis medications were trialled24. Where there are concerns over calcium supplementation, for example inability to tolerate it, then a pure vitamin D supplement, together with augmented dietary calcium intake, may be a reasonable alternative 75, 76. In older adults, there is evidence that large intermittent doses of vitamin D (≥60,000 IU) are associated with increased falls risk 77, 78, so oral daily dosing is the preferred option wherever practicable.

*Smoking and alcohol intake:* Smoking cessation may reduce the risk of vertebral and hip fractures in women, and smoking cessation advice should be offered to patients at risk 79, 80. National guidelines recommend alcohol intake is limited to ≤ 2 units/day, as, in adults with previous alcohol dependence, BMD is significantly lower, but improves following 3-4 years of abstinence 81, 82.

## Pharmacological approaches (Table 4)

### Bisphosphonates

Bisphosphonates are synthetic analogues of the naturally occurring compound pyrophosphate and bind strongly to hydroxyapatite (the crystalline component of bone tissue), inhibiting bone resorption by inactivating osteoclasts 83. The most commonly prescribed oral bisphosphonate is alendronate. Upper GI side effects are uncommon if taken as advised (in the morning with a glass of water, 45 minutes before food, drink or other medications and remaining in an upright seated position (or standing) for about 30-60 minutes after the dose). However, for those who are unable to tolerate oral bisphosphonates, or in whom they are contraindicated (for example inability to sit upright, achalasia, oesophageal stricture, malabsorption or dysphagia), then an intravenous (IV) bisphosphonate, such as zoledronate (given yearly in a dose of 5mg by infusion over a minimum of 15 minutes) is an alternative. A common regimen is a 5 mg dose annually for 3 years, followed by subsequent doses guided by bone turnover markers, if available, and bone density scanning. Serum calcium, vitamin D levels and renal function should be monitored at baseline and annually before initiating and before each dose of IV bisphosphonate.

### Denosumab

Denosumab, a fully humanised antibody to receptor activator of nuclear factor kappa B ligand (RANKL) is a newer antiresorptive agent 83. RANKL, secreted by osteoblasts, is a major activator of osteoclastic bone resorption and mimics the action of osteoprotegerin (OPG). It is administered as a subcutaneous injection once every six months and its efficacy has been demonstrated in patients with renal impairment, although due consideration should be given to the possibility of underlying renal bone disease in CKD 4-5. Symptomatic hypocalcaemia may rarely occur, particularly if the patient is vitamin D deficient, or has renal impairment. Importantly, when denosumab is stopped, particularly after more than a few doses, there is a risk of rapid bone loss, which, very rarely, results in multiple vertebral fractures 84. It is essential that the dosing frequency of every six months plus or minus two weeks is maintained. Denosumab is therefore often most appropriately used in older patients where it can be continued lifelong (e.g. 10 years or more, without a strict requirement to stop at 10 years). If it does need to be stopped, then this should be undertaken under the advice of a metabolic bone clinic, most often covered with 2 doses of zoledronate 6 months apart 85. As for parenteral bisphosphonates, serum calcium, vitamin D levels and renal function should be checked before each dose. While denosumab may be used in severe renal impairment, it should be used with care because of the risk of profound hypocalcaemia.

### Selective Oestrogen Receptor Modulators (SERMs) – Raloxifene

Raloxifene is a selective oestrogen receptor modulator that has antiresorptive estrogenic effects on the skeleton without the unwanted risks of estrogen in the breast 83. Its use is also associated with a significant decrease in the risk of breast cancer. It has been shown to be effective in preventing post-menopausal bone loss and in preventing vertebral fractures. However there is little evidence that raloxifene prevents hip or non-vertebral fractures 86. Adverse effects include leg oedema, cramps, hot flushes and a two to threefold increase in the risk of venous thromboembolism.

### Hormone replacement therapy/menopausal hormone therapy

The evidential landscape regarding hormonal treatment in perimenopausal women has altered hugely in both directions over the last 50 years 87. The favourable effects of such treatment on women’s bone health, at least whilst using the medication, is demonstrated beyond doubt 87. Women who have had a hysterectomy may use oestrogen alone, with a slightly more favourable safety profile than oestrogen and progestogen combination therapy, which is required for uterine protection otherwise.87 Overall though, the safety profile for less than 10 years use post-perimenopause and under the age of 60 years, in the absence of key risk factors (relating to cardiovascular and cancer risks) is often favourable. Newer guidelines reflect this more permissive approach, and management is usually undertaken between primary care and the gynaecology clinic rather than solely in the neurology, or indeed, rheumatology service 87.

#### Adverse effects of anti-resorptives

Atypical femoral factures of the subtrochanteric region and femoral shaft may rarely occur in patients taking bisphosphonates or denosumab 83. These are usually located in the lateral cortex around which endosteal thickening may be observed prior to fracture occurrence. Individuals may have prodromal pain, and fractures typically are transverse, sometimes bilateral and may occur after minimal trauma. They appear more commonly in patients taking these therapies for a prolonged duration. Overall, the fragility fractures prevented greatly outnumber those atypical events potentially resulting from medication 88. Osteonecrosis of jaw is extremely rarely observed during therapy for osteoporosis (<1/100,000/yr) for individuals on oral bisphosphonates 89, but occurs more commonly when higher doses of bisphosphonates are given intravenously for treatment of bone metastases. A causal link to bisphosphonates is unproven but international guidance suggests a prudent approach, encouraging patients to maintain good oral hygiene and have regular dental visits, with invasive dental work performed before commencement of bisphosphonate or denosumab therapy 90.

### Teriparatide, abaloparatide and romosozumab

These medications are anabolic agents, which actively build new bone 91. They are administered as subcutaneous injections, with dosing as outlined in Table 3. In the UK, teriparatide use is predicated by NICE on age, BMD and fracture history; abaloparatide, which is only recently approved by NICE, on the basis of very high fracture probability assessed by FRAX; romosozumab may be used in severe osteoporosis where a major fracture has occurred in the last 2 years. Teriparatide is licensed for use in men and women and for glucocorticoid-induced osteoporosis. Abaloparatide and romosozumab are currently only licensed for women in the UK. All these agents can be used first line in patients at very high risk of fracture (within specific guidelines) and are used for a limited time. In the majority of cases they should be followed by antiresorptive therapy. Such use would be instigated and supervised through a specialist metabolic bone clinic, but it is useful for a neurologist to know the indications for referral.

# Approach to long-term management

Current UK guidance has moved towards a reassessment of the need for treatment after 3-6 years of intravenous bisphosphonate/subcutaneous denosumab, and 5-10 years of oral bisphosphonate 1. For high-risk patients, continuation of treatment is usually warranted, but in lower risk settings, where there have been no incident fractures and bone mineral density has improved, a modest period (1-2 years) without treatment may be recommended. In the context of neurological disease, postmenopausal women and older men are likely to be at lifelong high fracture risk and therefore any pause in treatment, as is sometimes advocated in individuals who become low risk, may well be inappropriate 1, 92. If there is a decision to pause treatment at any point, this must be in the context of a long-term plan to reassess risk within 1 to 2 years. A summary of the NOGG approach is present in **Figure 2**.

For patients with neurological disease, there may well be other considerations such as young age, and progressive limitations to swallowing and ability to sit upright. The latter may require transition from oral to parenteral medications. The reduction in falls risk with increasing immobility should also be considered. The rationale for intervention in premenopausal women and younger men is discussed earlier in this article. The key imperative is that the approach to bone health is viewed through a lifetime horizon. For younger patients, this may well mean periods on medication and periods off, but this must be undertaken through an integrated lifelong management plan to minimise fracture risk.

# When to refer to a metabolic bone service

Referral to a specialist metabolic bone service should be considered for patients with a FRAX probability in the ‘very high’ zone of the NOGG nomogram, for assessment and consideration of anabolic treatment. Referral might also be considered where there are complex comorbidities and therapeutic decisions, or patients have continued to experience fragility fractures on medication. 93 Additional reasons may include contraindication to oral and/or parenteral bisphosphonate therapy, young onset of osteoporosis, atraumatic vertebral fracture despite normal BMD or suspicion of other metabolic bone disease.

# Case Study example

68-year-old female who presents to neurology outpatient clinic for a routine follow up appointment. She has a past medical history of hypertension, Parkinson’s Disease for the past 5 years and she is currently on Carbidopa-Levodopa to manage her symptoms. She reports a history of a recent fall, from standing position, as she missed a step coming downstairs at home. Following further enquiries, this was her second fall in the past year. She has never been on oral corticosteroids; she does not smoke or drink alcohol. Her weight is 65kg and her height is 160cm. She has no parental history of hip fracture. She is complaining of back pain. Examination demonstrates some tenderness at the level of T8. Blood tests demonstrate no abnormalities.

Taking the above information into account, her FRAX score (without any adjustments and before BMD measurement) is: 14 % for a MOF and 3.3 % for a hip fracture (Risk factors for osteoporosis include: age, Parkinson’s Disease (answer “Yes” to “rheumatoid arthritis” check box) (Case History Case History Figure A).

Screens screenshot of a computer

AI-generated content may be incorrect.

Case History Figure A: Questionnaire used to calculate 10-year probability of fracture without BMD; Risk factors in our case include age and the presence of Parkinson's disease.

According to NOGG guidelines as seen below, there is an indication for BMD measurement as this patient has intermediate risk for fracture (Case History Figure B). It is then recommended to measure BMD and recalculate fracture risk. If BMD measurement is not feasible, practical or not available, offer treatment if risk is at or above the Intervention threshold shown.

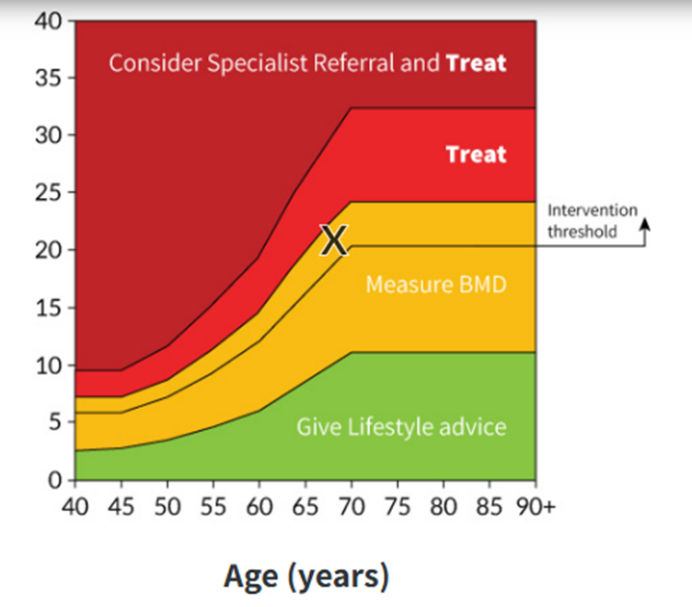
A diagram of a patient's level

AI-generated content may be incorrect.

Case History Figure B: NOGG assessment, intervention and risk thresholds for major osteoporotic fracture probability (MOF) in the UK with the use of FRAX. In our case, the patients is on intermediate risk and further assessment with BMD measurements is required, if available

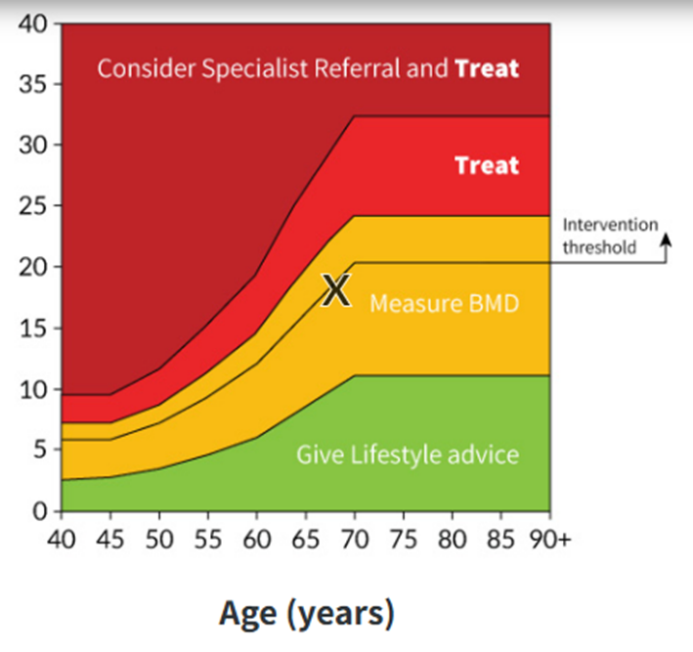
In this case, few other considerations are necessary before a decision is made regarding treatment for osteoporosis.

1. She reports a recent fall and back pain; this should be investigated with a radiograph or vertebral fracture assessment from a DXA scan to confirm evidence of vertebral fracture. A vertebral fracture would be considered a major osteoporotic fracture and a fracture within the past 2 years is a particularly strong risk factor for subsequent fracture. Adjustments of FRAX for recency and number of prior fractures are available. In this example, thoracic and lumbar radiographs confirmed the evidence of a T8 fracture. Her FRAX will then be adjusted accordingly : MOF risk: 14 x 1.5 = 21 %, Hip risk: 3.3 x 1.4= 4.62 % 94 (Case History Figure C).
   1. Based on the adjusted FRAX score (after adjusting for recent MOF without BMD measurements available), she remains at intermediate risk of fracture (This can be done manually <https://www.nogg.org.uk/manual-data-entry>), but she is now above the intervention threshold (see Graph ); In this case, treatment will be recommended (especially in view of a vertebral fracture).



Case History Figure C: NOGG assessment, intervention and risk thresholds for major osteoporotic fracture probability (MOF) in the UK following adjustment for fracture recency 94.

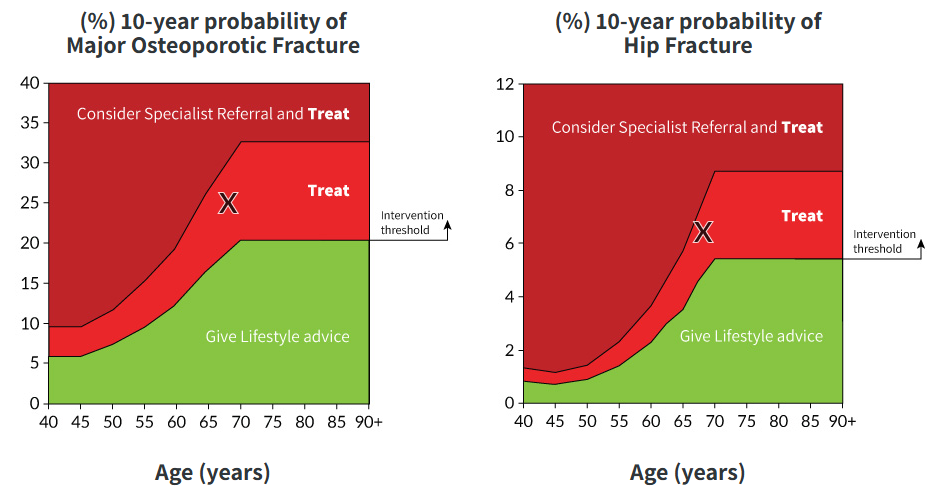
1. The patient also reports recurrent falls. Falls risk assessment should be considered to identify the factors that are associated with the falls to prevent future ones; her FRAX score can also be adjusted for the number of falls 61. In this example her MOF and hip fracture risk, in the absence of BMD, will be 14 x 1.3= 18.2 % and 3.3 x 1.4= 4.62 % respectively (Case History Figure D). Based on the adjusted FRAX score for recurrent falls only, the risk remains intermediate but just on the intervention threshold; a discussion with the patient is appropriate to discuss risks and benefits of treatment, if BMD measurements are not available.



Case History Figure D93: NOGG assessment, intervention and risk thresholds for major osteoporotic fracture probability (MOF) in the UK following adjustment for recurrent falls 61 .

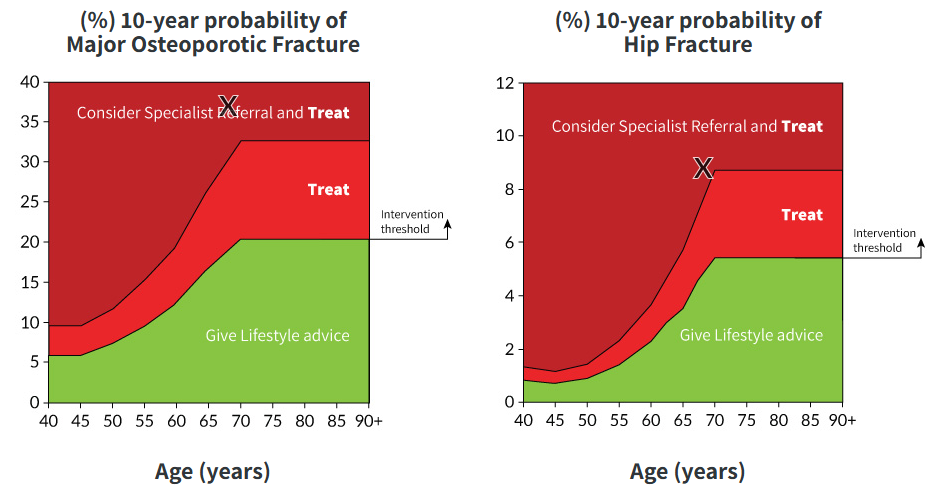
1. Current recommendations caution against the use of multiple adjustments. When multiple adjustments are feasible, it is crucial to determine which variables are most important for a particular patient. Therefore, adjustments should be made for the most significant factor. In this case, the recent vertebral fracture is the most important factor, so FRAX adjustment for fracture and the presence of the fracture should be used for decision-making.

She then has a DXA scan performed and BMD measurements are available: T scores on her spine, left femoral neck and left hip are -2.0, -2.3, -1.7 respectively. Her vertebral fracture assessment confirms evidence of moderate T8 vertebral fracture. FRAX with BMD measurements is now 25% for MOF and 6.4% for hip fracture (yes to recent fracture and to “rheumatoid arthritis” section) (Case History Figure E). Treatment should be offered, considering the patient’s values and preferences; a first line appropriate treatment in a 68-year-old female could be oral Bisphosphonates; Oral formulations are shown to provide anti-fracture efficacy in vertebral and non-vertebral fractures 93. Intravenous bisphosphonates such as zoledronate, or Denosumab can also be considered as a treatment option if oral Bisphosphonates are not tolerated; Denosumab’s safety and efficacy is maintained over 10 years of treatment; as previously discussed in Pharmacological approaches, Denosumab remains a preferred option in older patients where it can be continued lifelong (10 years or more).



Case History Figure E: NOGG thresholds for intervention and/or referral using major osteoporotic fracture (MOF) and hip fracture (HF) probabilities in the UK. The panels show the thresholds following the recalculation of FRAX after the input of BMD. As our patient has a recent MOF and her Femoral T score is -2.3, she is now above the treatment threshold and treatment should be offered. Her FRAX was adjusted only for prior fracture but not adjusted further for recency of fracture.

FRAX can also be adjusted further in this case for recency of fracture (as this took place within 2 years) with BMD measurements (for a 70 years old person with a recent vertebral fracture); MOF risk: 25 x 1.48= 37 %, Hip risk: 6.4 x 1.38 = 8.8 (Case History Figure 6) 94 . Based on the adjusted FRAX scores, she is now at very high risk for further fracture and consideration of parenteral or anabolic treatment is appropriate alongside referral to a specialist bone clinic (see Teriparatide, abaloparatide and romosozumab) 93.



Case History Figure F:NOGG thresholds for intervention and/or referral using major osteoporotic fracture (MOF) and hip fracture (HF) probabilities in the UK. The panels show the thresholds following the recalculation of FRAX after the input of BMD and after adjusting further for recency of fracture. After manually adjusting for recency of fracture (Kanis), manual entry to <https://www.nogg.org.uk/manual-data-entry> is required to receive the updated FRAX scores.

# Conclusion

Fracture risk should be a major clinical consideration in people with neurological disorders. Easily usable clinical pathways are set out in guidelines from the UK National Osteoporosis Guideline Group, based on the calculation of absolute fracture probability using clinical risk factors, together with bone mineral density if available. The FRAX® tool is central to this approach, and the probability can be modified further to accommodate other adjunctive factors such as the dose of glucocorticoids. Where specific considerations relating to neurological disease and its treatment cannot be captured quantitatively in risk assessment, they should be incorporated qualitatively into clinical decision-making. Where patients are at very high fracture risk, referral to the metabolic bone clinic is advised. Management of bone health is a lifelong consideration and should be an integral part of disease management.

# Acknowledgements

NC Harvey, F Laskou, EM Curtis, EM Dennison acknowledge funding from the UK Medical Research Council [MC\_PC\_21003; MC\_PC\_21001] and the NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, UK. For the purpose of Open Access, the author has applied a Creative Commons Attribution (CC BY) licence to any Author Accepted Manuscript version arising from this submission.

# Conflict of interest statement

F Laskou has no conflict of interest in relation to this work.

EM Curtis has received lecture fees or conference support from Amgen, Eli Lilly, Pfizer, Theramex, Thornton & Ross and UCB, outside of this work.

A Varatharaj has no conflict of interest in relation to this work.

EM Dennison has received consultancy and speaker fees from UCB, Pfizer and Lilly

NC Harvey has received consultancy/lecture fees/honoraria/grant funding from Alliance for Better Bone Health, Amgen, MSD, Eli Lilly, Radius Health, Servier, Shire, UCB, Consilient Healthcare, Kyowa Kirin, Theramex and Internis Pharma.

# Figures

A screenshot of a computer

AI-generated content may be incorrect.

**Figure 1:** Recommended approach for fracture risk assessment and guidance for short- and long-term management of osteoporosis. Derived from the UK National Osteoporosis Guideline Group recommendations (NOGG)1.BP= Bisphosphonates , DXA= Dual-energy-X ray Absorptiometry, VFA= Vertebral fracture assessment , GC= Glucocorticoids , BMD= Bone Mineral Density

A chart of risk levels

Description automatically generated with medium confidence

**Figure 2:** NOGG assessment, intervention, and risk thresholds for major osteoporotic fracture probability (MOF) in the UK with the use of FRAX. Individuals with probabilities below the lower assessment threshold (LAT) are considered for lifestyle advice. Those at intermediate risk (probabilities between the upper assessment threshold (UAT) and lower assessment threshold (LAT) are further assessed with BMD measurement. Where probabilities calculated using BMD lie above or below the intervention threshold (IT), treatment or lifestyle advice, respectively, is recommended. Patients with probabilities above the upper assessment threshold (UAT) are considered for treatment. Those with probabilities above the very high risk threshold (VHRT) should be considered for specialist referral. Where BMD measurement is not practical (e.g., when individuals are frail and unable to get onto a DXA table, or lie flat on a DXA table), patients with probabilities above the IT are considered for treatment.1

# Tables

**Table 1:** Clinical risk factors for fracture 1.

|  |  |
| --- | --- |
| Non modifiable | Modifiable (when possible) |
| Age | Excessive alcohol intake; ≥2 units /day |
| Female sex | Smoking |
| Parental history of hip fracture | Low body mass index |
| History of previous fracture  Rheumatoid arthritis | Poor nutrition, particularly calcium, vitamin D, protein  Type 2 diabetes |
| Premature/surgical menopause |  |
| Medications: specifically for neurology patients include GC, ASMs, anticoagulants, antidepressants, sedatives, PPI | Eating disorders |
| Neurological diseases: any condition likely to affect mobility or falls risk | Immobility |
|  |  |
| Other secondary causes:  Type I (insulin-dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition or malabsorption, chronic renal failure (dialysis independent) and chronic liver disease. | Frequent falls |

GC: glucocorticoids, ASM: anti-seizure medication, PPI: proton pump inhibitor.

**Table** 2**:** Suggested investigations to assess fracture risk in patients with neurological disease 1.

|  |  |
| --- | --- |
| **Routine** | **Other procedures, if indicated** |
| * Clinical history * Physical examination including measurement of height and assessment of thoracic kyphosis * Full blood cell count * Erythrocyte sedimentation rate or C-reactive protein * Serum calcium, albumin, creatinine, phosphate, alkaline phosphatase and liver transaminases (renal, bone and liver profiles) * Serum 25-hydroxyvitamin D * Thyroid function tests * DXA scan including vertebral fracture assessment | * Serum electrophoresis, serum immunoglobulins and serum free light chain assay * Plasma parathyroid hormone (PTH) * Serum testosterone, sex hormone binding globulin, follicle stimulating hormone, luteinizing hormone * 24-hour urinary free cortisol/overnight dexamethasone suppression test * Serum prolactin * Serum magnesium if hypocalcaemic * Tissue transglutaminase antibodies, +/- endomysial antibodies * 24 hour urinary calcium excretion * Markers of bone turnover (e.g., CTX, P1NP) * Isotope bone scan (malignancy, Paget’s disease) |

**Table 3:** Modification of FRAX® fracture probability estimates based on the dose of prednisolone 95. Tick the ‘glucocorticoids’ box and then multiply the resulting fracture probability by the modifier below.

|  |  |  |  |
| --- | --- | --- | --- |
| **Dose** | **Prednisolone equivalent (mg/day)** | **Average adjustment: hip fracture probability** | **Average adjustment: major osteoporotic fracture probability** |
| Low | <2.5 | 0.65 | 0.8 |
| Medium | 2.5–7.5 | None | None |
| High | ≥7.5 | 1.20 | 1.15 |

**Table 4:** List of available anti-osteoporosis medications and route of administration.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Medication | Route | Dose | Frequency | Gender |
| BISPHOSPHONATES | | | | |
| Alendronate | PO | 70mg | Weekly | F/M |
|  | PO | 10mg | Daily | F/M |
| Ibandronate | PO | 150mg | Monthly | F |
|  | IV | 2mg | Every 3 months | F |
| Risedronate | PO | 35mg | weekly | F/M |
| Zoledronic acid | IV | 5mg | Once a year | F/M |
| RANK LIGAND (RANKL) INHIBITOR | | | | |
| Denosumab | SC | 60mg | Every 6 months | F/M |
| OESTROGEN | | | | |
| HRT (Oestrogen, with cyclical progestogen in women with a uterus) | PO | 1 or 2mg | Daily | F |
|  | Transdermal | One patch | Twice weekly/weekly | F |
| Oestrogen agonist | | | | |
| Raloxifene | PO | 60mg | Daily | F |
| ANABOLIC AGENTS | | | | |
| PTH ANALOG | | | | |
| Teriparatide | SC | 20mcg | Daily | F/M |
| Abaloparatide | SC | 80mcg | Daily | F |
| SCLEROSTIN INHIBITOR | | | | |
| Romosozumab | SC | 210mg  2 injections of 105mg | Monthly | F |

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