



Management of fracture risk in Parkinson's: A revised algorithm and focused review of treatments

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ABSTRACT

Introduction: Falls and fractures are a cause of substantial morbidity in Parkinson's. Despite an excess risk of both falls and osteoporosis, people with Parkinson's perceive that they are less likely to fracture than their peers, despite actually being at higher fracture risk. Recognising this increased risk, in 2014 we published an algorithm to guide management of fracture risk in this high-risk population. Recently, the National Osteoporosis Guideline Group (NOGG) published new guidance revising the 10 year fracture probability intervention thresholds for those over 70 years old to 20.3% for major osteoporotic fracture and 5.4% for hip fracture.

Methods: In light of the new guidance, we have reappraised the use of two fracture prediction tools, Qfracture and FRAX, and have updated the algorithm to guide the management of bone health and fracture risk in people with Parkinson's.

Results: We outline the treatment options available with particular consideration given to Parkinson specific factors that influence treatment choices.

Conclusion: This guidance is relevant to all healthcare specialist managing Parkinson's including neurologists, geriatricians and primary care practitioners.

1. Introduction

Parkinson's disease (PD), the commonest neurodegenerative disorder after Alzheimer's disease, affects 145,000 adults in the UK [1]. In Parkinson's falls are common and the consequent fractures account for substantial morbidity [2]. People with Parkinson's are more than twice as likely to have osteoporosis compared to unaffected individuals of the same age [3] and twice as likely to sustain a fracture, likely resulting from the combination of increased fall risk and osteoporosis [4]. Despite this, awareness of fracture risk within the Parkinson's population is lacking; women with Parkinson's perceive themselves 'as likely or less likely' to fracture a bone compared with their peers [5]. This is perhaps not surprising as clinicians often overlook fracture risk; the 2015 UK Parkinson's Audit highlighted widespread lack of bone health assessment in Parkinson's outpatients [6].

The increased fracture risk associated with Parkinson's is particularly marked at the hip, with patients typically lacking the rapid protective abduction of the arms during falls [7]. Of the osteoporotic fractures, hip fractures have the greatest impact on functional recovery

and mortality, with particularly adverse outcomes in Parkinson's patients [8,9]. Hip fracture admissions account for 4.2% of all Parkinson's admissions in England, with an average yearly cost estimated at £13.7 million [10].

Men with Parkinson's seem to be at particular risk of hip fracture. In a prospective study of primary care records from 3.1 million UK patients (0.2% having a diagnosis of Parkinson's), Parkinson's was associated with a 3-fold increased risk of hip fracture in men (Hazard Ratio 3.0 [95%CI 2.4,3.8]), and a 2-fold increase in women (2.0 [1.8,2.4]) [11]. Our own analyses of English Hospital Episodes Statistics have shown a year-on-year increase in the absolute number of men with Parkinson's sustaining a hip fracture in England, such that by 2014 almost as many men with Parkinson's fractured as did women with Parkinson's (Fig. 1), whilst the most recent meta-analysis demonstrates that patients with Parkinson's are 4 times (hazard ratio 4.02 [95% CI 4.00, 4.03]) more likely to sustain a hip fracture than their peers ([12], manuscript in review). Critically, now in the US each year 17.6% of women with Parkinson's aged 65 years or older will sustain a clinical fracture, and 4.6% will sustain a hip fracture; amongst men of a similar

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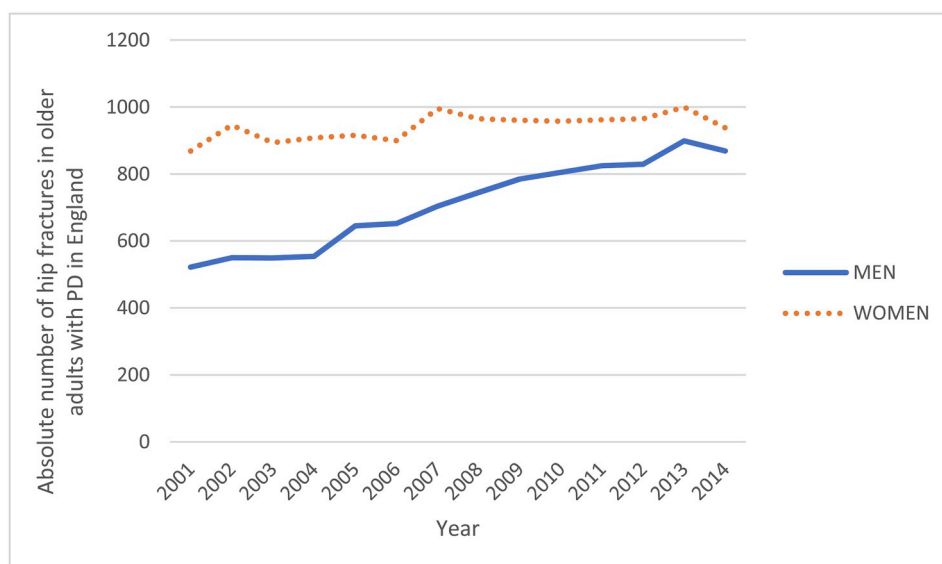


Fig. 1. Total number of men and women aged 65 or older with idiopathic Parkinson's, who sustained a hip fracture each year from 2001 to 2014 in England.

age 11.7% will sustain a clinical fracture with 2.9% experiencing a hip fracture ([12], manuscript in review).

2. Aims

In 2014, we published the first algorithm to guide the assessment and management of fracture risk in people with Parkinson's [13]. This original algorithm comprised 6 steps, sometimes requiring two different risk calculation tools. The complexity of this approach, though necessary at the time to reconcile Parkinson's-specific assessment with national guidance, likely contributed to sub-optimal uptake [6]. This, combined with the recent publication of new national guidelines by the UK-based National Osteoporosis Guideline Group (NOGG) [14], means there is now a requirement for a revised updated algorithm amenable to widespread clinical use in the UK. This revised 'BONE-PARK' algorithm, which applies NOGG guidance specifically to Parkinson's patients, streamlines fracture risk assessment and is applicable to the practice of both primary and secondary care clinicians.

3. Fracture risk intervention thresholds

In 2017 NOGG published new guidelines containing revised fracture risk intervention thresholds directing use of anti-osteoporosis treatments [14]. This new NOGG guidance, accredited by the National Institute for Health and Care Excellence (NICE) [15], recommends that fracture risk be assessed using the FRAX tool in all postmenopausal women, and in men age 50 years or older, who have risk factors for sustaining a fracture; Parkinson's is now listed as such a risk factor [14].

FRAX calculates a person's probability of sustaining a hip fracture and a major osteoporotic fracture (MOF), over the next 10 years. NOGG then applies thresholds for intervention to the FRAX probability of MOF to make a recommendation that either reassurance and lifestyle advice be provided to the patient, or for a Dual-energy X-ray absorptiometry (DXA) to be performed to quantify bone mineral density (BMD), or for initiation of bone-protective therapy. As before, up until the age of 70 years the intervention threshold for treatment is set at a risk equivalent to that associated with a prior fracture, and therefore rises with age. Now from age 70 years, fixed thresholds are applied ensuring older patients without a history of a prior fracture have equitable access to treatment. The fixed intervention thresholds equate, after DXA scanning, to the mean probability at age 70 of sustaining a MOF (20.3%) [16]. This threshold of 20.3% captures approximately 92% of fracture cases over the age of 75 [16]. The alternative intervention threshold,

based on probability of hip fracture, is set as the mean probability at age 70, for a woman with BMI 24 kg/m² and a prior fracture, of sustaining a hip fracture, which is 5.4% [16]. Intervention thresholds for men and women are similar. Optional addition of measured BMD can then refine fracture risk prediction if needed, by adding femoral neck T-score into the FRAX algorithm.

4. Application of intervention thresholds on populations with Parkinson's

It is notable that the NOGG recommendations are principally based upon calculated MOF probabilities rather than those for hip fracture alone. This is of relevance in Parkinson's (particularly for men) where hip fracture risk is substantially elevated compared to other MOF fracture sites, potentially rendering the NOGG algorithm less applicable to men with Parkinson's.

The discordance between the probabilities of MOF versus hip fracture by sex and the potential risk of gender inequity when applying intervention thresholds in Parkinson's is shown in Fig. 2. These data, gathered systematically from unselected Parkinson's patients assessed in routine outpatient clinics across two typical NHS hospitals, show the relative dominance of calculated hip fracture risks in men compared with that of MOF in women (Fig. 2a), and the effect of the adaptation of FRAX as suggested in the next section (Fig. 2b).

5. Choice and application of fracture risk assessment tools in Parkinson's

NICE [17] has endorsed two fracture risk assessment tools for use in the UK – FRAX [18] and QFracture [11]. FRAX, supported by NOGG [14], is the mostly widely used. However, each has limitations in the context of Parkinson's.

5.1. FRAX and Parkinson's

One caveat to FRAX utility is the absence of Parkinson's as a specified clinical risk factor within the FRAX tool. However, Parkinson's is associated with an increased risk of both osteoporosis and fractures [3,4], likely for reasons of reduced mobility, low vitamin D, poor nutrition and medication effects [19]. This increased fracture risk seen in Parkinson's is equivalent to, and arguably exceeds, many of the 'secondary osteoporosis' conditions listed within the FRAX tool. Whilst a number of secondary causes of osteoporosis are not included in FRAX,

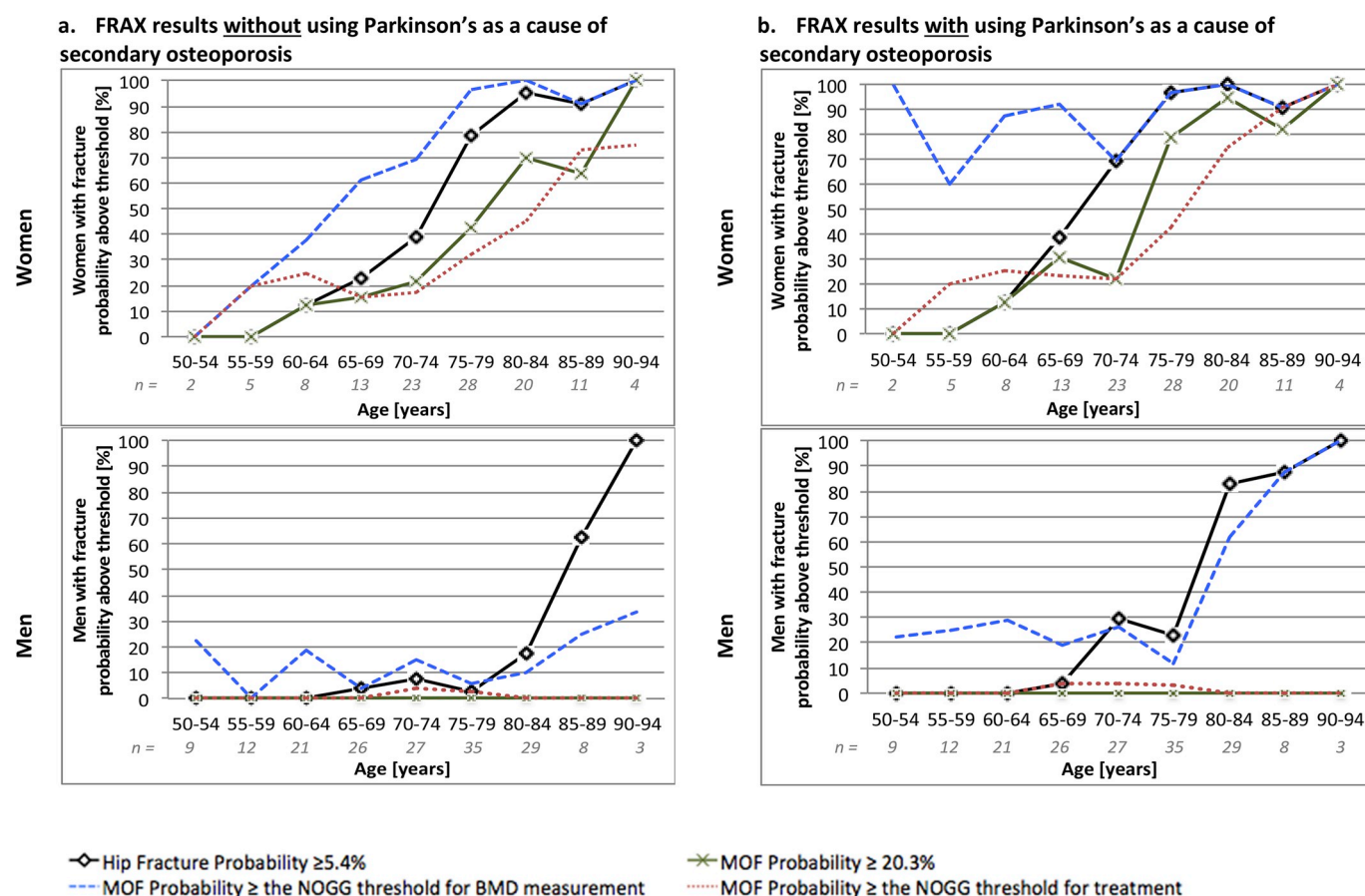


Fig. 2. Proportion of FRAX results above threshold for investigation or intervention, by age and sex, in 284 Parkinson's patients from 2 typical outpatient clinics, [mean age 73.0 years (SD 9.4), 60% male, median BMI 26.4 (IQR 23.2–29.0)].

Men		90	16.0	16.0	15.0	15.0	14.0	13.0	13.0	12.0	12.0	11.0	10.0	10.0	9.5	9.0	7.6
Age		85	13.0	12.0	12.0	11.0	11.0	10.0	10.0	9.6	9.2	8.8	8.4	8.0	7.6	7.2	6.0
		80	9.9	9.4	9.0	8.6	8.2	7.6	7.3	6.9	6.5	6.2	5.8	5.5	5.2	4.8	4.1
		75	7.3	6.9	6.5	6.2	5.8	5.4	5.0	4.7	4.3	4.0	3.7	3.5	3.3	3.2	2.7
		70	5.2	4.8	4.5	4.0	3.8	3.5	3.2	2.9	2.7	2.5	2.2	2.1	2.0	1.9	1.6
		65	3.6	3.3	2.9	2.7	2.4	2.2	2.0	1.8	1.6	1.5	1.3	1.3	1.2	1.1	1.0
		60	2.3	2.1	1.9	1.7	1.5	1.3	1.2	1.1	1.0	0.9	0.8	0.7	0.7	0.7	0.6
		55	1.3	1.2	1.1	1.0	0.9	0.8	0.7	0.6	0.5	0.5	0.4	0.4	0.4	0.4	0.3
Women		85	30.0	29.0	28.0	27.0	25.0	24.0	23.0	22.0	20.0	19.0	18.0	17.0	16.0	15.0	13
Age		80	25.0	24.0	22.0	21.0	19.0	18.0	17.0	15.0	14.0	13.0	13.0	11.0	11.0	10.0	8.7
		75	18.0	17.0	15.0	14.0	13.0	12.0	11.0	9.7	8.8	8.0	7.1	6.8	6.5	6.1	5.2
		70	12.0	11.0	9.6	8.7	7.8	7.0	6.3	5.7	5.0	4.5	4.0	3.8	3.6	3.5	3.0
		65	7.1	6.4	5.7	5.1	4.5	4.0	3.6	3.2	2.8	2.5	2.2	2.1	2.0	1.9	1.7
		60	4.2	3.7	3.3	2.9	2.6	2.3	2.0	1.8	1.6	1.4	1.2	1.2	1.1	1.1	0.9
		55	2.3	2.0	1.8	1.6	1.4	1.2	1.1	1.0	0.9	0.7	0.7	0.6	0.6	0.6	0.5
			15	16	17	18	19	20	21	22	23	24	25	26	27	28	31
			BMI														

Probability of a Hip fracture in men and women with 'Secondary osteoporosis' selected as only FRAX risk factor. Above the solid bold line, 10-year hip fracture probability is above the threshold of 5%. The figures are not coloured as NOGG does not apply guidance directly to hip fracture calculated probability.

Fig. 3. The effect of including Parkinson's as a secondary cause of osteoporosis on hip fracture probability for men and women with PD across a range of ages and BMIs.

including Parkinson's, FRAX authors have listed Parkinson's as an example of immobility-induced secondary osteoporosis [20]. Thus it reasonable to consider Parkinson's pragmatically as a secondary cause of osteoporosis when calculating FRAX. The effect of this approach for

men and women is illustrated in Fig. 2b and demonstrated across a range of ages and BMIs in Fig. 3 for hip fracture and Supplementary Data 1 for major osteoporotic fracture in men and women.

5.2. FRAX and falls

Of people living with Parkinson's, 60% fall each year, with 39% falling recurrently [21]. However, FRAX does not accommodate falls as a clinical risk factor and likely underestimates fracture probability in those who fall [22]. In 2011 a joint position statement concluded that clinicians should recognize that patients with frequent falls are at higher fracture risk than currently estimated by FRAX and consider this when decision-making [22]. Specifically, they recommended that FRAX reports should include the statement "Data from the Study of Osteoporotic Fractures suggest that in comparison to individuals without a fall in the previous year, a history of each fall (up to 5 falls or more) in the previous year increases the 10-year hip fracture risk by approximately 30% in women". Thus, a 4% hip fracture probability in a patient with two recent falls would inflate to 6.2%. This assumes that the US population in the Study of Osteoporotic Fractures, on which this statement is based, is generalisable to the UK [23]. Although it may be argued that patients whose fracture risk is driven more by falls than low bone density might have less to gain from agents affecting bone metabolism, there is strong evidence that fracture risk reduction is achieved irrespective of a BMD diagnosis of osteoporosis [24].

5.3. QFracture and Parkinson's

QFracture, which is less widely used than FRAX, is derived from prospective primary care data from 3.1 million UK patients; 0.2% had a Parkinson's diagnosis [11]. Its advantages include (i) inclusion of Parkinson's and falls as independent clinical risk factors, and (ii) the ability to generate fracture risk estimates for annual increments up to 10 years; this flexibility aids decision making where life expectancy is challenged by progressive degenerative disease. However, QFracture, which is lengthier to complete than FRAX, cannot incorporate BMD measurement and furthermore, whilst independent external validation in the UK has shown QFracture predicts hip fracture well and comparably with FRAX, the calibration for MOF tends to over-estimate risk compared with FRAX [25], which may be explained by data deficiencies in the computerised primary care records from which QFracture was originally derived [26].

On balance, given the widespread use of FRAX and newly revised intervention thresholds from NOGG, FRAX seems a better tool to use in the context of Parkinson's. However, in certain circumstances QFracture may be better suited to calculate hip fracture risk, for example in those with multiple comorbidities including falls, and in individuals with short life expectancies such as is seen in Progressive Supranuclear Palsy (PSP) or Multiple System Atrophy (MSA), where calculation of fracture risk over a shorter timeframe (e.g. < 5 years) may be helpful.

In light of the new NOGG guidance, we introduce here a revised algorithm BONE-PARK (Fig. 4), to guide assessment and management of fracture risk, in Parkinson's. This algorithm should be considered within the context of a multifactorial assessment of fall risk factors. Clinicians should consider additional factors alongside bone health that are amenable to intervention such as medication review [27], physiotherapy intervention [28], exercise [29] and environmental modification.

5.4. Step 1: Optimise calcium and vitamin D intake and lifestyle factors

There is a high prevalence of vitamin D deficiency in people with Parkinson's with 91% of those insufficient and 67% deficient (at mean Hoehn and Yahr stage 2, average age 66 years) [30]. Recurrent falls amongst Parkinson's patients supports consideration of testing [21,31]. Vitamin D deficiency and insufficiency should prompt vitamin D replacement, then maintenance, with or without calcium supplementation according to dietary calcium intake [31]. Interestingly the Scientific Advisory Committee on Nutrition (SACN) recommends daily supplementation in all those aged ≥ 65 years with inadequate sun

exposure [32].

5.5. Step 2: Assess prior falls and fractures

All patients should be routinely asked about the occurrence of falls, near falls and any previous fractures with referral to multi-disciplinary falls services as needed. A history of height loss, acute back pain or kyphosis disproportionate to their neuromuscular condition, should prompt investigation with lateral thoraco-lumbar radiographs to identify occult morphometric vertebral fractures; of note the majority of vertebral fractures fail to present to medical attention [33]. Incidental findings of vertebral fracture on radiological investigations performed for other indications must not be disregarded but reported and included as a prior fracture when assessing future risk [34]. BONE-PARK must be applied in conjunction with a comprehensive falls prevention strategy that tackles both generic and Parkinson's-specific risk factors [27].

5.6. Step 3: Calculate the 10-year probability of hip and MOF using the FRAX tool

The presence of Parkinson's should be considered as a secondary cause of osteoporosis when calculating FRAX. Using UK FRAX permits direct linkage to NOGG guidance.

5.7. Step 4: Use the NOGG intervention guidance

If the MOF probability warrants treatment, follow the guidance given, and in relatively fit or younger patients aged ≤ 70 years, consider baseline BMD measurement by DXA for future reference (see below).

If BMD measurement is recommended a DXA scan should be requested where feasible and appropriate (see below). Where DXA is impractical, we propose empirical anti-osteoporosis treatment if the hip fracture probability is $\geq 5\%$ in men, and in women if the probabilities of MOF are $\geq 20\%$ and for hip fracture $\geq 5\%$.

If NOGG guidance suggests that lifestyle advice only is warranted, this should be considered with the caveat that falling patients with a MOF probability close to the BMD measurement threshold may be considered for DXA where feasible, or if not feasible, for treatment as per the intervention thresholds given above. Patients fulfilling the criteria for treatment by NOGG and the BONE-PARK algorithm should be considered for anti-osteoporosis medication, as well as falls intervention and lifestyle advice.

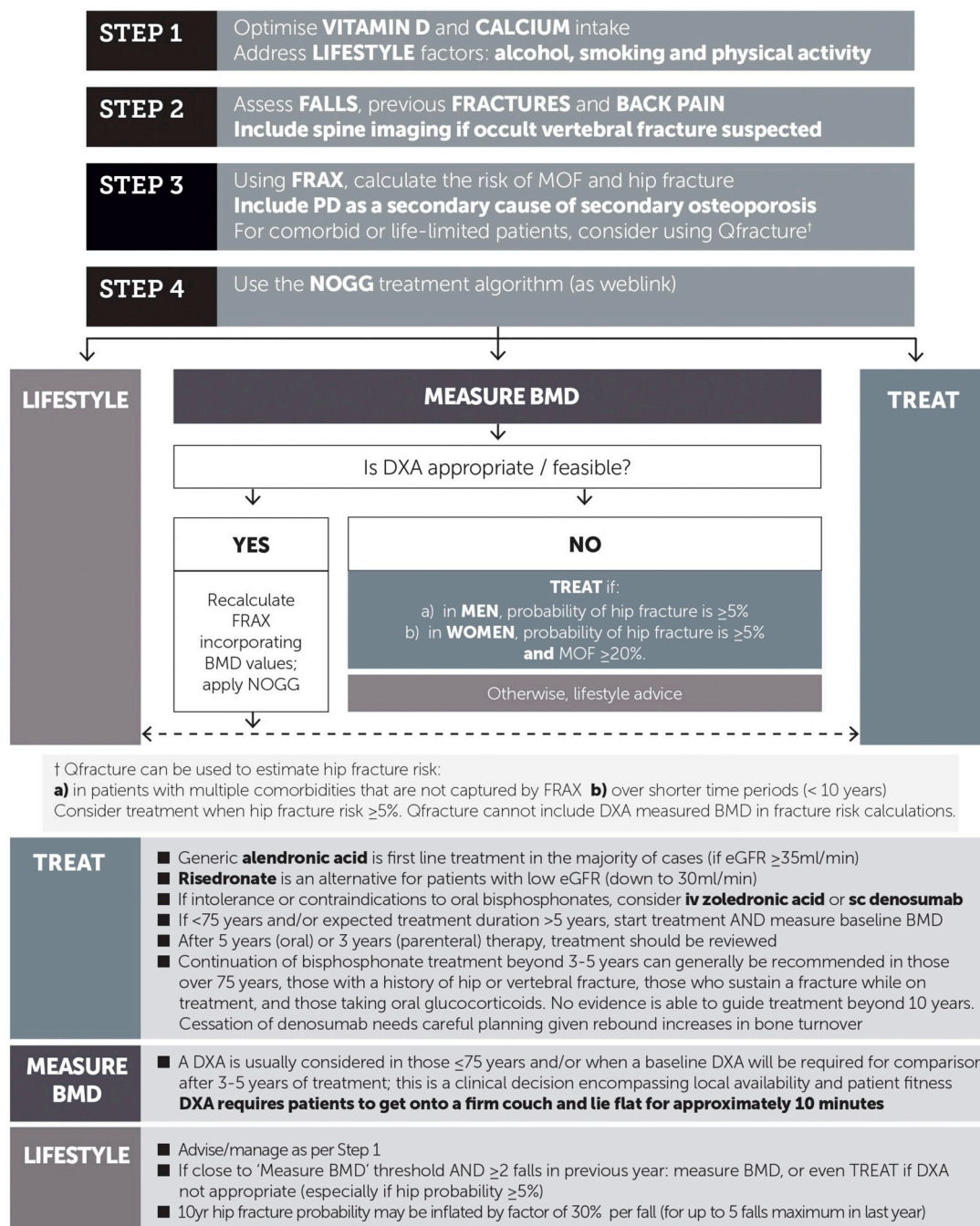
5.8. BMD measurement considerations

A DXA scan can refine the FRAX fracture risk prediction and/or provide a baseline BMD for future comparison in, for example, 3–5 years' time. Hence DXA should be considered in those at an early enough stage of their movement disorder where re-testing of BMD is expected to be possible. BMD quantification by DXA should prompt recalculation of FRAX probabilities. Anti-osteoporosis treatment should be reviewed after 5 years (3 years if treating with annual Zoledronic Acid infusions) and continued in cases of prior hip or vertebral fracture, recurrent fractures, current glucocorticoid treatment, or in those aged > 75 years, although in the case of recurrent fracture the type of anti-osteoporosis treatment may need to change [14].

Access to DXA may be restricted by local resource or patient ability as testing necessitates climbing onto a fixed height unpadded table, lying supine and maintaining this position for approximately ten minutes. Though BMD measurement can refine fracture risk calculations and guide treatment, barriers to obtaining BMD should not preclude empirical anti-osteoporosis treatment where appropriate.

BONE-PARK—Algorithm for Fracture Risk Assessment & Bone Health Management in Parkinson's Disease

This algorithm is designed for use in all outpatients (in primary and secondary care) with a diagnosis of Parkinson's Disease or a related movement disorder. Fracture risk and adherence to previous management decisions should be reviewed annually. This guidance is not applicable in end-stage disease when a patient is unable to mobilise from bed or is in the last year of life.



MOF: Major osteoporotic fracture risk; PD: Parkinson's disease; DXA: Dual-energy X-ray absorptiometry;
NOF: Neck of femur fracture risk; NOGG: National Osteoporosis Guideline Group; BMD: Bone Mineral Density
FRAX: www.sheffield.ac.uk/frax

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Fig. 4. The BONE-PARK algorithm for the assessment and management of fracture risk in Parkinson's.

5.9. Special populations and circumstances

In those with limited life expectancy, multiple comorbidities or where quantification of fracture probability over a shorter time (< 5 years) period is desired, QFracture can be used and a treatment threshold of $\geq 5\%$ for hip fracture applied. This may have particular utility for those assessed in a more complex phase of their Parkinson's, or with a more rapidly progressive movement disorder.

5.10. Scope of the BONE-PARK algorithm

Given the increase in fracture risk, seen even in early Parkinson's [8], and the time taken to gain treatment benefit with anti-osteoporosis medications (> 12 months), this BONE-PARK algorithm is appropriate for use in the majority of patients, from Hoehn and Yahr stages 1–4 and in patients with Parkinsonian disorders with high falls risk such as PSP and Dementia with Lewy Bodies. In the later stages of life, the transition to a more palliative management approach should prompt re-evaluation of treatment interventions balanced against, what is often by then, very high fall and fracture risks.

6. Assessment schedule and treatment review

In Parkinson's, bone health should be reviewed annually, including assessment of treatment adherence (including calcium and vitamin D). Poor adherence to oral bisphosphonates is common and associated with higher fracture rates [35]; treatment is frequently discontinued due to intolerance, insufficient motivation or concern over potential side effects [36]. This should prompt consideration of parenteral anti-osteoporosis treatment options. BONE-PARK is designed to help guide clinical decision making but individual treatment strategies should be determined in discussion with the patient, together weighing the potential burden of additional medication versus the benefit of fracture risk reduction.

7. Treatment options

NOGG provides guidance on anti-osteoporosis treatment options; these are included within BONE-PARK, adapted for Parkinson's.

All patients should be counselled to avoid smoking, increase physical activity levels and limit alcohol intake. Adequate vitamin D maintenance should be instigated in all those aged > 65 years with inadequate sunlight exposure; SACN recommends a minimum dose of 800 IU cholecalciferol for postmenopausal women and for men > 50 years at risk of fracture [31]. It is standard practice to recommend a combined calcium and vitamin D preparation to older patients. In those who feel their diet is replete in calcium, a calcium calculator can quantify intake and can support a decision to supplement vitamin D alone [37].

Oral bisphosphonates, particularly alendronic acid (70 mg weekly), are first-line pharmacological treatments for osteoporosis with high quality evidence for important fracture risk reductions after three years of treatment [14]. Oral bisphosphonates have little difference in tolerability; however, risendronate (35 mg weekly) is licenced for use at a slightly lower eGFR of 30 ml/min (vs. 35 ml/min for alendronic acid) [38]. Evidence specific to patients with Parkinson's is lacking, but efficacy is likely to be as good and absolute risk reductions likely greater in this high risk population. However, the dosing schedule for oral bisphosphonates includes a strict early-morning fasting regime, ideally prior to other tablet taking, with a full glass of water, maintaining an upright position with further fast for ≥ 30 min post-dose. Problematic dysphagia, compromised posture, cognitive impairment, poor gastrointestinal motility and/or already complex drug regimens may often limit utility of oral anti-resorptive agents in those with Parkinson's. Monthly ibandronate can be considered; however, its evidence-base is mainly limited to vertebral fracture reduction [14,39]. Swallow issues

may be ameliorated by the use of liquid alendronic acid but non-inferiority trial data are scant. Hence, intravenous zoledronic acid, usually given yearly for 3 years, represents an attractive and affordable option [40], with substantial fracture risk reductions achieved by 3 years (40% non-vertebral and 75% vertebral fracture relative risk reduction) [41]. Interestingly, a single, one-off infusion appears to yield 5 years of reduced bone turnover with sustained gains in BMD and therefore has particular appeal in those patients less able to attend yearly clinics for infusions [42]. However, it is notable that there have been no trials in a Parkinson's population of single-dose Zoledronic acid with BMD or fracture outcomes. Zoledronic acid is highly efficacious even in those without DXA defined osteoporosis (defined by BMD T-score < -2.5), and equally efficacious irrespective of prior fracture history [43]. Zoledronic acid has also been shown to reduce the risk of death, myocardial infarction and cancer suggesting that there are systemic benefits beyond fracture reduction [43,44].

Denosumab, a human monoclonal antibody to Receptor activator of nuclear factor kappa-B ligand (RANKL), given subcutaneously on a six-monthly basis, is a further parenteral anti-resorptive treatment option. It lacks the renal restrictions of the bisphosphonates, and trials included participants with eGFR as low as 15 ml/min [45]. The risk of secondary hypocalcaemia is increased in poorer renal function and concerns have been raised when stopping denosumab, due to rebound increases in bone turnover which may be associated with a paradoxical increased risk of vertebral fracture [46]. Therefore the advice is not to stop denosumab treatment without first considering alternative treatments to ameliorate the transient period of high bone turnover [46]. However, bearing these points in mind, both zoledronic acid and denosumab, which convey similar levels of fracture risk reduction, offer the Parkinson's population worthy treatment options.

Other treatment options include raloxifene and oestrogen replacement in women, and subcutaneous teriparatide although its high cost severely restricts its use to those at very high risk of vertebral fractures [47].

8. Conclusion

This revised BONE-PARK algorithm, underpinned by FRAX and informed by the newly updated NOGG guidance, is a simple guide for Parkinson's clinicians. A small subset of patients with complex comorbidities and/or short life expectancy may benefit from QFracture assessment of hip fracture risk. BONE-PARK can be applied whether or not BMD measurement is available and includes recommendations for the frequency of reviews of both fracture risk and treatment.

The accurate and timely assessment of fracture risk in Parkinson's remains a challenge to clinicians. Multiple motor and non-motor symptoms compete for attention during review, patients are unlikely to raise fracture risk as an issue, and movement disorder specialists may be less familiar with fracture risk assessment and management. However, the chronicity of the condition of Parkinson's gives ample opportunities to reduce the risk of falls and consequent fractures by timely assessment and intervention. We propose BONE-PARK is routinely adopted into non-motor management of Parkinson's by primary and secondary care physicians.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.parkreldis.2019.03.021>.

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