County Durham and Darlington
Area Prescribing Committee

Guideline for the management of osteoporosis in primary care

This guideline has been prepared and approved for use within County Durham & Darlington Clinical Commissioning Groups

This guideline is not exhaustive and does not override the individual responsibility of health professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This guideline should be used in conjunction with the following guidelines:

- NICE TA160
- NICE TA161
- NICE TA204
- NICE CG146
- NICE TA464
- NOGG Osteoporosis clinical guideline for prevention and treatment
- SIGN 142

Full details of contra-indications and cautions for individual drugs are available in the BNF or in the Summary of Product Characteristics (available in the Electronic Medicines Compendium) www.emc.medicines.org.uk

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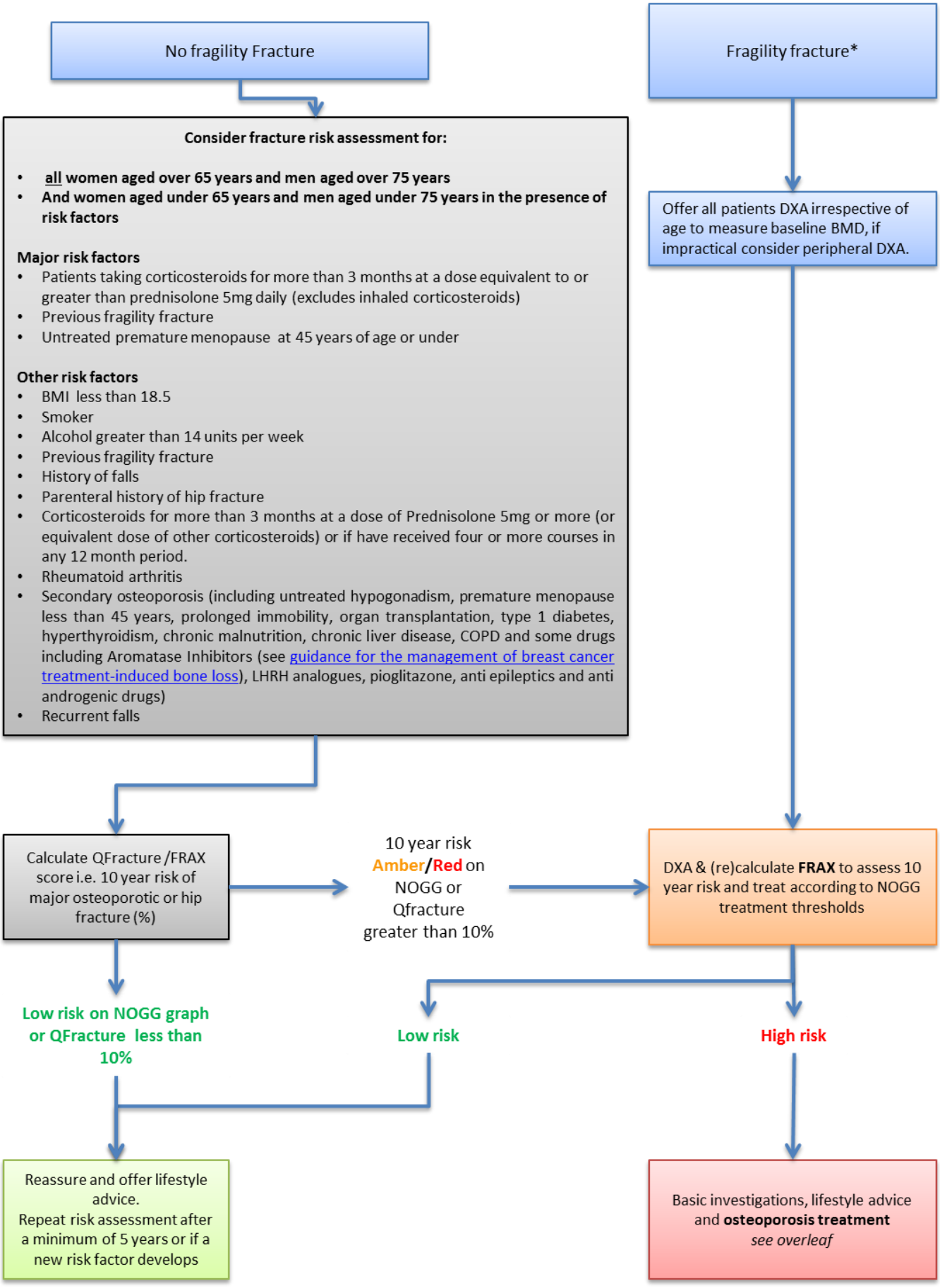
Fracture Risk Assessment Algorithm



Fracture Risk Assessment/ Osteoporosis Treatment Threshold – Additional Information

Do not routinely assess fracture risk in patients aged under 50 years unless major risk factors present because they are unlikely to be at high risk
NICE CG146 gives these major risk factors as; current of frequent recent use of oral or systemic glucocorticoids, untreated premature menopause or previous fragility fracture and these patients must have a risk assessment carried out.

Quantifying the risk of fracture.

Fracture risk assessment should be carried out, prior to DXA in patients with clinical risk factors for osteoporosis and in whom anti-osteoporosis treatment is being considered. QFracture or FRAX can be used.

The FRAX and QFracture risk-assessment tools are freely available at https://www.shef.ac.uk/FRAX/tool.aspx?country=1 and http://www.qfracture.org/

If using risks generated by either tool, NOGG thresholds can be manually entered at: https://www.sheffield.ac.uk/NOGG/manual_data_entry.html

QFracture has some advantages over other methods for calculating fracture risk: it has been extensively validated in the UK population, it predicts fracture risk over a wider age range, predicts risk in different ethnic groups, more accurate prediction in different groups including the elderly, calculates risk over varying timeframes, dose/risk is modelled for alcohol and cigarette consumption, and a longer list of risk factors is included, notably recurrent falls and diabetes. However it doesn't take DXA readings into account so can only be used as a screening tool pre-DXA, not as an outcome measure to assess patient's response to therapy and suitability for a drug holiday.

A strength of **FRAX** is that femoral neck BMD measurements can be included in the assessment whereas this is not possible for the QFracture algorithm and FRAX is therefore suitable for evaluating risk after DXA.

DXA Scan

Ideally all patients should have a DXA scan before treatment to confirm the diagnosis of osteoporosis and to establish a baseline bone density for measuring treatment effects. However there may be circumstances where the clinician uses their clinical judgement on whether to start treatment without measuring bone density, for example for very elderly patients who have suffered a hip fracture where DXA may be impractical.

Fragility fracture is often referred to as a low-trauma fracture; that is, a fracture sustained as the result of a force equivalent to the force of a fall from a height equal to, or less than, that of an ordinary chair. Osteoporotic fragility fractures occur most commonly in the vertebrae, hip and wrist, and are associated with substantial disability, pain and reduced quality of life. **NICE TA161**

Consider secondary care advice for managing the following groups at high risk of fractures – Patient specific advice will be provided to primary care clinicians where relevant with the patient's DXA results

- Patients that continue to lose bone mineral density (BMD) or sustain fracture despite being fully concordant with treatment for 1 year or more
- Breast cancer patients on aromatase inhibitors who are unable to tolerate 1st line treatment or continue to lose bone despite being fully concordant with treatment
- Prostate cancer patients on hormone treatments who sustain a fracture
- Patients who are at risk of varices and there is a need for IV or SC treatment
- Fracture in Paget's patients, osteogenesis imperfecta, hyperparathyroidism and thyrotoxicosis

Corticosteroids
Consider osteoporosis assessment in advance based on likely duration of therapy and patient's age: This should be done using FRAX or QFracture.

- All patients aged over 65 years: consider bisphosphonate at commencement of corticosteroids
- Patients aged less than 65 at high risk and requiring corticosteroids for more than 3 months: DXA and consider bisphosphonate if T-score less than -1.5
- Risk assessment should also be performed for patients who have been prescribed four or more courses of corticosteroids in a 12 month period, e.g. COPD rescue packs.
- Give vitamin D and calcium (see CDD formulary choices) while on corticosteroids.

Patients with inflammatory bowel and coeliac disease

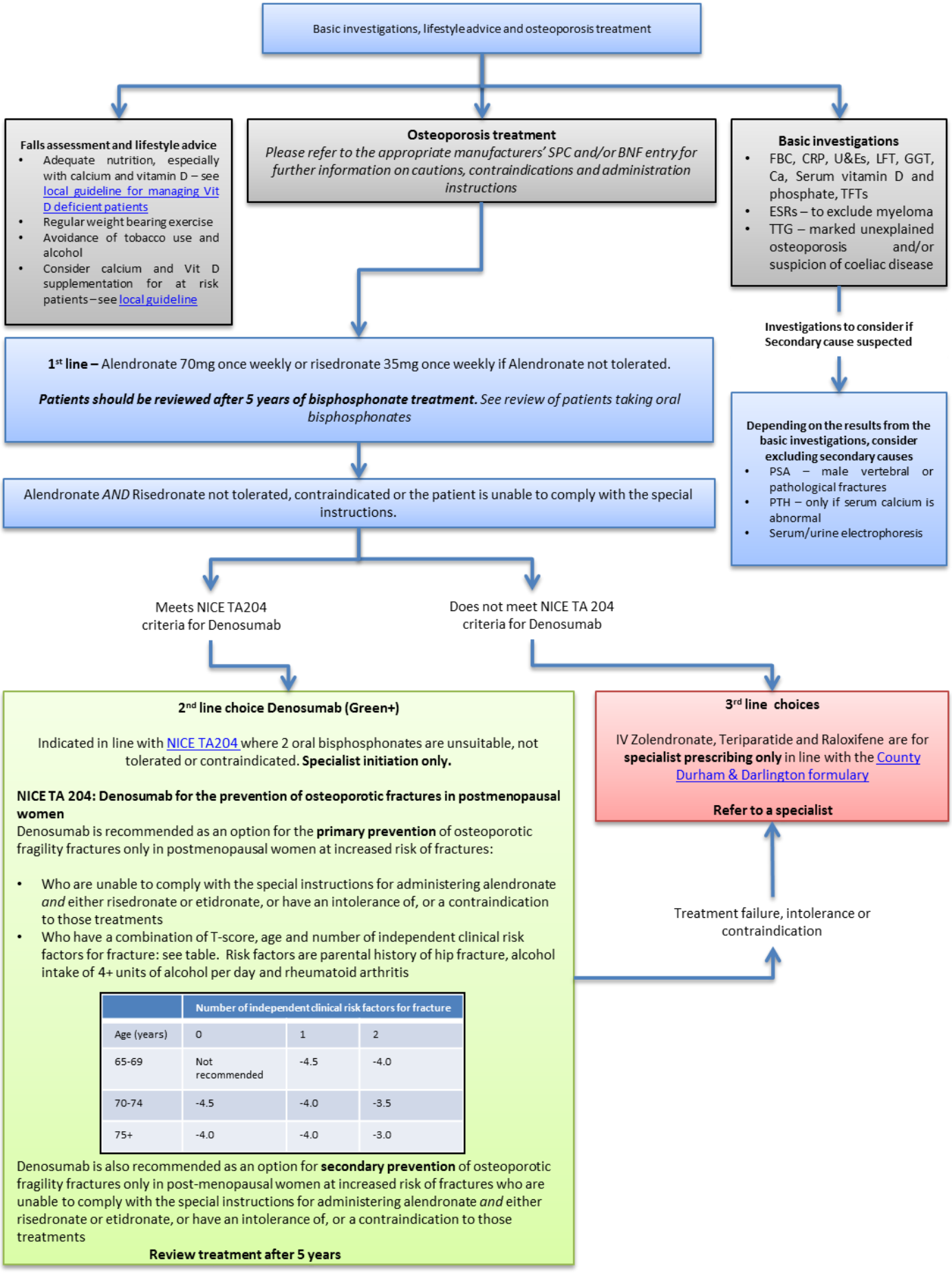
Bone density should be measured in those at high risk of osteoporosis; see British Society of Gastroenterology www.bsg.org.uk/images/stories/clinical/ost_coe_ibd.pdf .

Repeat bone density investigations (generally after ≥2 years) should otherwise be considered in patients who have low bone density on index measurement following initiation of appropriate treatment, or who have evidence of ongoing villous atrophy or poor dietary adherence.

Offer DXA scan to those at higher risk of osteoporosis e.g. 2 or more of the following BSG criteria:
- Continuing active disease (IBD)
- Persisting symptoms (coeliac disease) despite gluten free diet for more than 1 year (please review gluten free diet before referring for DXA – BMD can improve dramatically with adherence to a gluten free diet)
- Weight loss greater than 10%
- BMI less than 20kg/M^2
- Age greater than 70 years

Women taking aromatase inhibitors Exemestane, Anastrazole and Letrozole should have lower thresholds for initiating treatment. See: Guidance for the Management of Breast Cancer Treatment-induced Bone Loss

Osteoporosis Treatment Algorithm



Osteoporosis Treatment - Additional Information

Where possible, shared decisions about treatment should be made between clinicians and patients, incorporating the patient's values and preferences as well as the best medical evidence. It may be appropriate to consider life expectancy of patient and other co-morbidities with their 10 year risk of fracture.

First Line Treatments

Oral bisphosphonates - <u>alendronate 70mg once weekly or risedronate 35mg once weekly</u>

- Other oral bisphosphonates e.g. Ibandronic acid 50mg tablets are not approved for osteoporosis prevention and treatment
- Etidronate (Didronel PMO) has been discontinued

MHRA - Bisphosphonates Use and Safety; Oesophageal reactions

Oral formulations of the bisphosphonates alendronate, ibandronate and risedronate are associated with serious oesophageal adverse reactions including:

- oesophagitis
- oesophageal ulcers
- oesophageal strictures
- oesophageal erosions

Warnings about the risk of oesophageal reactions with oral alendronate, ibandronate and risedronate and clear instructions on how to take these medicines are provided in their product information.
In order to reduce the risk of oesophageal reactions healthcare professionals are advised that:

- alendronate and oral ibandronate should not be given to patients with abnormalities of the oesophagus and/or other factors which delay oesophageal emptying such as stricture or achalasia and Risedronate should be used with caution in such patients
- alendronate, oral ibandronate and risedronate should be used with caution in patients with active or recent upper gastrointestinal problems
- in patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of alendronate and risedronate on an individual basis. Oral ibandronate should be used with caution in patients with known Barrett's oesophagus
- patients should be advised about the importance of adhering to dosage instructions:
    - tablets should be swallowed whole with at least 200 ml of water on an empty stomach immediately after getting up in the morning
    - patients should stay fully upright for at least 30 minutes or one hour after taking the tablet and before taking any food, drink or other medicine
- patients should be advised to stop taking the tablets and to seek medical attention if they develop any symptoms of oesophageal irritation such as difficulty or pain upon swallowing, chest pain, or new or worsening heartburn

MHRA - Bisphosphonates Use and Safety; Osteonecrosis Of The Jaw

A Europe-wide review on the risk of osteonecrosis of the jaw (ONJ) in association with the use of bisphosphonates carried out in 2009 concluded that the risk is greater for patients receiving intravenous bisphosphonates for cancer than for patients receiving oral bisphosphonates for osteoporosis or Paget's disease of bone.

ONJ related to bisphosphonates is defined as an area of exposed or dead bone in the jaw that has lasted for more than 8 weeks, in a patient who has been or is currently being exposed to a bisphosphonate and has not has radiation therapy on the jaw.

All patients receiving intravenous bisphosphonates should have a dental check-up before bisphosphonate treatment. Urgent bisphosphonate treatment should not be delayed, however, a dental check-up should be carried out as soon as possible.
All other patients who start oral bisphosphonates should only have a dental examination before starting treatment if they have poor dental health.

During all bisphosphonate treatments, patients should be encouraged to:

- maintain good oral hygiene
- receive routine dental check-ups
- report any oral symptoms such as dental mobility, pain, or swelling

MHRA - Bisphosphonates Use and Safety; Atypical femoral fractures

Atypical femoral fractures have been reported rarely with bisphosphonate therapy, mainly in patients receiving long-term treatment for osteoporosis. The fractures occurred after minimal or no trauma, and some patients experienced thigh pain weeks to months before presenting with a completed femoral fracture.

Fractures were frequently bilateral, therefore the contralateral femur should be examined in bisphosphonate-treated patients who have a femoral shaft fracture. Poor healing of these fractures was also reported.

Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered while they are evaluated, and should be based on an assessment of the benefits and risks of treatment.

During bisphosphonate treatment, patients should be advised to report any thigh, hip or groin pain. Any patient who presents with such symptoms should be evaluated for an incomplete femur fracture.

MHRA – Bisphosphonates: very rare reports of osteonecrosis of the external auditory canal

The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms, including chronic ear infections, or in patients with suspected cholesteatoma

Steroid use and chemotherapy are possible risk factors, these could be with or without local risk factors such as infection or trauma

Patients should be advised to report any ear pain, discharge from the ear, or an ear infection during bisphosphonate treatment.

Contra-indications

- Abnormalities of oesophagus, factors which delay gastric emptying such as stricture or achalasia, hypocalcaemia.
- Avoid if eGFR less than 35ml/minute/1.73m (alendronate), 30ml/minute/1.73m² (risedronate)

Counselling

Take on an empty stomach first thing on a morning at least 30 minutes before food and drink or other medicines. Swallow whole with at least 200mL of water while sitting or standing and remain upright for at least 30min after taking.

Adherence with bone protection treatments

- Ask if the patient adherent with bisphosphonate.
- Ensure the patient understands what is being treated and is aware of the risks of non-adherence.
- Ask if the patient able to comply with specific instruction to take bisphosphonates.
- Do not refer the patient for a DXA if the patient has been significantly non-adherent (the bone clinic uses bone turnover markers to assess this).
- Ask if the patient suffering from any adverse effects.

Gastrointestinal effects with bisphosphonates e.g. dyspepsia or reflux

- Complying with the administration directions can help reduce GI adverse effects.
- If GI side effects intolerable on alendronate, consider switching to risedronate:

  Prescription-event monitoring studies in the UK found that dyspepsia is less common after one month of treatment with risedronate than with alendronate, with 26.9 events per 1000 patient-months compared to 32.3 events. The background rate of dyspepsia in women over 60 is 6 events per 1000 patient-months
- If patients develop upper oesophageal pathology during treatment (e.g. stricture, achalasia, Barrett's) on bisphosphonates; STOP the bisphosphonate consider if patient fits NICE criteria for denosumab and refer for consideration of other parenteral bone sparing agents if denosumab not suitable.

Second Line Treatments- If intolerance or compliance issues with first line therapy – For specialist initiation

Denosumab 60mg SC pre filled syringe every 6 months **GREEN PLUS DRUG**

Contraindicated in hypocalcaemia, therefore must be corrected prior to treatment by adequate intake of calcium and vitamin D before initiating therapy.
Check serum 25OH Vitamin D and if less than 50nmol/L correct according to local advice

Denosumab is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures 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 and
- who have a combination of T-score, age and number of independent clinical risk factors for fracture (see section 1.3) as indicated in the following table.

T-scores (SD) at (or below) which denosumab is recommended when alendronate and either risedronate or etidronate are unsuitable

	Number of independent clinical risk factors for fracture		
Age (years)	0	1	2
65-69	*	−4.5	−4.0
70-74	−4.5	−4.0	−3.5
75 or older	−4.0	−4.0	−3.0
*Treatment with denosumab is not recommended.			
Independent clinical risk factors for fracture are defined as; parental history of hip fracture, alcohol intake of 4 or more units per day and rheumatoid arthritis.			

MHRA Advice July 2015; Denosumab (Xgeva▼, Prolia); intravenous bisphosphonates: osteonecrosis of the jaw—further measures to minimise risk

Osteonecrosis of the jaw (ONJ) is a known side effect of denosumab and. To date, the MHRA have received 45 Yellow Card reports of ONJ in people taking denosumab (all doses) and 323 reports in people taking a bisphosphonate.

In patients treated for osteoporosis (regardless of route of administration), the risk of ONJ is small compared with that in patients treated with the higher doses used for cancer-related conditions. Other drug-specific risk factors for ONJ include drug potency (higher risk for highly potent compounds such as zoledronate, pamidronate and denosumab), route of administration (higher risk for parenteral administration) and cumulative dose

Before prescribing denosumab or intravenous bisphosphonates:

- give patients the patient reminder card for their medicine
- explain the risk of osteonecrosis of the jaw and advise patients on precautions to take—advise patients to:
  - tell their doctor if they have any problems with their mouth or teeth before starting treatment; if they wear dentures they should make sure their dentures fit properly before starting treatment
  - maintain good oral hygiene and get routine dental check-ups during treatment
  - tell their doctor and dentist that they are receiving denosumab or an intravenous bisphosphonate if they need dental treatment or dental surgery
  - tell their doctor and dentist immediately if they have any problems with their mouth or teeth during treatment (e.g. loose teeth, pain, swelling, non-healing sores or discharge)

MHRA Advice December 2014; Denosumab 60mg (Prolia) Rare cases of atypical femoral fracture with long-term use

Two cases of atypical femoral fracture have been confirmed in patients receiving denosumab 60 mg for 2.5 or more years participating in the ongoing open-label extension study of the pivotal phase 3 fracture trial in postmenopausal osteoporosis (FREEDOM). These events occurred rarely (in ≥ 1/10 000 to < 10/10 000 patients),

Advice for healthcare professionals:

- during denosumab treatment, patients should be advised to report new or unusual thigh, hip, or groin pain; patients presenting with such symptoms should be evaluated for an incomplete femoral fracture
- atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur
- the contralateral femur should be examined in denosumab-treated patients who have sustained a femoral shaft fracture, as atypical femoral fractures are often bilateral (as noted from the bisphosphonates assessment)
- discontinuation of denosumab treatment should be considered if an atypical femur fracture is suspected, while the patient is evaluated; an individual assessment of the benefits and risks should be performed

MHRA Advice June 2017; Denosumab (Prolia, Xgeva▼): reports of osteonecrosis of the external auditory canal

Advice for healthcare professionals:

- the possibility of osteonecrosis of the external auditory canal should be considered in patients receiving denosumab who present with ear symptoms including chronic ear infections or in those with suspected cholesteatoma
- possible risk factors include steroid use and chemotherapy, with or without local risk factors such as infection or trauma
- advise patients to report any ear pain, discharge from the ear, or an ear infection during denosumab treatment
- report cases of osteonecrosis of any bone suspected to be associated with denosumab or any other medicine on a Yellow Card

MHRA Advice September 2014; Denosumab: updated recommendations - Minimising the risk of osteonecrosis of the jaw; monitoring for hypocalcaemia.

Denosumab is also associated with a risk of hypocalcaemia. This risk increases with the degree of renal impairment. Hypocalcaemia usually occurs in the first weeks of denosumab treatment, but it can also occur later.

Hypocalcaemia
Denosumab 60 mg (osteoporosis indication)

- Check calcium levels:
  - before each dose
  - within two weeks after the initial dose in patients with risk factors for hypocalcaemia (eg, severe renal impairment, creatinine clearance less than 30 ml/min)
  - if suspected symptoms of hypocalcaemia occur.

Tell all patients to report symptoms of hypocalcaemia to their doctor (eg, muscle spasms, twitches, or cramps; numbness or tingling in the fingers, toes, or around the mouth).

Contra-indications

- Hypersensitivity to the active substance or to any of the excipients.
- Hypocalcaemia and vitamin D deficiency (patients can develop life threatening hypocalcaemia if not vitamin D replete at treatment) Correct before initiation see local guideline
- No dose adjustment is required in patients with renal Impairment, however, if patient creatinine clearance is less than 30 ml/min or receiving dialysis there is greater risk of developing hypocalcaemia.

There is little consensus on the recommended duration of treatment with denosumab, but data from the Freedom trial suggests it is safe and effective for 10 years. Patients should be advised to report symptoms suggestive of atypical fracture (e.g. hip or thigh pain) and be reviewed periodically.

Third Line - For specialist prescribing only.

Zolendronic acid intravenous infusion 5mg once a year RED DRUG – secondary care must prescribe

NICE TA 464:
Intravenous bisphosphonates (ibandronic acid and zoledronic acid) are recommended as options for treating osteoporosis in adults only if:

- the person is eligible for risk assessment as defined in NICE's guideline on osteoporosis (recommendations 1.1 and 1.2) and
- the 10-year probability of osteoporotic fragility fracture is at least 10% or
- the 10-year probability of osteoporotic fragility fracture is at least 1% and the person has difficulty taking oral bisphosphonates (alendronic acid, ibandronic acid or risedronate sodium) or these drugs are contraindicated or not tolerated.

MHRA Advice July 2008; Bisphosphonates: atrial fibrillation

Clinical trial results suggest an increased risk of atrial fibrillation for zoledronic acid (Aclasta▼), pamidronic acid, and possibly for alendronic acid, although the balance-risk remains favourable for bisphosphonates.

MHRA Advice April 2010; Intravenous zoledronic acid: adverse effects on renal function

Zoledronic acid is associated with reports of renal impairment and renal failure, especially in patients with pre-existing renal dysfunction or other risk factors

The following precautions should be taken into account to minimise the risk of renal adverse reactions with zoledronic acid:

- renal function should be measured before each infusion of zoledronic acid
- patients, especially elderly patients and those receiving diuretic therapy, should be appropriately hydrated before administration of zoledronic acid
- the duration of infusion of zoledronic acid should be at least 15 minutes
- monitoring of renal function after zoledronic acid infusion should be considered, particularly in at-risk patients such as: those with pre-existing renal dysfunction; those of advanced age; those using concomitant nephrotoxic drugs or diuretic therapy; or those who are dehydrated
- zoledronic acid should be used with caution when used concomitantly with medicines that could affect renal function
- A single dose of Aclasta▼ for the treatment of osteoporosis and Paget's disease of the bone should not exceed 5 mg Aclasta▼ should not be used in patients with creatinine clearance <35 mL/min

MHRA Advice July 2015; Denosumab (Xgeva▼, Prolia); intravenous bisphosphonates: osteonecrosis of the jaw—further measures to minimise risk

Osteonecrosis of the jaw (ONJ) is a known side effect of denosumab and. To date, the MHRA have received 45 Yellow Card reports of ONJ in people taking denosumab (all doses) and 323 reports in people taking a bisphosphonate.

In patients treated for osteoporosis (regardless of route of administration), the risk of ONJ is small compared with that in patients treated with the higher doses used for cancer-related conditions. Other drug-specific risk factors for ONJ include drug potency (higher risk for highly potent compounds such as zoledronate, pamidronate and denosumab), route of administration (higher risk for parenteral administration) and cumulative dose

Before prescribing denosumab or intravenous bisphosphonates:

- give patients the patient reminder card for their medicine
- explain the risk of osteonecrosis of the jaw and advise patients on precautions to take—advise patients to:
    - tell their doctor if they have any problems with their mouth or teeth before starting treatment; if they wear dentures they should make sure their dentures fit properly before starting treatment
    - maintain good oral hygiene and get routine dental check-ups during treatment
    - tell their doctor and dentist that they are receiving denosumab or an intravenous bisphosphonate if they need dental treatment or dental surgery
    - tell their doctor and dentist immediately if they have any problems with their mouth or teeth during treatment (e.g. loose teeth, pain, swelling, non-healing sores or discharge)

Contra-indications

- Hypersensitivity to the active substance, to any bisphosphonates or to any of the excipients
- Hypocalcaemia and vitamin D deficiency
- Severe renal impairment with creatinine clearance less than 35 ml/min

Recommended duration of treatment with zoledronate is not currently known. Patients should be advised to report symptoms suggestive of atypical fracture (e.g. hip or thigh pain) and be reviewed periodically. – see above for further information on atypical fractures

Teriparatide 250microgram/ml, 2.4ml prefilled syringe – 20 microgram daily In line with NICE TA161 RED DRUG – secondary care must prescribe

NICE TA 161: Teriparatide is recommended as an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women**:**

- Who are unable to take alendronate and risedronate, or have a contraindication to or are intolerant of alendronate and risedronate (as defined in section 1.6), or who have had an unsatisfactory response (as defined in section 1.8) to treatment with alendronate or risedronate and
- Who are 65 years or older and have a T-score of –4.0 SD or below, or a T-score of –3.5 SD or below plus more than two fractures, or who are aged 55–64 years and have a T-score of –4 SD or below plus more than two fractures.

Contra-indications
Pre-existing hypercalcaemia, skeletal malignancies, metabolic bone disease including Pagets and hyperparathyroidism, previous radiation to the skeleton

Raloxifene 60mg tablets – Once daily in line with NICE TA 161

NICE TA 160: Raloxifene is **not** recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women

NICE TA 161: Raloxifene is recommended as an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women:

- Who are unable to comply with the special instructions for the administration of alendronate and risedronate, or have a contraindication to or are intolerant of alendronate and risedronate and
- Who also have a combination of T-score, age and number of independent clinical risk factors for fracture (see section 1.5) as indicated in the following table.

	Number of independent clinical risk factors for fracture		
Age (years)	**0**	**1**	**2**
50-54	*	-3.5	-3.5
55-59	-4.0	-3.5	-3.5
60-64	-4.0	-3.5	-3.5
65-69	-4.0	-3.5	-3.0
70-74	-3.0	-3.0	-2.5
75+	-3.0	-2.5	-2.5
*treatment with Raloxifene is not recommended			
Independent clinical risk factors for fracture are defined as; parental history of hip fracture, alcohol intake of 4 or more units per day and rheumatoid arthritis.			

Contra-indications
Cholestasis, endometrial cancer, history of venous thromboembolism and undiagnosed uterine bleeding.

Calcium and Vitamin D for patients taking bisphosphonates and denosumab

Estimate calcium intake. These resources can help:
Healthy Bones The National Osteoporosis Society
Rheumatological Diseases Unit calcium calculator

- Ensure that the patient has at least intake of 700mg calcium / day :
- Patients should be advised on eating higher levels of calcium containing foods such as cheese and dairy products, oily fish and green vegetables. Intake can be estimated using a calcium calculator, a patient information sheet can be found here
- If more than 700mg there is no need for extra calcium, unless there is concern about calcium malabsorption e.g. IBD, corticosteroids.
- If calcium intake cannot be managed by diet, one tablet of a combined calcium/vitamin D supplement should be sufficient, current formulary choices are Accrete D_3 and Evacal in primary care and Adcal D3 or Calcichew D3 Forte in secondary care - see CDD formulary
- Beware groups at risk of hypercalcaemia: primary e.g. hyperparathyroidism and sarcoidosis, who must not receive calcium supplements.

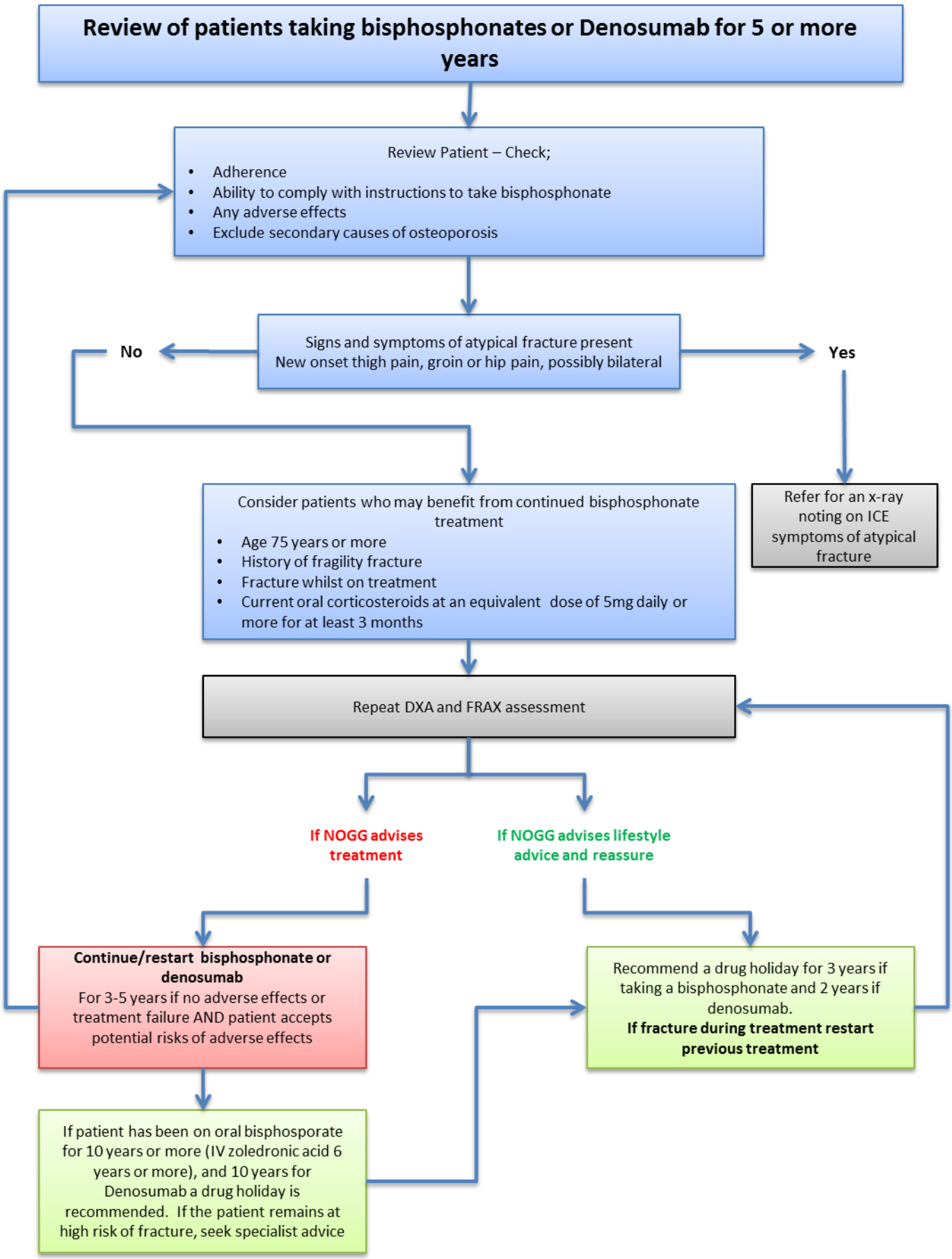
Estimate risk of vitamin D insufficiency/deficiency. Common groups at risk of vitamin D deficiency / insufficiency

See Local guidance on managing vitamin D deficiency and insufficiency

Example of groups at risk of vitamin D deficiency are:

- Non-white skin, lack of sunlight exposure (including concealing clothing, medications)
- Vegetarians (in particular non-fish eaters)
- Pregnant & breastfeeding women, babies, children and adolescents
- Older housebound or institutionalised people
- Liver and renal disease
- On medication that blocks the enterohepatic circulation of vitamin D (e.g. Colesevelam, or Colestyramine).

If at risk of insufficiency – Colecalciferol 10microgram (400 units) daily should be recommended if lifestyle/dietary changes are inappropriate. Self-care may be appropriate for most patients


Review of patients taking bisphosphonates or Denosumab for 5 or more years
Review Patient – Check;
Adherence
Ability to comply with instructions to take bisphosphonate
Any adverse effects
Exclude secondary causes of osteoporosis
Signs and symptoms of atypical fracture present
New onset thigh pain, groin or hip pain, possibly bilateral
No
Yes
Refer for an x-ray noting on ICE symptoms of atypical fracture
Consider patients who may benefit from continued bisphosphonate treatment
Age 75 years or more
History of fragility fracture
Fracture whilst on treatment
Current oral corticosteroids at an equivalent dose of 5mg daily or more for at least 3 months
Repeat DXA and FRAX assessment
If NOGG advises treatment
If NOGG advises lifestyle advice and reassure
Continue/restart bisphosphonate or denosumab
For 3-5 years if no adverse effects or treatment failure AND patient accepts potential risks of adverse effects
Recommend a drug holiday for 3 years if taking a bisphosphonate and 2 years if denosumab.
If fracture during treatment restart previous treatment
If patient has been on oral bisphosporate for 10 years or more (IV zoledronic acid 6 years or more), and 10 years for Denosumab a drug holiday is recommended. If the patient remains at high risk of fracture, seek specialist advice

Review of patients taking bisphosphonates and denosumab for 5 years or more – additional information

Good practice guidance recommends adherence should be checked at 4 months and annually after initiating treatment.

This guidance is proposed as a pragmatic approach to the patient who has been compliant with oral bisphosphonate or denosumab therapy for 5 years. By this point, the majority of the fracture risk reduction benefit has already accrued and the risk of atypical fractures and other long term complications of therapy begins to increase. The risk benefit balance of therapy therefore becomes less favourable and a period off therapy ("holiday") should be considered where appropriate.

Fracture risk may still be high for a significant number of patients; the principle is that the patient's fracture risk has been reduced and that they are benefiting from a sustained reduction in fracture risk even after discontinuing the treatment.

The evidence is limited as to how long the effects of bisphosphonates/denosumab continues and what the optimal period of time before treatment should be restarted is.

At review, the following should be discussed:

1. **Check Adherence with therapy**

Typically only 67% of patients are still compliant with oral bisphosphonate therapy at 12 months[13], therefore it is important to check adherence to treatment. If the patient is significantly non-adherent to the point where it is felt they are unlikely to have taken effective therapy for the past few years, then consideration should be given to alternative, more acceptable forms of therapy rather than a drug holiday.

2. **Check for Atypical Fractures:**

Does the patient have any signs or symptoms of an atypical fracture (new onset thigh, groin or hip pain, which may be bilateral)

At initiation of therapy patients should be advised of the small risk (1/1,000 / year) of atypical femoral fracture and advised to seek medical advice at onset of new hip or thigh pain. Atypical femoral fractures are a specific kind of stress fracture that can occur after minimal or no trauma in a very small number of patients. Symptoms include new onset thigh, hip or groin pain, and can be bilateral. The diagnosis is made by radiological confirmation of certain specific features, including site of fracture, transverse or oblique configuration, non-comminution etc. All patients should be screened at their 3-5 year review for possible atypical fractures and an x-ray of both hips and both femora requested if symptoms are present.

Before referring for DXA, consider if appropriate – some clinical judgment may be required if a DXA scan would not change clinical management e.g. end of life decision to stop treatment.

3. **Repeat DXA, repeat FRAX and discuss the risks and benefits of continuing treatment**

Repeat DXA to enable calculation of current FRAX score – this is particularly important if they were started on therapy before FRAX scores were widely used. (see also Note 4). If it is not possible or practical to repeat DXA then the patient should continue to take the bisphosphonate for 1 further 5 years and seek specialist advice at 10 years if DXA still not practical.

NOGG suggests that "continuation of bisphosphonate treatment beyond 3-5 years can generally be recommended in individuals age ≥75 years, those with a history of hip or vertebral fracture, those who sustain a fracture while on treatment, and those taking oral glucocorticoids (≥7.5mg prednisolone/day or equivalent)"

There are two options at this stage: either to continue therapy for a further 5 years or to stop for a period ("drug holiday") with the intention to possibly restart when conditions are right.

4. Continuing treatment with a bisphosphonate after 5 years for people at continued high risk of a fragility fracture

This is based on (expert opinion by NOGG and FLEX Extension study):

- Women with a T Score of less than -2.5 after 5 years of treatment have fewer non-vertebral fractures if they continue for up to 10 years
- Continuing treatment with alendronate after 5 years of treatment, for a further 5 years, is associated with a small reduction in clinically apparent vertebral fractures but no difference overall in fracture incidence at least for the first 2 years.

Some adverse events have been reported with long-term bisphosphonates. These are based on observational and post-marketing studies; there is a possible association but not proven causality with bisphosphonate use. Incidence of all is very rare. Further information can be found at:

http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con120237.pdf

5. Stopping bisphosphonate treatment for a "drug holiday" after 5 years

This recommendation is based on:

- Evidence that a drug holiday after 5 years of treatment with alendronate is associated with only a small increase in clinically apparent vertebral fractures, but no increase in other types of osteoporotic fractures.
- Evidence of rare but serious adverse effects of bisphosphonates, the incidence of which increases with continuing treatment.
- In patients who have taken continuous oral alendronate for 10 years, zoledronic acid for 6 years and denosumab for 10 years , a drug holiday is strongly recommended.

Assessment of bone health during a "drug holiday"

The principle here is to attempt to assess changes in the patient's skeleton whilst off therapy to inform decisions about future. Little evidence exists for how this should best be done; a pragmatic approach based on clinical consensus is suggested here.

Serial DXA scans may show a fall in BMD off bisphosphonate therapy, but absolute changes are small (1-2% fall per year) and may be close to the precision error and co-efficient of variation of the scanner. Large changes are required to be sure the effect seen is genuine, so a period of 24-36 months should be allowed between scans.

After 3 years off bisphosphonate therapy, if there are signs on DXA of deteriorating bone health then a further assessment using FRAX should be undertaken, to decide whether it is appropriate to restart therapy for a further 5 years. Choice of agent is the same as set out in the treatment algorithm on page 5. Note that patients should continue with calcium / vitamin D supplementation during the drug holiday.

Some patients may have stable BMD and/ or ongoing suppression of bone turnover well beyond 2 years; it is appropriate for these patients to remain off therapy with ongoing monitoring of DXA. However due to the difference in the mode of action of bisphosphonates and denosumab, the effect on bone turnover is lost more quickly with denosumab, hence why these patients should have a shorter drug holiday before reassessment.

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