BNSSG duration of oral osteoporosis drug therapy, denosumab and medication pauses guidelines for GPs

This guidance covers oral bisphosphonates, plus denosumab on page 3

Bisphosphonates

There have been reports that prolonged treatment with bisphosphonates is associated with an increased risk of rare adverse events including atypical femoral fractures (approximate risk of 100 atypical fractures per 100,000 people on prolonged oral bisphosphonates[1]) and osteonecrosis of the jaw (approximate risk of 1-90 per 100,000 years of patient exposure to oral bisphosphonates, more common in those with poor dental hygiene, dental interventions, cancer or on steroids[2]). These adverse events are rare, but they have raised questions about the optimal duration of therapy. **However, the risk/benefit ratio of bone protective agents remains favourable provided their use is limited to those at high risk of fracture.** Therefore, recommendations have been produced with the aim of re-evaluating the need for continued therapy after prolonged treatment, and the possible use of drug holidays. This document summarises current expert opinion and is based on the National Osteoporosis Guidelines Group (NOGG) 2017 update[3].

Recommendation 1: Treatment should be reserved for patients at high risk of fracture, and should be reviewed after 5 years of treatment with alendronate, risedronate or ibandronate (and after 3 years of treatment with zoledronic acid)

A key component of this reassessment is to identify if the patient had vertebral fractures or a previous hip fracture at baseline, and to identify any new *low-trauma* fractures that have occurred during treatment.

(a) If the patient had vertebral fractures or a previous hip fracture at baseline, or new low-trauma fractures have occurred during treatment (particularly new hip or new vertebral fractures): (1)check adherence to medication; (2)exclude secondary causes of osteoporosis; and then (3)consider continuing treatment for a further 5 years. If a new low trauma hip or vertebral fracture has occurred, treatment **should** be continued for a further 5 years. If a new low trauma **non-vertebral or non-hip** has occurred, **consider** continuing treatment for a further 5 years.

To be effective, patients must take oral bisphosphonates first thing in the morning with a large glass of water whilst sitting or standing bolt upright. The patient must not eat or drink anything else except water (including no tablets and no calcium/vit D supplements) for at least 30 minutes. Adherence of less than 80% is associated with increased fractures and increased healthcare utilisation[4]. In this situation, NICE recommends alternative medications should be considered e.g. parenteral[5].

(b) If the patient did not have vertebral fractures or a previous hip fracture at baseline, and no new low-trauma fractures have occurred: (1)reassess fracture risk using FRAX with DXA every 5 years; and then (2)use the thresholds of 20% for a major fracture or 5% for a hip fracture to decide on the need for ongoing therapy

- If the patient's fracture risk falls below the intervention threshold (20%/5%) and hip BMD T score is greater than -2.5, consider a medication pause.
- If the patient is above the intervention threshold (20%/5%) or hip BMD T score is below -2.5, then (1)check adherence to medication; (2)exclude secondary causes of osteoporosis; and then (3) consider continuing treatment for a further 5 years.

Recommendation 2: After 5 years of treatment, if the patient's fracture risk falls below the intervention threshold and hip BMD T score is greater than -2.5, consider a medication pause.

Withdrawal of treatment is associated with decreases in BMD and increased bone turnover after 2-3 years for alendronate and 1-2 years for ibandronate and risedronate[6-8]. In the case of zoledronic acid, withdrawal after 3 years' treatment was associated with only a very small decrease in BMD after a further 3 years without treatment. Suggested lengths of medication pauses are therefore:

Medication	Recommended length of medication pause
Alendronate	2-3 years
Risedronate	1-2 years
Ibandronate	1-2 years
Zoledronic acid	3 years

During a medication pause, fracture risk should be reassessed after any new low trauma fracture, or at the end of the pause to decide whether treatment needs to be restarted.

Recommendation 3: Continuation of treatment up to 10 years can generally be recommended for patients with high fracture risk

Based on evidence from extension studies of the pivotal randomised controlled trials [9], treatment beyond 5 years can generally be recommended in the following situations:

1. If the patient had vertebral fractures or a previous hip fracture at baseline, or new low-trauma fractures have occurred during the initial 5-year treatment period
2. Age 70 years or more
3. Current treatment with oral glucocorticoids ≥7.5mg prednisolone/day or equivalent

Recommendation 4: There is little evidence to guide decisions about treatment beyond 10 years and management of such patients should be considered on an individual basis

In a nationwide cohort study from Denmark[10], use of alendronate in excess of 10 years was associated with a 30% lower risk of hip fracture and no increase in the risk of fractures of the sub-trochanteric femur and femoral shaft, supporting an acceptable risk benefit balance in terms of fracture outcomes.

References:
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[3] NOGG 2017: Clinical guideline for the prevention and treatment of osteoporosis. Archives of Osteoporosis DOI 10.1007/s11657-017-0324-5.
[4] Caro JJ et al (2004) The impact of compliance with osteoporosis therapy on fracture rates in actual practice. Osteoporos Int 15:1003-1008.
[5] NICE Technology Appraisal Guideline 204.
[6] Ensrud KE et al (2004) Randomised trial of effect of alendronate continuation versus discontinuation in women with low BMD: results from the FIT long-term extension. J Bone Miner Res 19:1259-1269.
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[8] Watts NB et al (2008) Fracture risk remains reduced one year after discontinuation of risedronate. Osteoporos Int 19:365-372.
[9] Black DM et al (2006) Effects of continuing or stopping alendronate after 5 years of treatment: the FIT Long-term Extension (FLEX): a randomised trial. JAMA 296:2927-2938.
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Denosumab

Denosumab doses should be at regular 6 monthly intervals. There is increasing evidence that withholding or stopping treatment with denosumab may be associated with an increase in bone turnover and a rebound increased risk of fractures, particularly an increased risk of vertebral fractures[11]. There have been several cases reports describing multiple vertebral fractures occurring 2 to 16 months after denosumab cessation, more common in those with previous vertebral fractures[12-13]. There is concern that this rebound increased risk of fracture is greater than the potential for rare adverse effects such as osteonecrosis of the jaw with continued treatment.

Recommendation 5: Denosumab doses should be at regular 6 monthly intervals. DO NOT stop or withhold denosumab without considering an alternative treatment plan to prevent the likely rebound increased risk of fractures

If it is necessary to stop or withhold denosumab, an alternative management plan may be required to prevent the possible rebound increased risk of fractures. This should be considered on an individual basis, but may include IV Zoledronic acid (including as a one-off dose), restarting oral bisphosphonates[14] or discussion with secondary care. Continuation of denosumab can also be considered until results from ongoing trials become available. **If you are unsure what to do, please continue denosumab whilst seeking advice from the patient's rheumatology or elderly care team.**

Recommendation 6: Continuation of denosumab treatment up to 10 years can generally be recommended for patients with high fracture risk

There is good safety and effectiveness data for the use of denosumab up to 10 years[15]

1. If the patient had vertebral fractures or a previous hip fracture at baseline, or new low-trauma fractures have occurred during the initial 5-year treatment period
2. Age 70 years or more
3. Current treatment with oral glucocorticoids ≥7.5mg prednisolone/day or equivalent

Recommendation 7: There is little evidence to guide decisions about denosumab treatment beyond 10 years and management of such patients should be considered on an individual basis

If the patient's fracture risk falls below the intervention threshold (20%/5%) and hip BMD T score is greater than -2.5, consider a medication pause. If denosumab is stopped, further treatment with IV zoledronic acid[16] (usually as a single dose 6 months after last denosumab injection) or an oral bisphosphonate should be considered (as long as renal function allows). Further advice may need to be sought from your local rheumatology or elderly care bone health service.

References:
[11] Tsourdi E et al (2017) Discontinuation of denosumab therapy for osteoporosis: A systematic review and position statement by ECTS. Bone DOI 10.1016/j.bone.2017.08.003
[12] Brown JP et al (2016) Discontinuation of denosumab and associated fracture incidence: Analysis from FREEDOM and its extension. J Bone Miner Res 31 (Suppl 1).
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