A GUIDE TO

deprescribing

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An Australian Government Initiative

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CPS Experts in Medicines
CONSULTANT PHARMACY SERVICES

BISPHOSPHONATES

KEY POINTS

Oral bisphosphonates are effective in the prevention of secondary fractures with one fracture avoided for every 40-90 patients treated for 1-3 years.

Many patients who have had 5 years of continuous treatment with an oral bisphosphonate may have ongoing benefit for a further 5 years after cessation of the bisphosphonate.

Some patients with very low BMD or recurrent fractures during a bisphosphonate-free period may require recommencement of osteoporosis treatment.

Where treatment for osteoporosis is required beyond 5 years of bisphosphonate therapy, options other than bisphosphonates, such as denosumab, may be considered, particularly if non-compliance with bisphosphonate treatment is suspected.

CONTEXT

This guide considers the use of oral bisphosphonates in the treatment of osteoporosis. The information in this guide does not apply to denosumab treatment.

BENEFIT VERSUS HARM

	Favours Continuing Medication	Favours Deprescribing Medication
Main Benefits Reduction in fractures and/ or falls	**Increased Benefit** • High fracture risk (low BMD, high falls risk) • Recurrent fractures during treatment (that is not associated with non-compliance) • Adequate calcium and vitamin D supplementation	**Decreased Benefits** • Normal Bone Mineral Density • Limited life expectancy due to comorbidities (dementia, heart failure, airways disease, malignancy) • Low fracture risk • Five or more years of continuous treatment
Main Harms Hypocalcaemia	**Reduced Harms** • Calcium and vitamin D supplementation	**Increased Harms** • Invasive dental procedures (increased risk of osteonecrosis of the jaw) • Hypocalcaemia and/or severe vitamin D deficiency • Renal dysfunction (CrCl < 30ml/min)

RECOMMENDED DEPRESCRIBING STRATEGY

- Patients with a history of osteoporosis who have had 5 years of bisphosphonate treatment and whose risk of fracture is now low could have their bisphosphonate ceased for 5 years (see **Figure 1**).
- Use risk calculators such as the Garvan Institute's Fracture Risk Calculator (available here: https://www.garvan.org.au/promotions/bone-fracture-risk/calculator/index.php) or the Fracture Risk Assessment Tool (FRAX) (available here: https://www.sheffield.ac.uk/FRAX/tool.aspx?country=31) to estimate a patients risk of fracture in the next 2, 5 or 10 years. Both calculators can incorporate T scores to help determine fracture risk, but risk can still be estimated in the absence of a T score.
- Shared decision making with patient, including informing them about slight potential increase in fracture risk upon discontinuation
- A plan for regular (e.g. biennial) monitoring of bone mineral density may be of benefit to monitor for any decline.
- Patients who re-fracture during this time should be considered for recommencement of antiresorptive therapy.
- Cessation can be abrupt, no discontinuation syndromes have been described.
- Calcium and vitamin D supplementation may be ceased after the cessation of bisphosphonate treatment.

BACKGROUND

Bisphosphonates are potent inhibitors of bone-resorbing cells (osteoclasts). They work to inhibit bone resorption by interfering with normal osteoclast function and inducing osteoclast apoptosis. As they are rapidly sequestered into bone (from where they are only slowly released) and eliminated by the kidney, exposure to soft tissues, including bone marrow, is transient.

Alendronate and risedronate are taken orally while intravenous zoledronic acid is given annually.

DENOSUMAB

Denosumab is a fully human monoclonal antibody that binds to the receptor activator of nuclear factor-KB ligand (RANKL), inhibiting the differentiation, action and survival of osteoclasts, therefore inhibiting bone resorption.[1,2] Following subcutaneous injection with denosumab, bone resorption markers decrease rapidly and significantly (>80% from baseline) within 12 hours, reaching nadir at approximately 1 month and remaining low for 6 months. Therefore, the dose of denosumab is 60mg administered as a subcutaneous injection every 6 months. This twice yearly dosing may be more suited to older patients with polypharmacy and increased tablet load or those that are unable to remain upright after oral bisphosphonate administration, as well as increasing persistence to treatment.[3]

There are several studies that compare the efficacy of denosumab in patients that were previously treated with bisphosphonates. Denosumab has been shown to be superior to risedronate, alendronate, zoledronic acid and ibandronate in regards to increases in BMD and reduction in bone resorption markers.[3] Denosumab is also not excreted renally and can be used in patients with renal impairment in contrast to bisphosphonates.[4] Adverse effects of denosumab include muscle pain, hypercholesterolemia (common), hypocalcaemia, ONJ, atypical femur fractures and infections (less common).[5]

Strict adherence to the twice yearly denosumab injections is crucial. Unlike bisphosphonates, discontinuing denosumab often leads to a rapid reversal of its inhibitory effects on bone remodelling, characterised by an increase in bone resorption markers and a reduction in BMD.[6] Results from phase 2 trials with denosumab showed the increase in bone mass after 2 years of treatment was lost after 12 months of discontinuation. The increase of bone resorption markers were greater than baseline, suggestive of a hyper-resorptive state.[7]

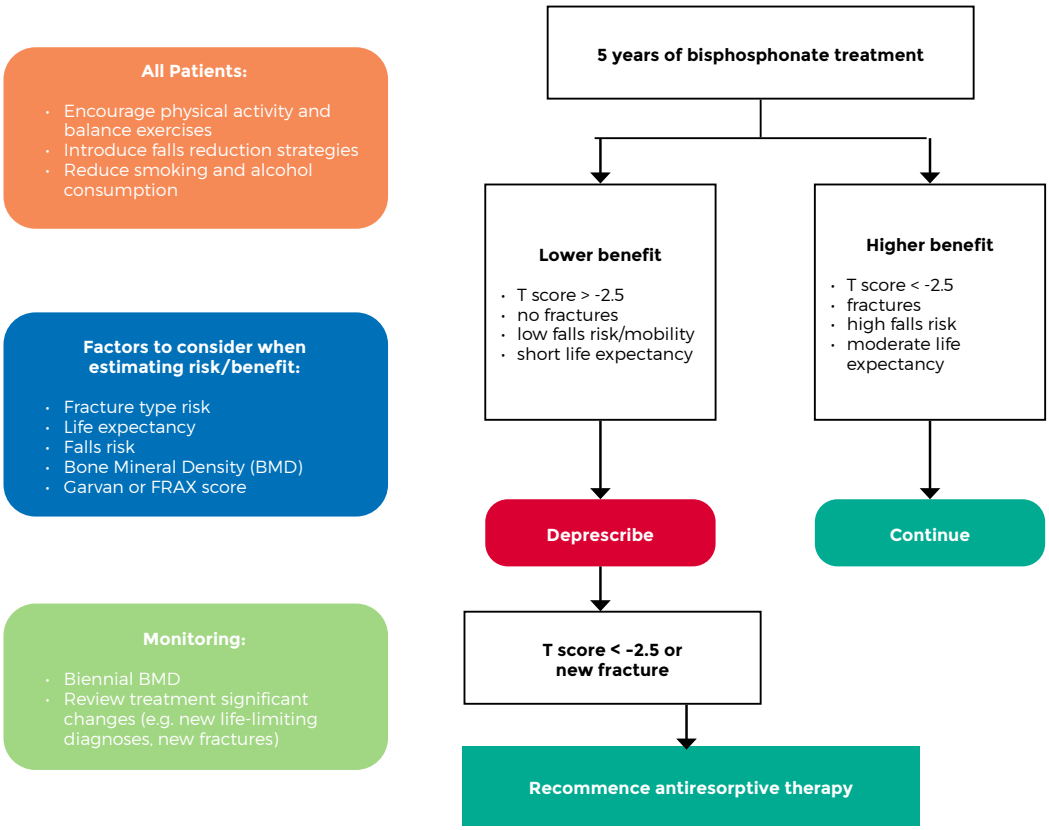

Figure 1: Cessation of Bisphosphonates after 5 years of treatment

EFFICACY

Both US and Australian osteoporosis treatment guidelines recommend antiresorptive therapy with a bisphosphonate or another agent to reduce the risk of vertebral and non-vertebral fractures in postmenopausal women and men over the age of 50 at high risk of fracture (those with osteoporosis by bone mineral density [BMD] criteria or a prior minimal trauma fracture).[1, 2]

A systematic review of 315 studies looked at the effectiveness and adverse events of a range of treatments to prevent fractures.[3] Their findings indicate strong evidence for the efficacy of a number of bisphosphonates. The magnitude of the effect indicated a NNT of between 40 and 89 over 1-3 years of treatment to prevent one fracture in women.[3]

A meta-analysis of 10 RCTs involving over 23,000 post-menopausal women with osteoporosis found that 12.4 months (95% CI, 6.3-18.4 months) of bisphosphonate treatment was needed to prevent 1 nonvertebral fracture per 100 women. Around 20.3 months (95% CI, 11.0-29.7 months) was needed to prevent 1 hip fracture per 200 women. Furthermore, bisphosphonate treatment for 12.1 months (95% CI, 6.4-17.8 months) prevented 1 clinical vertebral fracture.[4] These findings demonstrate the importance of time-to-benefit, in regards to life expectancy and change in clinical status.

The current Australian guidelines also suggest reconsidering the need to continue bisphosphonate therapy after 5–10 years in postmenopausal women and men over the age of 50 with osteoporosis who have responded well to treatment (T-score ≥–2.5 and no recent fractures). This recommendation is largely based on the results of the FLEX trial.

The FLEX trial looked at the legacy effect of alendronate for patients who had been treated in the FIT trial for 5 years.[5] They found that there was no difference in non-vertebral fracture risk in patients who continued alendronate for a further 5 years, compared to those that took a placebo for the five years. There was however an increase in the number of clinical vertebral fractures in patients who took placebo instead of alendronate (23/437; 5.3%) vs 16/662; 2.4% respectively; NNT 34 for one vertebral fracture over 5 years.

The same authors reanalysed the data at a later date to look more closely at those patients with nonvertebral fractures.[6] They clarified that in those patients without a previous vertebral fracture and a T score of -2.5 or less (when they had completed 5 years of alendronate treatment) that there was a benefit in fracture risk reduction (14.7% vs 28%, NNT ~7 over 5 years) compared to no benefit in those patients with a T score of -2.5 or above,[6] i.e. in patients with an ongoing high risk of vertebral fracture, there may be benefit of continuing treatment.

The Australian guidelines acknowledge this. By suggesting "If BMD remains low (T-score ≤–2.5) and/or there are incident vertebral fractures, continue treatment." And also "Treatment should be restarted if there is evidence of bone loss, especially at the hip, or if a further minimal trauma fracture is sustained."[2]

ADVERSE EFFECTS

Oral bisphosphonates are poorly absorbed (less than 5% bioavailable) and as such require relatively strict administration procedures. It is recommended that patients do not lie down for 30min after taking an oral bisphosphonate and that it be taken at least an hour before the first food, beverage or other oral medicines of the day.[7] The only oral bisphosphonate that does not need to be separated from food is enteric coated risedronate, however staying upright for 30min after dosing is still required.[8] Due to local irritant effects , a range of upper gastrointestinal and abdominal symptoms (abdominal pain ~ 7%, acid dyspepsia, regurgitation and nausea (all ~ 4%) can be problematic.[7]

Long term bisphosphonate use has been associated with an increased risk of atypical femoral fractures.[10] A report of a nationwide study of bisphosphonate use in Sweden indicated a markedly increased relative risk of femoral shaft fracture in both women (RR 55; 95% CI 39-79) and men (RR 54; 95% CI 15-192), with the cumulative risk increasing with duration of use during the 4 year follow up.[11] The absolute risk remained low (11 per 10,000 years of patient use; Annual NNH 909) and the risk decreased rapidly (by 70% per year) after cessation of bisphosphonate.

Bisphosphonate associated osteonecrosis of the jaw (ONJ) is a rare, but serious clinical condition caused by anti-osteoclastic, antiangiogenic and anti-human endothelial cell proliferation effects of bisphosphonates, which inhibit bone turnover.[12] ONJ more often develops in those patients who are receiving either long term IV bisphosphonate therapy alone or have associated invasive dental procedures.[12] The incidence of ONJ is difficult to ascertain with one of the major drug companies estimating an incidence rate of 0.7 per 100,000 patients (0.0007%) for oral therapy.[13] Estimates of 0.001% to 0.01% have been proposed by other authors (Annual NNH of 1000-10,000).[14-17]

FACTORS TO CONSIDER

IN FAVOUR OF DEPRESCRIBING

Low risk of falls/Immobility

If patients have a low risk of falls, there may no longer be ongoing benefit to non-vertebral fracture risk reduction. Indeed if the reduced falls risk is due to prolonged immobility, even the requirement to sit upright to administer the oral bisphosphonate may be sufficient reason to reconsider the therapy.

No previous vertebral fractures and 5 years or more of treatment

In patient with only non-vertebral fractures, there seems to be little ongoing benefit of bisphosphonates for the first 5 years after an initial 5 years treatment period, particularly if their T score is above -2.5 at the end of the first 5 years.

FACTORS AGAINST DEPRESCRIBING

High Fracture Risk (Low T Score, high falls risk, steroids etc.)

Patients with a higher risk of fractures, such as those with a very low T score (-2.5 or below) may have ongoing benefit from fracture risk reduction treatment with a bisphosphonate or another antiresorptive agent.

DISCONTINUATION SYNDROMES

Bisphosphonates can be stopped abruptly without the need for tapering.

However, discontinuation of bisphosphonates may be associated with a slight increase in risk of hip fractures. In a propensity score-matched cohort study from 2022, it was found that risk of hip fractures was greater amongst participants who had received risedronate therapy followed by a period of time without the drug (a drug holiday) in comparison to those who had received alendronate therapy followed by a drug holiday (12.4 and 10.6 events respectively, per 1000 patient years). This may be attributed to the shorter half-life of risedronate.[18]

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AUTHORSHIP

This guide was prepared for Primary Health Tasmania by Xenia Jak and reviewed by the Deprescribing Project Advisory Group, Angus Thompson, Pharmacist Clinical Editor, Primary Health Tasmania and Dr David Dunbabin, Geriatrician.

DEPRESCRIBING PROJECT ADVISORY GROUP

DECEMBER 2022