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 will have ongoing benefit for a further 5 years after cessation of the bisphosphonate.**
  - **If BMD remains low (T-score ≤–2.5) and/or there are incident vertebral fractures, continue treatment.**
- **Some patients with very low BMD or recurrent fractures during a bisphosphonate-free period may require recommencement or osteoporosis treatment.**
- **Where ongoing treatment for osteoporosis is required, options other than bisphosphonates may be safer.**

CONTEXT

This guide considers the use of oral bisphosphonates in the prevention of osteoporotic fractures.

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 should have their bisphosphonate ceased for up to 5 years.
- If BMD remains low (T-score ≤–2.5) and/or there are incident vertebral fractures, continue treatment.
- 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.

BENEFIT VERSUS HARM

Main Benefits
- Reduced Fracture Risk

Main Harms
- Hypocalcaemia

Favours Continuing Medication	Favours Deprescribing Medication
Increased Benefit › High fracture risk (low BMD, high falls risk) › Recurrent fractures during treatment › Adequate calcium and vitamin D supplementation	**Decreased Benefits** › Low fracture risk (low falls risk) › Five or more years of continuous treatment
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)

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 usually taken orally on a daily (alendronate 10 mg, risedronate 5 mg) or weekly (alendronate 70 mg, risedronate 35 mg) basis. Intravenous bisphosphonates (once yearly 5 mg zoledronic acid) can be used as a first-line osteoporosis therapy but are often used in patients intolerant to oral preparations or likely to be non-adherent to oral medications.

EFFICACY

Both American 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. 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]**

The current Australian guidelines also suggest reconsideration of 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.[4] 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 later to look more closely at those patients with nonvertebral fractures.[3] They clarified that in those patients without a previous vertebral fracture and with 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.[5]

Thus, **in patients who's fracture risk remains high, there may be ongoing benefit.**

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]

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

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 fracture risk reduction benefit from treatment with a bisphosphonate or another antiresorption agent.

DISCONTINUATION SYNDROMES

Bisphosphonates can be stopped abruptly without the need for tapering.

RESOURCES

- GENERAL INFORMATION
- ALLOPURINOL
- ANTIHYPERGLYCAEMICS
- ANTIHYPERTENSIVES
- ANTIPSYCHOTICS
- ASPIRIN
- BENZODIAZEPINES
- BISPHOSPHONATES
- CHOLINESTERASE INHIBITORS
- GLAUCOMA EYE DROPS
- NSAIDS
- OPIOIDS
- PROTON PUMP INHIBITORS
- STATINS
- VITAMIN D AND CALCIUM

AUTHORSHIP

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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 the agent and that it be taken at least an hour before the first food or beverage of the day. They are highly irritant to the oesophageal mucosa and can cause a range of upper abdominal and gastrointestinal symptoms (abdominal pain ~ 7%, acid dyspepsia, regurgitation and nausea (all ~ 4%).[6]

Long term use has been associated with an increased risk of atypical fractures. A report of a Nationwide study of bisphosphonate use in Sweden indicated a markedly increased relative risk of fracture of the femoral shaft in both women (RR 55; 95% CI 39-79) and men (RR 54; 95% CI 15-192), with the risk increasing with duration of use.[7] The absolute risk remained low (11 per 10,000 years of patient use; 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.[8] ONJ more often develops in those patients who are receiving either long term nitrogenous intravenous bisphosphonate therapy alone (pamidronate or zoledronate) or have associated invasive dental procedures.[8] Incidence is difficult to ascertain with one of the major drug companies estimating an incidence rate of 7 per million patients (0.0007%) for oral therapy.[9] Estimates of 0.001% to 0.01% have been proposed by other authors (Annual NNH of 1000-10,000).[10-13]

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