Medication selection and patient compliance in the clinical management of osteoporosis

Charles A Inderjeeth, Andrisha-Jade Inderjeeth, Warren David Raymond

Background

Osteoporosis contributes significantly to morbidity and mortality. Antiresorptive therapy is effective in primary and secondary fracture prevention, but compliance with bisphosphonate therapy is poor, resulting in poorer patient outcomes.

Objectives

The objectives of this article are to aid clinicians' treatment selection and improve patient adherence.

Discussion

A literature review of treatment options and factors contributing to poor patient treatment adherence was conducted for this article. The effectiveness of osteoporosis treatment is reduced because of poor adherence. This is associated with a lack of patient understanding of their condition, perception of fracture risk and concerns about adverse events. Appropriate treatment selection and novel oral and parenteral options may help improve compliance. Increasing treatment adherence requires clinicians to improve patient education. Discussion around patient preferences, implications of fragility fractures, minimising side effects and efficacy of treatment is essential despite the lack of any tangible 'symptom' benefit.

Fragility fractures are a common cause of hospitalisation, with significant cost, morbidity and mortality.[1–3] Studies have demonstrated the benefit of treatment in primary prevention (first fracture) and treatment (prevalent fracture) in patients with osteoporosis.[4–6]

The association between poor adherence and fracture risk highlights the importance of compliance and persistence.[7] Medications (alendronate, risedronate, zoledronic acid and denosumab) are listed on the Pharmaceutical Benefits Scheme (PBS)[8] for primary and secondary fracture prevention in patients with prevalent fracture (Table 1).

Less than 20% of women and 10% of men with osteoporotic fractures receive treatment. Half do not take their treatment as prescribed (poor compliance) and 47% discontinue therapy within six months (lack of persistence).[5,9] There are multiple reasons for poor adherence (eg patient perception, side effects, dosing intervals).[4,7,9] This article considers the barriers to osteoporosis treatment, and discusses evidence-based strategies to improve adherence.

This informal literature review is an extension of the review completed by Lee et al in 2011.[9] A MEDLINE search for more recent articles identified 50 additional articles from 2011 to 2015. The main search terms were 'bisphosphonates', 'denosumab', 'osteoporosis' 'fracture', 'adherence', 'compliance', 'persistence' and 'efficacy'.

Patient perceptions and adherence

Forgetfulness is a concern that can be addressed using reminder systems.[10–13]

Table 1. Bisphosphonates available in Australia and approved indications for use[8]

	Osteoporosis		Corticosteroid-induced osteoporosis	
	Prevention	Treatment	Prevention	Treatment
Alendronate sodium	✓	✓	✓	✓
Risedronate sodium	✓	✓	✓	✓
Risedronate sodium (enteric coated)	✓	✓	✓	✓
Zoledronic acid	✓	✓	✓	✓

Electronic reminder systems are effective in improving patient drug compliance.[11,12] While 'forgetting' is a compliance issue, it is no longer recognised as a primary reason for poor compliance.[13] Research suggests that some patients choose not to take medication.[13] The major reasons for non-adherence include asymptomatic disease manifestation ('silent disease') and an underestimation of the risk of fracture.[14] The Global Longitudinal Study of Osteoporosis in Women found that only half of women with osteoporosis with multiple risk factors and receiving treatment for the disorder perceived themselves to be at increased risk of fracture.[15]

A Cochrane review on strategies to improve adherence highlighted the importance of more frequent patient interaction and regularly discussing compliance.[16] Other studies cited the benefit of improving patient–provider relationships and patient education through regular follow-up, risk assessment and treatment monitoring.[17,18]

Poor compliance compounds poor bioavailability of bisphosphonates

Oral bisphosphonates are poorly absorbed by the gastrointestinal system because of their low lipophilicity, large molecular structure and negative charge.[19] Typically, only 0.3–1.0% of the dose is absorbed after ingestion.[19,20] Taking these medications with food can decrease the bioavailability of the bisphosphonate by 60–90% because of physicochemical interactions between medicines and compounds present in the food, especially calcium and dairy products.[20] Low bioavailability of oral bisphosphonates results in a clinically insignificant amount of the drug reaching its target, thereby diminishing efficacy.[20] In some circumstances, measuring bone turnover markers may be useful in confirming compliance.

Fasting and the '30 minutes before food or drink' requirement to improve bioavailability are commonly reported as reasons for patients failing to comply with oral bisphosphonate therapy.[9,14] This barrier may be overcome by patients using enteric-coated, delayed-release weekly risedronate tablets, zoledronic acid infusion or subcutaneous denosumab.[21] These may also be the preferred treatment modality for patients who, for example, are unable to fast for medical or other reasons, have cognitive impairment, or are identified by their clinicians as being poorly compliant patients.[20] However, oral bisphosphonates should not be taken with calcium and dairy products.

Adopting a patient-centred, flexible approach to dosing intervals

Bisphosphonate dosing intervals are noted as being inconvenient and a barrier to adherence.[9,22,23] An alternative to frequent oral bisphosphonate dosing is an annual intravenous bisphosphonate (zoledronic acid) or six-monthly subcutaneous injections with denosumab, a rank ligand inhibitor. Patients have reported increased satisfaction with zoledronic acid or denosumab, compared with weekly oral bisphosphonate medications.[9]

Less frequent dosing (ie twice yearly denosumab or yearly zoledronic acid) may guarantee absolute compliance. However, because of needle phobia, acute phase reactions, infusion centre costs and scheduling reminders for both agents, persistence with zoledronic acid is not guaranteed. By contrast, more frequent dosing develops regular routines, which may aid adherence.[9] Clinicians should optimise the dosing regimen on the basis of the patient's preference and characteristics.

Timing of initiation and clinician's choice of treatments

Earlier treatment is recommended for patients presenting with fracture, as early fracture risk is greatest and benefits occur as early as three to six months.[24] Results from randomised controlled trials investigating fracture prevention outcomes have confirmed differences in efficacy onset and offset between bisphosphonate options and treatment (Table 2).[24]

Inherent differences in dose, frequency and biological activity (binding affinity and potency) each affect time to efficacy onset and offset. A clinician's choice of bone-sparing agent will aim to maximise benefit for treating the patient's disease by balancing the time to efficacy onset with possible side effects while managing the patient's risk of osteoporotic fracture(s). For example, for older and more frail patients at higher fracture risk and with a shorter life expectancy, the primary treatment goal would be the simplest dosing and fastest efficacy onset, as opposed to treatment durability (Table 3).[24] Clinicians need to balance the benefit of a weekly routine versus the convenience

Table 2. Results of all relevant studies showing the range of earliest onset of fracture efficacy and ranking of effect offset[24]

	Vertebral fracture	Nonvertebral fracture	Hip fracture	Any clinical fracture	Rapidity of effect offset ranking
Aledronate	6–48 months	12–24 months	18–48 months	12–48 months	Second
Risedronate	6–12 months	6–36 months	6–36 months	6–36 months	First
Zoledronic acid	12–24 months	24–36 months	36 months	12–36 months	Third

of a monthly routine versus the ensured compliance of less frequent parenteral options, with the added logistical considerations of arranging treatment.

Managing adverse upper gastrointestinal side effects with oral bisphosphonates – Balancing benefit and risks

Patients initiated on oral bisphosphonates are three times more likely to see their general practitioner (GP) within six weeks because of adverse upper gastrointestinal effects.[25] Where this is not remediable, alternative modalities of bisphosphonate delivery, such as parenteral zoledronic acid, less frequent oral dosing or non-bisphosphonate options (denosumab or raloxifene), may be preferable.[9]

In circumstances where oral bisphosphonates remain the preference despite persistent gastrointestinal symptoms (rarely), co-administration with a proton pump inhibitor (PPI) or H_2 receptor antagonists (H_2RAs) may be considered. This co-administration is effective in reducing adverse gastrointestinal effects.[23–25] Although some studies suggest that PPI use may be associated with a modest decrease in alendronate efficacy, a post-hoc analysis of three clinical trials with risedronate suggested no such effect.[26–28] A reasonable approach to PPI prescription would be to use the lowest effective dose for the shortest duration, or consider prescribing an H2RA that has not been reported to affect bisphosphonate efficacy.[23,24]

Osteonecrosis of the jaw and atypical femur fractures with oral bisphosphonates – Balancing benefits and risks

Bisphosphonate prescription in Australia is declining, in part because of reports linking bisphosphonate use with osteonecrosis of the jaw.[29–31] In Canada, over a three-year period, the cumulative incidence for bisphosphonate-associated osteonecrosis of the jaw was 1.04 per 100,000 patient years in osteoporosis or metabolic bone disease, and 442 per 100,000 patient years in cancer patient observations.[31] The risk is low with good dental hygiene and care, and precautions with timing of invasive dental care (wait three to six months after last dose where possible).[31]

Atypical fractures are reported to increase after three to four years of bisphosphonate therapy.[32,33] Putting the risk into perspective, major osteoporotic fracture in women at high risk is 3100 per 100,000 patient years, and bisphosphonates reduce fractures by 20–70%; atypical fracture attributed to long-term bisphosphonate therapy is 78 per 100,000 patient years at eight years, and significantly many more osteoporotic fractures would be prevented.[30,32–34]

While the unlikely possibility of atypical fractures should be considered among patients who report unexplained thigh pain in the context of long-term bisphosphonate therapy, concern about over-suppression of bone turnover is not a reason to stop therapy in the majority of women at high risk for osteoporotic fracture.[33]

Table 3. Available dosing forms of bisphosphonates for osteoporosis[8]

	Oral dosing			Intravenous
	Daily	Weekly	Monthly	
Alendronate sodium	5 mg and 10 mg	35 mg and 70 mg		–
Risedronate sodium	5 mg	35 mg	150 mg	–
Risedronate sodium (enteric coated)		35 mg		–
Zoledronic acid				5 mg annually

Consider the consequences of ceasing bisphosphonate treatment

Bisphosphonates accumulate in the bone and are variably released for years after treatment cessation. Hence, it is important to consider the clinical question of 'how long to treat?' Answering this question requires holistic consideration of the patient's risk factors, therapeutic options and differences in onset and offset, which are drug-specific.

Data from long-term studies with bisphosphonates (up to 10 years) suggest that some patients may be able to take a break from treatment without incurring additional fracture risk after three to five years.[29] The safety of ceasing denosumab is unknown at this stage because of concerns about rebound increase in bone turnover and risk of fracture. However, the continuing benefit of antiresorptive agents for up to 10 years in selected patients at high risk of fractures has been reported.[29] The duration of initial treatment and length of any proposed treatment break should be guided by the patient's absolute risk.[29] Risk assessment tools (eg Fracture Risk Assessment Tool [FRAX]) can be used to estimate an individual patient's risk of fractures with or without known bone densitometry scores.[34] Reassessment of fracture risk is a critical first step before discontinuation of treatment is considered.[29] If treatment is suspended, risk assessment should be repeated annually and treatment restarted if necessary.

Conclusion

Treatment adherence is influenced by multiple factors. The patient–provider relationship is critical through regular follow up and review of disease risk, progression, patient characteristics and preference, and treatment options. Patient education and understanding of disease and treatment risks and benefits is crucial in an asymptomatic disease. Reminder systems are useful where forgetfulness is a concern. Strategies to improve adherence include discussing novel drug formulations (eg delayed-

release enteric coating) and the use of parenteral options. This is evident in the shift to the preference for six-monthly denosumab over bisphosphonates. A clinician protocol for ongoing patient risk–benefit assessment and re-evaluation at each successive appointment is essential. Specific therapy-related barriers may be addressed on a case-by-case approach specific to each patient.

Authors

Charles A Inderjeeth MBChB, MPH, FRACP, NHMRC-NICS DVA Fellow, Clinical Professor, School of Medicine & Pharmacology, University of Western Australia, Nedlands, WA; Consultant Physician (Geriatrician & Rheumatologist), Clinical Epidemiologist, Director of Clinical Training, Research and Programs, Sir Charles Gairdner and Osborne Park Hospital Group, WA. Charles.Inderjeeth@health.wa.gov.au

Andrisha-Jade Inderjeeth MBBS, Medical Officer, Sir Charles Gairdner Hospital Group, WA; School of Medicine & Pharmacology, University of Western Australia, Nedlands, WA

Warren David Raymond BHealthSci, BEc, Sir Charles Gairdner and Osborne Park Hospital Group, WA; School of Medicine & Pharmacology, University of Western Australia, Nedlands, WA

Competing interests: None.

Provenance and peer review: Not commissioned, externally peer reviewed.

References

1. Ebeling PR. The burden of brittle bones: Epidemiology, costs and burden of osteoporosis in Australia – 2007. Sydney: International Osteoporosis Foundation and Osteoporosis Australia, 2007. Available at www.iofbonehealth.org/sites/default/files/PDFs/white_paper_australia-23-06-08.pdf [Accessed 13 September 2016].
2. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA 2009;301(5):513–21.
3. Center JR, Bliuc D, Nguyen TV, Elsman JA. Risk of subsequent fracture after low-trauma fracture in men and women. JAMA 2007;297(4):387–94.
4. Gold D. Understanding patient compliance and persistence with osteoporosis therapy. Drugs Aging 2011;28(4):249–55.
5. Center JR, Bliuc D, Nguyen ND, Nguyen TV, Eisman JA. Osteoporosis medication and reduced mortality risk in elderly women and men. J Clin Endocrinol Metab 2011;96(4):1006–14.
6. Bolland MJ, Grey AB, Gamble GD, Redi IR. Effect of osteoporosis treatment on mortality: A meta-analysis. J Clin Endocrinol Metab 2010;95(3):1174–81.
7. Silverman S, Gold DT. Compliance and persistence with osteoporosis medications: A critical review of the literature. Rev Endocr Metab Disord 2010;11(4):275–80.
8. Department of Health. Pharmaceutical Benefits Scheme. Canberra: Commonwealth of Australia, 2015. Available at www.pbs.gov.au/pbs/home [Accessed 10 October 2016].
9. Lee S, Glendenning P, Inderjeeth CA. Efficacy, side effects and route of administration are more important than frequency of dosing of anti-osteoporosis treatments in determining patient adherence: A critical review of published articles from 1970 to 2009. Osteoporos Int 2011;22(3):741–53.
10. Haynes RB, McDonald H, Garg AX, Montague P. Interventions for helping patients to follow prescriptions for medications. Cochrane Database Syst Rev 2002(2):CD000011.
11. Bolandm MV. Automated telecommunication-based reminders and adherence with once-daily glaucoma medication dosing: The automated dosing reminder study. JAMA Ophthalmol 2014;132(7):845–50.
12. Raynor DK, Booth TG, Blenkinsopp A. Effects of computer generated reminder charts on patients' compliance with drug regimens. BMJ 1993;306(6886):1158–61.
13. Silverman SL, Schousboe JT, Gold DT. Oral bisphosphonate compliance and persistence: A matter of choice? Osteoporos Int 2011;22(1):21–26.
14. International Osteoporosis Foundation. The adherence gap: Why osteoporosis patients don't continue with treatment. Nyon: IOF, 2005. Available at www.iofbonehealth.org/sites/default/files/PDFs/adherence_gap_report_2005.pdf [Accessed 10 October 2016].
15. Siris ES, Gehlbach S, Adachi JD, et al. Failure to perceive increased risk of fracture in women 55 years and older: The Global Longitudinal Study of Osteoporosis in Women (GLOW). Osteoporos Int 2011;22(1):27–35.
16. Nieuwlaat R, Wilczynski N, Navarro T, et al. Interventions for enhancing medication adherence. Cochrane Database Syst Rev 2014;(11):CD000011.
17. Shu AD, Stedman MR, Polinski JM, et al. Adherence to osteoporosis medications after patient and physician brief education: Post hoc analysis of a randomized controlled trial. Am J Manag Care 2009;15(7):417–24.
18. Cadarette SM, Burden AM. Measuring and improving adherence to osteoporosis pharmacotherapy. Curr Opin Rheumatol 2010;22(4):397–403.
19. Lin JH. Bisphosphonates: A review of their pharmacokinetic properties. Bone 1996;18(2):75–85.
20. Sakuma S, Tanno FK, Masaoka Y, et al. Effect of administration site in the gastrointestinal tract on bioavailability of poorly absorbed drugs taken after a meal. J Control Release 2007;118(1):59–64.
21. McClung MR, Miller PD, Brown JP, et al. Efficacy and safety of a novel delayed-release risedronate 35 mg once-a-week tablet. Osteoporos Int 2012;23(1):267–76.
22. Sunyecz J. Optimizing dosing frequencies for bisphosphonates in the management of postmenopausal osteoporosis: Patient considerations. Clin Interv Aging 2008;3(4):611–27.
23. Weiss TW, Gold DT, Silverman SL, McHorney CA. An evaluation of patient preferences for osteoporosis medication attributes: Results from the PREFER-US study. Curr Med Res Opin 2006;22(5):949–60.
24. Inderjeeth CA, Chan K, Kwan K, Lai M. Time to onset of efficacy in fracture reduction with current anti-osteoporosis treatments. J Bone Miner Metab 2012;30(5):493–503.
25. Roughead EE, McGeechan K, Sayer GP. Bisphosphonate use and subsequent prescription of acid suppressants. Br J Clin Pharmacol 2004;57(6):813–16.
26. de Vries F, Cooper AL, Cockle SM, van Staa TP, Cooper C. Fracture risk in patients receiving acid-suppressant medication alone and in combination with bisphosphonates. Osteoporosis Int 2009;20(12):1989–98.
27. Abrahamsen B, Eiken P, Eastell R. Proton pump inhibitor use and the antifracture efficacy of alendronate. Arch Intern Med 2011;171(11):998–1004.
28. Roux C, Goldstein JL, Zhou X, Klemes A, Lindsay R. Vertebral fracture efficacy during risedronate therapy in patients using proton pump inhibitors. Osteoporos Int 2012;23(1):277–84.
29. Diab DL, Watts NB. Bisphosphonate drug holiday: Who, when and how long. Ther Adv Musculoskelet Dis 2013;5(3):107–11.
30. Girgis CM, Seibel MJ. Atypical femur fractures: A review of the evidence and its implication to clinical practice. Ther Adv Musculoskelet Dis 2011;3(6):301–14.
31. Khan AA, Rios LP, Sándor GK, et al. Bisphosphonate-associated osteonecrosis of the jaw in Ontario: A survey of oral and maxillofacial surgeons. J Rheumatol 2011;38(7):1396–402.
32. Reid IR. Controversies in osteoporosis management. Intern Med J 2016;46(7):767–70.
33. Pazianas M, Kim SM, Yuen T, Sun L, Epstein S, Zaidi M. Questioning the association between bisphosphonates and atypical femoral fractures. Ann N Y Acad Sci 2015;1335:1–9.
34. Unnanuntana A, Gladnick BP, Donnelly E, Lane JM. The assessment of fracture risk. J Bone Joint Surg Am 2010;92(3):743–53.

correspondence **afp@racgp.org.au**