

CADTH RAPID RESPONSE REPORT: REFERENCE LIST

# Duration of Bisphosphonate Treatment for Patients with Osteoporosis: Clinical Evidence and Guidelines

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## Research Questions

1. What is the clinical evidence for varying treatment duration and courses of bisphosphonates for osteoporosis?
2. What are the evidence-based guidelines regarding length of treatment with bisphosphonates for osteoporosis?

## Key Findings

One health technology assessment, six systematic reviews (one with meta-analyses), three randomized controlled trials, and five non-randomized studies were identified regarding the clinical evidence for varying treatment duration and courses of bisphosphonates for osteoporosis. Six evidence-based guidelines were identified regarding the length of treatment with bisphosphonates for osteoporosis.

## Methods

A limited literature search was conducted by an information specialist on key resources including Medline via OVID, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were bisphosphonates and osteoporosis. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and August 16, 2019. Internet links were provided, where available.

## Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

**Table 1: Selection Criteria**

<b>Population</b>	Patients of any age with osteoporosis who are on bisphosphonates
<b>Intervention</b>	Q1-2: Prescribed length of treatment (e.g., indefinite, specific timeframe [e.g. 5 years only, 10 years only], based on bone mass density readings, drug holidays)
<b>Comparator</b>	Q1: An alternative length of treatment or treatment course Q2: N/A
<b>Outcomes</b>	Q1: Clinical evidence (e.g., decreased fractures, quality of life, mortality, adverse events) Q2: Evidence based guidelines on recommended length of treatment of bisphosphates
<b>Study Designs</b>	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and evidence-based guidelines

## Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, and evidence-based guidelines.

One health technology assessment,<sup>1</sup> six systematic reviews (one with meta-analyses),<sup>2-7</sup> three randomized controlled trials,<sup>8-10</sup> and five non-randomized studies<sup>11-15</sup> were identified regarding the clinical evidence for varying treatment duration and courses of bisphosphonates for osteoporosis. Six evidence-based guidelines were identified regarding the length of treatment with bisphosphonates for osteoporosis.<sup>16-21</sup>

Additional references of potential interest are provided in the appendix.

### Health Technology Assessments

1. Davis S, Martyn-St James M, Sanderson J, et al. A systematic review and economic evaluation of bisphosphonates for the prevention of fragility fractures. *Health Technol Assess.* 2016;20(78):  
<https://www.journalslibrary.nihr.ac.uk/hta/hta20780/#/abstract>  
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### Systematic Reviews and Meta-analyses

2. Dennison EM, Cooper C, Kanis JA, et al. Fracture risk following intermission of osteoporosis therapy. *Osteoporos Int.* 2019 Jun.  
[PubMed: PM31175404](https://pubmed.ncbi.nlm.nih.gov/31175404/)
3. Fink HA, MacDonald R, Forte ML, et al. Long-term drug therapy and drug discontinuations and holidays for osteoporosis fracture prevention: a systematic review. *Ann Intern Med.* 2019 Apr.  
[PubMed: PM31009947](https://pubmed.ncbi.nlm.nih.gov/31009947/)
4. Nayak S, Greenspan SL. A systematic review and meta-analysis of the effect of bisphosphonate drug holidays on bone mineral density and osteoporotic fracture risk. *Osteoporos Int.* 2019 Apr;30(4):705-720.  
[PubMed: PM30623214](https://pubmed.ncbi.nlm.nih.gov/30623214/)
5. Anagnostis P, Paschou SA, Mintziari G, et al. Drug holidays from bisphosphonates and denosumab in postmenopausal osteoporosis: EMAS position statement. *Maturitas.* 2017 Jul;101:23-30.  
[PubMed: PM28539165](https://pubmed.ncbi.nlm.nih.gov/28539165/)
6. Adler RA, El-Hajj Fuleihan G, Bauer DC, et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a Task Force of the American Society for Bone and Mineral Research. *J Bone Miner Res.* 2016 Jan;31(1):16-35.  
[PubMed: PM26350171](https://pubmed.ncbi.nlm.nih.gov/26350171/)
7. Eriksen EF, Diez-Perez A, Boonen S. Update on long-term treatment with bisphosphonates for postmenopausal osteoporosis: a systematic review. *Bone.* 2014 Jan;58:126-135.  
[PubMed: PM24120384](https://pubmed.ncbi.nlm.nih.gov/24120384/)

## Randomized Controlled Trials

8. Black DM, Reid IR, Cauley JA, et al. The effect of 6 versus 9 years of zoledronic acid treatment in osteoporosis: a randomized second extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res*. 2015 May;30(5):934-944.  
[PubMed: PM25545380](#)
9. Bauer DC, Schwartz A, Palermo L, et al. Fracture prediction after discontinuation of 4 to 5 years of alendronate therapy: the FLEX study. *JAMA Intern Med*. 2014 Jul;174(7):1126-1134.  
[PubMed: PM24798675](#)
10. Cosman F, Cauley JA, Eastell R, et al. Reassessment of fracture risk in women after 3 years of treatment with zoledronic acid: when is it reasonable to discontinue treatment? *J Clin Endocrinol Metab*. 2014 Dec;99(12):4546-4554.  
[PubMed: PM25215556](#)

## Non-Randomized Studies

11. Adams AL, Adams JL, Raebel MA, et al. Bisphosphonate drug holiday and fracture risk: a population-based cohort study. *J Bone Miner Res*. 2018 Jul;33(7):1252-1259.  
[PubMed: PM29529334](#)
12. Drieling RL, LaCroix AZ, Beresford SAA, et al. Long-term oral bisphosphonate therapy and fractures in older women: the Women's Health Initiative. *J Am Geriatr Soc*. 2017 Sep;65(9):1924-1931.  
[PubMed: PM28555811](#)
13. Fung P, Bedogni G, Bedogni A, et al. Time to onset of bisphosphonate-related osteonecrosis of the jaws: a multicentre retrospective cohort study. *Oral Dis*. 2017 May;23(4):477-483.  
[PubMed: PM28039941](#)
14. Mignot MA, Taisne N, Legroux I, Cortet B, Paccou J. Bisphosphonate drug holidays in postmenopausal osteoporosis: effect on clinical fracture risk. *Osteoporos Int*. 2017 12;28(12):3431-3438.  
[PubMed: PM28875236](#)
15. Wang CC, Lu HT, Dusetzina SB, Wu CH. The association between long-term bisphosphonate use and the risk of fracture among women aged 50 or older with osteoporosis. *J Womens Health*. 2016 Jul;25(7):738-746.  
[PubMed: PM27096405](#)

## Guidelines and Recommendations

16. National Osteoporosis Guideline Group. NOGG 2017: clinical guideline for the prevention and treatment of osteoporosis. Sheffield (UK): Centre for Metabolic Bone Diseases, University of Sheffield; 2018 Jul:  
<https://www.sheffield.ac.uk/NOGG/NOGG%20Guideline%202017.pdf>  
*See: Section 7: Duration and monitoring of bisphosphonate therapy*  
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17. Simm PJ, Biggin A, Zacharin MR, et al. Consensus guidelines on the use of bisphosphonate therapy in children and adolescents. *J Paediatr Child Health*. 2018 Mar;54(3):223-233. <https://www.ncbi.nlm.nih.gov/pubmed/29504223>
18. Compston J, Cooper A, Cooper C, et al. UK clinical guideline for the prevention and treatment of osteoporosis. *Arch Osteoporos*. 2017 Dec;12(1):43.  
<https://www.ncbi.nlm.nih.gov/pubmed/28425085>  
*See: Duration and monitoring of bisphosphonate therapy*
19. Qaseem A, Forcica MA, McLean RM, Denberg TD. Treatment of low bone density or osteoporosis to prevent fractures in men and women: a clinical practice guideline update from the American College of Physicians. *Ann Intern Med*. 2017 Jun;166(11):818-839. [https://annals.org/aim/fullarticle/2625385/treatment-low-bone-density-osteoporosis-prevent-fractures-men-women-clinical?\\_ga=2.71122704.1078387334.1565969012-1675310348.1565969012](https://annals.org/aim/fullarticle/2625385/treatment-low-bone-density-osteoporosis-prevent-fractures-men-women-clinical?_ga=2.71122704.1078387334.1565969012-1675310348.1565969012)  
*See: Duration of Pharmacologic Therapy*  
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20. The Royal Australian College of General Practitioners and Osteoporosis Australia. Osteoporosis prevention, diagnosis and management in postmenopausal women and men over 50 years of age. 2<sup>nd</sup> ed. East Melbourne, Victoria: RACGP; 2017:  
<https://www.racgp.org.au/FSDEDEV/media/documents/Clinical%20Resources/Guidelines/Joint%20replacement/Osteoporosis-guidelines.pdf>  
*See: Duration of therapy*  
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21. Anderson K, Meade M, Anthony L, et al. Diagnosis and management of osteoporosis. Winnipeg (MB): Winnipeg Regional Health Authority; 2014 Oct:  
<https://www.wrha.mb.ca/extranet/eipt/files/EIPT-031-001.pdf>  
*See: IV. Strategies for Fracture Prevention: Pharmacologic*  
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## Appendix — Further Information

### Previous CADTH Reports

22. Bisphosphonate use in patients with osteopenia and low risk of fractures: clinical effectiveness and guidelines (*Rapid Response Summary of Abstracts*). Ottawa (ON): CADTH; 2015 Apr: <https://www.cadth.ca/sites/default/files/pdf/htis/apr-2015/RB0842%20Biophosphonates%20in%20osteopenia%20and%20low%20risk%20fracture%20Final.pdf>  
Accessed 2019 Aug 22

### Clinical Practice Guidelines – Unclear Methodology

23. Bisphosphonates: addressing the duration conundrum. Dunedin (NZ): bpacnz; 2019 Jan: <https://bpac.org.nz/2019/docs/bisphosphonates.pdf>  
*See: Determining an appropriate duration of bisphosphonate use*  
Accessed 2019 Aug 22
24. Kaiser Permanente Guideline Oversight Group. Osteoporosis screening, diagnosis, and treatment guideline. Seattle (WA): Kaiser Foundation Health Plan of Washington; 2019 Apr: <https://wa.kaiserpermanente.org/static/pdf/public/guidelines/osteoporosis.pdf>  
*See: Recommended pharmacologic options*  
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25. Caires ELP, Bezerra MC, Junqueira A, Fontenele SMA, Andrade SCA, d'Alva CB. Treatment of postmenopausal osteoporosis: a literature-based algorithm for use in the public health care system. *Rev Bras Reumatol (Rio J)*. 2017 May - Jun;57(3):254-263. [PubMed: PM28535898](#)
26. Toward Optimized Practice (TOP) Osteoporosis CPG Committee. Diagnosis and management of osteoporosis: clinical practice guideline. Edmonton (AB): TOP; 2016 Feb: <http://www.topalbertadoctors.org/download/1907/Osteoporosis%20CPG.pdf>  
*See: DISCONTINUING BISPHOSPHONATE THERAPY*  
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27. Gonzalez-Macias J, Del Pino-Montes J, Olmos JM, Nogues X, en nombre de la Comision de Redaccion de las Guias de Osteoporosis de la S. Clinical practice guidelines for posmenopausal, glucocorticoid-induced and male osteoporosis. Spanish Society for Research on Bone and Mineral Metabolism (3rd updated version 2014). *Rev Clin Esp*. 2015 Dec;215(9):515-526. [PubMed: PM26434811](#)

### Position Statements

28. Meier C, Uebelhart B, Aubry-Rozier B, et al. Osteoporosis drug treatment: duration and management after discontinuation. A position statement from the SVGGO/ASCO. *Swiss Med Wkly*. 2017;147:w14484. [PubMed: PM28871570](#)

29. Lee SH, Gong HS, Kim TH, et al. Position statement: drug holiday in osteoporosis treatment with bisphosphonates in South Korea. *J Bone Metab.* 2015 Nov;22(4):167-174.

[PubMed: PM26713307](#)

## Non-Randomized Studies

### *No Comparator*

30. Bindon B, Adams W, Balasubramanian N, Sandhu J, Camacho P. Osteoporotic fractures during bisphosphonate drug holiday. *Endocr Pract.* 2018 Feb;24(2):163-169.

[PubMed: PM29144808](#)

31. Xu LH, Adams-Huet B, Poindexter JR, Maalouf NM. Determinants of change in bone mineral density and fracture risk during bisphosphonate holiday. *Osteoporos Int.* 2016 May;27(5):1701-1708.

[PubMed: PM26642963](#)

### *Alternative Outcome*

32. Boskey AL, Spevak L, Ma Y, et al. Insights into the bisphosphonate holiday: a preliminary FTIRI study. *Osteoporos Int.* 2018 03;29(3):699-705.

[PubMed: PM29204959](#)