

The Atraumatic Metatarsal Fracture: A Clinical Sign of Bisphosphonate-Associated Bone Fragility

Abstract

Beginning with some of the earliest publications that recognized the association between bisphosphonate treatment for osteoporosis and coincident skeletal fractures, the wide range of fractured bones reported have included the metatarsals. This paper presents a survey of the medical literature describing this association. Evidence is offered supporting definitions of inclusion rather than exclusion in seeking to define bisphosphonate-associated fractures. In addition we question the recent trend toward attributing fractures of the metatarsal as well as at other sites to "holidays" from bisphosphonate and other strong antiresorptive drugs. A recent paper proposed that the increased metatarsal fracture risk that persists years after stopping bisphosphonate therapy may be explained by the cessation of the antiresorptive drug. We propose instead that the frequency of this association justifies the inclusion of a prevalent or subsequent metatarsal fracture as one of the optional minor features defining the bisphosphonate-associated atypical femoral fracture.

1. Introduction

23 We have previously cited (1) what we believe to be the earliest
24 publication (2) acknowledging an association between bisphosphonate
25 (BP) therapy for osteoporosis and fractures of the metatarsal (MT)
26 bones. Earlier papers (3,4) had reported BP-associated fractures of
27 other bones. All these early reports involved the use of etidronate, a BP
28 which significantly inhibits matrix mineralization (5). These all were likely
29 etidronate-induced insufficiency fractures, since those which were
30 adequately described were reported to resolve upon cessation of
31 etidronate administration.

32 In July 2003, the first refereed article (6) was published reporting
33 fractures combined with a very high bone density (total body Z-score of
34 +2.5 using a scale (7) developed for children and adolescents) in a
35 young boy treated with high doses of a BP. The effects were described
36 as an induced osteopetrosis with atraumatic fragility fractures after long-
37 term administration of intravenous pamidronate, a moderately
38 antiresorptive BP which is much less inhibiting of mineralization than
39 etidronate. No MT involvement was reported, but this was the first report
40 to describe the fracturing potential of prolonged BPs in humans. This
41 publication was accompanied by an editorial (8) which sounded a clear
42 warning about BP-associated fracture complications. Remarkably, an
43 identical effect had been observed (9) in experimental animals some 30
44 years earlier. Mice treated with etidronate or clodronate were described

45 as tending toward "a slowing of bone remodelling with an osteopetrotic
46 skeleton resulting". Osteopetrosis is a human genetic syndrome
47 resulting in fracturing despite the associated high bone mineral density
48 in these individuals (10).

49 The relevance of osteopetrosis to a discussion of the effects of
50 bisphosphonates on femoral and metatarsal fractures is that, analogous
51 to the effect of BPs on osteoclasts, osteopetrosis osteoclasts are
52 deactivated and cannot remove damaged bone, with resultant fractures.
53 These two parallel but very different mechanisms – drug-induced or
54 congenital -- can produce similar fractures in the same bones, including
55 metatarsals. While some non-MT fragility fractures were observed in
56 the first published case (6) of BP-induced osteopetrosis, metatarsal
57 fractures have since been reported in genetic osteopetrosis (11). The
58 genetic deficit in osteopetrosis leads to a preponderance of formation
59 without remodeling repair of damaged areas. The target of the BP drugs
60 is, of course, the osteoclast-mediated resorption of bone. Indeed,
61 subtrochanteric/femoral transverse shaft fractures of lateral origin,
62 meeting the definition of atypical femoral fractures published (12, 13) by
63 the American Society of Bone and Mineral Research (ASBMR) have
64 been described in such individuals (14). In fact, an included literature
65 review of the period between 2009-2013 found an additional 19 other
66 examples of shaft or subtrochanteric femoral fractures reported in

67 osteopetrosis. This paper (14) made no reference to the resemblance to
68 the ASBMR-defined atypical femur fractures (AFF), a definition which
69 was completed in the same year.

70 Later in 2003, the first observations regarding the general association of
71 intermediate to long-term BP use with fragility fractures were described
72 (15) at a meeting of the ASBMR. This presentation mentioned
73 associated metatarsal (MT) fracturing, which was confirmed in the formal
74 publication (16).

75 In the present paper, we have surveyed the medical literature regarding
76 the occurrence of the metatarsal fracture in conjunction with
77 bisphosphonate therapy.

78 **2. Materials and methods**

79 We compiled this review in mid-November 2017 using OVID Medline In-
80 process & Non-indexed (English and non-English), Pubmed, and the
81 Embase database. We have included the material on MT fractures from
82 our earlier publication (1) surveying the literature on non-atypical femur
83 fracture BP-associated atypical fractures, thus bringing the earlier survey
84 up to the current date to the extent that MT fractures are concerned.

85 References 19, 23, 25, 26, 27, and 28 refer to cases described in Table
86 1 but not otherwise discussed in the text.

87 **3. Results**

88 A 2012 statistical evaluation (17) of the long-term courses and clinical
89 consequences experienced by 81 persons who had incurred one or
90 more bisphosphonate-associated atypical femoral fractures (AFFs) (12,
91 13) was notable for the high number of metatarsal fractures (MTFs)
92 incurred by the same individuals. In some cases the MTFs preceded the
93 AFFs. In all, 34.5% of the individuals with the femur lesion also
94 developed one or more MTFs. This report of the statistics for the AFF
95 support group did not include the detailed statistics for the MT fractures;
96 thus the treatment range in Table 1 is given for the whole group, not
97 specifically for the occurrence of the MT breaks. Also, because of the
98 nature of this analysis, we cannot be certain that some of these MTFs
99 may not also have been reported elsewhere in the medical literature.

100 Regarding the reports of MT fractures in patients treated for multiple
101 myeloma with BPs (21, 25), it is unlikely that the fractures were
102 pathologic lesions secondary to the malignancy. A survey (22) of the
103 Mayo Clinic records of 165 persons with the diagnosis of multiple
104 myeloma treated in the years 1945-2001 (before the use of intravenous
105 BP treatments) found no cases of spontaneous or pathologic metatarsal
106 fractures.

107 The last case listed (29) included two additional bone-active medications
108 after the last BP infusion. Several months after the last zoledronic acid
109 infusion, the patient was given a 24-month treatment with teriparatide

followed by a single infusion of denosumab. Foot pain began about 10 months after that single infusion and 2 months later a spontaneous Jones fracture ensued.

In summary, there are at least 52 cases reported in the medical literature where the individual sustained one or more MT fractures in association with BP therapy. More than 60 such fractures were observed in these individuals; the way in which these data were presented does not allow the determination of *how many* more. Four to five times as many atypical femur fractures (AFFs) were summarized in the initial (17) ASBMR survey, but the AFF is a far less common, and therefore more remarkable, fracture. Metatarsal fractures would not be expected to capture attention, and thus may go unreported. An illustration of this is provided by reference 19.

A summary of the cases found is presented in Table 1.

Author/ Year (Ref)	MT Fracture Features	# of Individuals /# of MT Fractures	Years of BP Use	Remarks
Guañabens/ 1994 (2)	Left, 2nd, mid- shaft	1/1	7 months	Patient was in 1st month of second 3-month etidronate cycle
Odvina/ 2003 (15)	n/a	"several"	various	In the preliminary presentation, no MT details were given. Alendronate was the only BP.
Odvina/ 2006 (16)	n/a	1/1	4	Only one MT fracture after alendronate was described in the followup publication.
Schneider/ 2006 (17)	Right, 2nd	1/1	7	The fracture healed after several months.
Wiel/2008 (19)	4 th basilar (2)	2/2	n/a	One on ibandronate, the other on risedronate. Both

				were atraumatic fractures. A bisphosphonate association was not recognized.
Armamento-Villareal/ 2009 (20)	n/a	4/7+ One pt had "multiple bilateral" MTFs	3½-8	Subsequent clinical courses were not described.
Waterman/ 2011 (21)	2nd (1), 4th(3), 5th (4), L(4), R(4)	6/8	5(1), 7(2), 8-10(3)	All were being treated for multiple myeloma with sequential IV pamidronate then zoledronate, or only IV zoledronate. (see MM clarification in text above).
Pradhan/ 2012 (23)	Left, 5th	1/1	8½	This was a Jones fracture. Earlier the patient had an AFF after 7 years on alendronate (continued).
Reichmister /2012 (24)	Left, 2nd (1 pt) Left (1 pt) Bilateral (1 pt)	3/4	12 14 5	First case MT fractured after alendronate 12 yrs, experienced an AFF 3 years later. The 2nd case MT fx on aln after 14 years, had an AFF 1 year later. The 3rd case had MT and AFF fx after 5 years on alendronate; then another MT fx and another AFF subsequently.
Schneider/ 2012 (17)	n/a	28/28+	1½-15	Details of the cases including MT fractures were not described but several of the AFF cases reported suffered more than one MT. (see text above)
Adam/ 2013 (25)	2nd	1/1	34 months	Czech paper read in abstract only. Atraumatic nature of the MT fracture was emphasized.
Al-Azzani/ 2015 (26)	Right, 5th	1/1	9	The individual described was treated with aln and then ibandronate. The MT fx preceded an AFF by several months
Murray/ 2016 (27)	Left	1/1	10	Two years after the MT, continuing alendronate, the patient sustained atraumatic tibial fractures
Muir/ 2017 (28)	Right, 5th	1/1	6½	The MT Jones fracture occurred spontaneously six months after bilateral AFFs
Hinshaw/	Right, 5th	1/1	13 alen	The MT Jones fracture

2017 (29)			3 zol	occurred ~ 3 years after the last zoledronic acid infusion. Polypharmacy intervened (see text above).
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Table 1 Cases identified in the medical literature

4. Discussion

In the two ASMBR committee reports seeking a definition of the AFF, sets of obligatory "major" and optional "minor" features were defined. We have shown that metatarsal fractures in an individual with an AFF can serve as support for defining the major fracture. We propose the inclusion of prevalent MT fracture(s) as a "minor feature". An example exists in the literature illustrating the importance of minor feature inclusion in identifying the AFF. A 12-year analysis (30) of the incidence of AFFs, defined only by the ASMBR-defined major features in a large cohort of women ≥ 50 and men ≥ 65 years of age based on the major features alone (called AFMs) did not detect an increase in AFFs over the last 10 years of the study corresponding to the rapid increase of BP therapy for osteoporosis. However, the combined use of the major features and any minor feature (called AFMms) revealed a steady increase in the fractures over the last 10 years of the study (Figure 1). The difference in the two data sets reflects the fact that 70% of the cohort included in this study had never been exposed to bisphosphonates, thus reducing the sensitivity of the incidence rates of bisphosphonate-related atypical femur fractures (AFFs). But as shown

in Figure 1, the increase in sensitivity obtained by including the minor features (AFMms) clearly does show an upward trend in AFFs during the 10 year period.

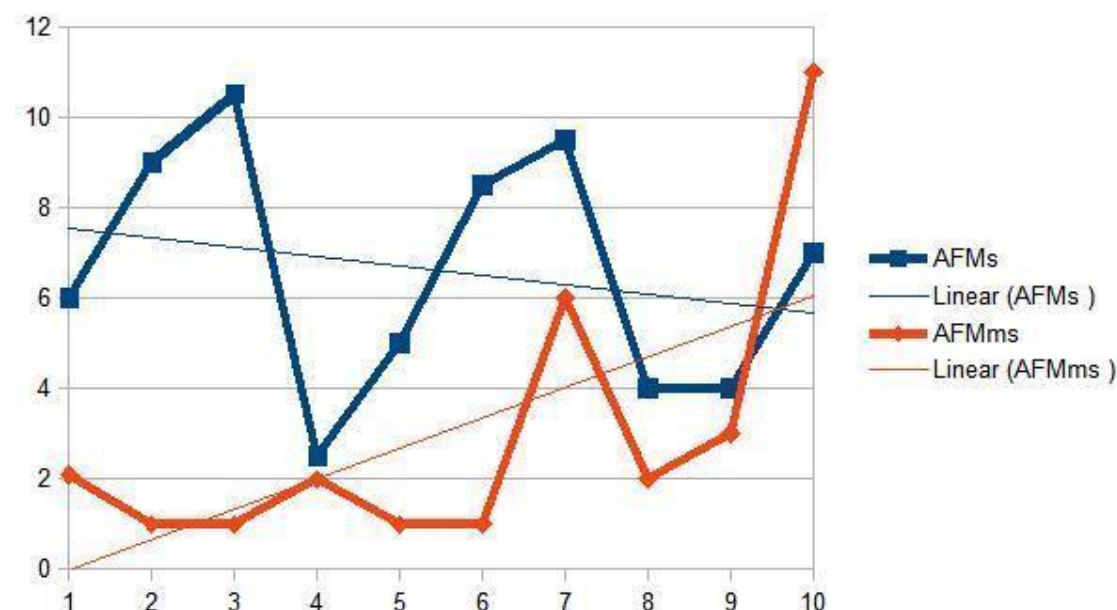


Figure 1 (adapted from reference 30: last 10 years of the study plotted against the # of identified fractures) AFMs show the annual incidence of AFFs using only the ASBMR major criteria (ref 14) AFMms show the annual incidence these AFFs that also had one or more minor criteria The least-squares regression technique was used to generate the trend lines

Evidence has accumulated of bisphosphonate-associated metatarsal fractures, as well as fractures in many other sites. Added to the fact that many of the metatarsal fractures described here either preceded or followed an AFF, these findings support the use of a BP-associated MT fracture as an optional minor feature important in defining the full incidence of BP-associated fractures. In the first report (12) of the ASBMR committee which was convened to address the mounting concerns about BP-associated AFFs, one of the "major features"

167 required for a given fracture to satisfy the AFF definition was "non-
168 comminution". By 2010, when this report was published, the atypical
169 femur fracture support group managed by Jennifer Schneider (17)
170 already had accumulated details of a number of convincing cases where
171 the BP-associated fractures were comminuted. We deemed that ASBMR
172 feature to be one of exclusion, providing no evident advantage for the
173 recognition of this problem and limiting the appreciation of its full extent.
174 In fact, the first complete individual AFF case reported in the literature
175 (18) was of a comminuted fracture. This report, which preceded the
176 ASBMR report by 4 years, was covered extensively in the news media,
177 with repeated use of the preoperative plain film as an illustration of an
178 AFF. When the present authors published, in 2012, a statistical
179 summary of that portion of our case histories which was acceptable to
180 the editors of the *Journal of Clinical Endocrinology and Metabolism*, four
181 comminuted fractures were included. We stated "we strongly feel that
182 the restriction of the AFF definition reached by the ASBMR Task Force
183 to noncomminuted fractures excludes many cases that clearly deserve
184 consideration". About that time the United Kingdom (31) and European
185 Union (32) authorities had issued criteria making non-comminution
186 optional, thus *de facto* reducing it to a minor feature. Two years later
187 (13), the ASBMR revised its definition somewhat, broadening but not
188 abandoning the excluding character by retaining it as a major feature.

A recent report (33) suggested that a "holiday" from bisphosphonate therapy may be associated with an increased risk of metatarsal fractures during the holiday interval. The assumption of causality brought on by the "holiday" must be challenged in the light of three important facts. First, the persistence of BP medications in bone is very long. The published pharmacodynamic data on the BPs is sparse but in a limited study (34) of menopausal women, who received 7.5 mg of alendronate IV daily for 4 consecutive days, the *maximum* individual calculated half life of the drug (half remaining in the body) was 17.4 years. There is no justification for an assumption that a bisphosphonate holiday will be accompanied by the significant clearance of the drug from the skeleton. Second, the incidence of second, contralateral, AFFs is reduced (but not eliminated) by stopping BP treatment in comparison to continuing the treatment after the first AFF (17). Third, we (17) and others (24) have reported prior occurrence, during BP treatment, of metatarsal fractures which herald rather than follow an AFF. These facts are inconsistent with the choice of MTFs as a marker of increased holiday risk.

5. Conclusions

The declared objective of the ASBMR Task Force on Atypical Subtrochanteric and Diaphyseal Femoral Fractures was to develop a case definition "so that subsequent studies report on the same condition". This was a proper concentration of effort when there were

many voices denying any connection between the BP drugs and these fractures. But as we have shown in this and earlier publications, many contributors to the medical literature currently assume that this connection extends far beyond the confines of the ASBMR definitions which narrowly define a subset of femur fractures. We conclude that the time has arrived to change the assumptions implicit in this policy of exclusion, which was designed to make the definition as precise as possible, but as a result excludes many supportable cases from the statistical analyses of potential risk. One example is exclusion of comminuted femoral fractures. As legitimate evidence appears of BP-associated fractures in addition to the original AFFs, such as the atraumatic metatarsal fractures we have illustrated here, our understanding of the scope of the impact of these drugs will depend on a recognition of all the characteristic effects. Accordingly we propose that the frequency of this association justifies the inclusion of a prevalent or subsequent metatarsal fracture as one of the optional minor features defining the bisphosphonate-associated atypical femoral fracture.

References

- (1) Hinshaw WB, Schneider JP. Bisphosphonate-associated Atypical Fractures that are not "Atypical Femoral Fractures", *Brit J Med Med Res*. 2017;19(7):1-17. Doi: 10.9734/BJMMR/2017/31269.

- 234 (2) Guañabens N, Peris T, Monegal AL, Collado A, Muñoz-Gómez.
235 Lower extremity stress fractures during intermittent cyclical etidronate
236 treatment for osteoporosis. *Calc Tiss Internat.*1994;54(5):431–43.
237
- 238 (3) Mautalen C, Gonzalez D, Blumenfeld EL, Santini Araujo E,
239 Schajowicz F. Spontaneous fractures of uninvolved bones in patients
240 with Paget's disease during unduly prolonged treatment with disodium
241 etidronate (EHDP). *Clin Orthop Relat Res.*1986;207:150-5.
- 242 (4) Eyres KS, Marshall P, McCloskey E, Douglas DL, Kanis JA.
243 Spontaneous fractures in a patient treated with low doses of etidronic
244 acid (disodiumetidronate). *Drug Safety.* 1992;7(2):162-5.
- 245 (5) Fleisch H. Bisphosphonates in the treatment of osteoporosis.
246 *Scandinav J Rheum.* 1998;27(sup107):64.
247 Doi:10.1080/03009742.1998.1172076.
- 248 (6) Whyte MP, Wenkert D, Clements KL, McAlister WH, Mumm S.
249 Bisphosphonate-induced osteopetrosis, *N Engl J Med.* 2003;349(5) 457-
250 63.
- 251 (7) Bachrach LK, Hastie T, Wang M-C, Narasimhan B, Marcus R. Bone
252 Mineral Acquisition in Healthy Asian, Hispanic, Black, and Caucasian
253 Youth: A Longitudinal Study. 1999; *J Clin Endo Met.* 84(12):4702-12.
- 254 (8) Marini J. Do Bisphosphonates Make Children's Bones Better or
255 Brittle? *N Engl J Med.* 2003;349(5):423-26.

256

257 (9) Reynolds JJ, Murphy H, Muhlbauer RC, Morgan DB, Fleisch H.
258 Inhibition by Diphosphonates of Bone Resorption in Mice and
259 Comparison with Grey-Lethal Osteopetrosis. *Calc Tiss Res.* 1973;12:59-
260 71.

261 (10) Shapiro F. Osteoporosis: Current Clinical Considerations, *Clin*
262 *Orthop Relat Res.* 1993;294(9):34-44.

263 (11) Chawla A, Kwek EBK. An unusual presentation of patella and
264 fifth metatarsal base fractures in a patient with osteopetrosis, *J Clin*
265 *Orthop Trauma.* 2017;9(supp 2):S49-S51.
266 Doi:10.1016/j.jcot.2017.10.012.

267 (12) Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA, Brown TD,
268 et al. Atypical subtrochanteric and diaphyseal femoral fractures: Report
269 of a task force of the American Society for Bone and Mineral Research.
270 *J Bone Miner Res.*2010;25(11):2267–2294.

271 (13) Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung A,
272 et al. Atypical subtrochanteric and diaphyseal femoral fractures: Second
273 report of a task force of the American Society for Bone and Mineral
274 Research. *J Bone Miner Res.* 2014;29(1):1-23.

275 (14) Aslan A, Baykal YB, Uysal E, Atay T, Kirdemir V, Baydar ML et al.
276 Surgical Treatment of Osteopetrosis-Related Femoral Fractures: Two

- 277 Case Reports and Literature Review. Case Rpts in Orthoped 2014:
278 Article ID 891963, 7 pages. Doi:10.1155/2014/891963.
- 279 (15) Odvina CV, Rao DS, Pak CYC, Maalouf N, Zerwekh JE. Adynamic
280 bone disease during bisphosphonate therapy:Should we be concerned?
281 American Society of Bone and Mineral Research Annual Meeting, 2003.
282 Presentation number SU344.
- 283 (16) Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak
284 CYC. Severely suppressed bone turnover: A potential complication of
285 alendronate Therapy. J Clin Endocrinol Metab. 2006;3:1294–1301.
- 286 (17) Schneider JP, Hinshaw WB, Su C, Solow P. Atypical femur
287 fractures: 81 individual personal histories. J Clin Endocrinol Metab.
288 2012;97(12):4324-4328.
- 289 (18) Schneider JP. Should bisphosphonates be continued indefinitely?
290 An unusual fracture in a healthy woman on long-term alendronate.
291 Geriat. 2006;61(1):31-33.
- 292 (19) Weill L, McEneaney PA, Prezioso J. Treatment of Fourth Metatarsal
293 Base Fracture Non-Unions in Middle Aged Women with Osteoporosis: A
294 Case Study, Foot Ankle J. 2008; 1(7):5-11.
- 295 (20) Armamento-Villareal R, Napoli, N, Diemer K, Watkins M, Civitelli R,
296 Titelbaum S, et al. Bone turnover in bone biopsies of patients with low-
297 energy cortical fractures receiving bisphosphonates: A case series. Calc
298 Tissue Int. 2009;85(1):37-44.

299

300 (21) Waterman GN, Yellin K, Jamshidinia K, Swift RA, Tamkin JA, Andell
301 RA, et al. Metatarsal stress fractures inpatients with multiple myeloma
302 treated with long-term bisphosphonates: A report of six cases. J Bone
303 Joint Surg – Amer. 2011;93(18):18:e106.

304

305 (22) Melton LJ, Kyle RA, Achenbach SJ, Oberg AL, Rajkumar SV.
306 Fracture risk with multiple myeloma: a population-based study. J Bone
307 Miner Res. 2004;20(3):487-493. DOI: 10.1359/JBMR.041131.

308

309 (23) Pradhan P, Saxena V, Yadav A, Mehrotra V. Atypical metatarsal
310 fracture in a patient on long term bisphosphonate therapy. Indian J
311 Orthop. 2012;46(5):589–592.

312

313 (24) Reichmister R, Jay P. Atypical fractures associated with long-term
314 bisphosphonate use. Clin Geriatr. 2012;20(2):17-21.

315

316 (25) Adam Z, Sprláková-Puková A, Chaloupka R. Atypical fracture of
317 metatarsal bone in a patient with multiple myeloma who was treated
318 long-term with bisphosphonates. Vnitri Lekarstvi 2013;59(11):1022-6.
319 PMID: 24279448.

320

(26) Al-Azzani WAK, Evans L, Speight L, Lea-Davies M, Stone MD, Lau D, et al. Hyperpharmacotherapy in ageing cystic fibrosis patients: The first report of an atypical hip fracture. *Respir Med Case Rep.* 2015;16:148e150.

(27) Murray JC, Audet MC, Bédard M, Michou L. Bilateral distal fibula fractures in a woman on long-term bisphosphonate therapy. *Osteoporos Int.* 2016;27(2):833–836.

(28) Miura LN, Srikantom SV, Schenck J, Double Fixation: Bilateral Bisphosphonate-Related Hip Fractures. *Am J Med* 2017;130(1):e13-15. DOI:10.1016/j.amjmed.2016.06.044.

(29) Hinshaw WB, Schneider JP. Bisphosphonate-Associated Bilateral Atraumatic Ulna Fractures. *Internat J Med Pharmaceut Case Rep.* 2017;9(1):1-6.2017. DOI:10.9734/IJMPCR/2017/33170.

(30) A. C. Feldstein, D. Black, N. Perrin, et al., "Incidence and Demography of Femur Fractures With and Without Atypical Features. *J Bone Miner Res* 2012;27(5):977–986.

342 (31) [https://www.gov.uk/drug-safety-update/bisphosphonates-atypical-](https://www.gov.uk/drug-safety-update/bisphosphonates-atypical-femoral-fractures)
343 femoral-fractures. Accessed 11/12/2017.

344

345 (32)
346 [http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_doc](http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Bisphosphonates_31/WC500117118.pdf)
347 ument/Bisphosphonates_31/WC500117118.pdf. Accessed 11/12/2017.

348

349 (33) Bindon B, Adams W, Balasubramanian N, Sandhu J, Camacho P.
350 Osteoporotic Fractures During Bisphosphonate Drug Holiday. Endocrine
351 Practice. 2018;24(2):163-169. DOI:10.4158/EP171975.OR.

352

353 (34) Khan SA, Kanis JA, Vasikaran S, Kline WF, Matuszewski BK,
354 McCloskey EV, et al. J Bone Miner Res. 1997;12(10):1700-1707.