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# Bisphosphonate-Related Osteonecrosis

Etiology, Risk and Patient Management Considerations

THIS ARTICLE HAS BEEN PEER-REVIEWED

## Abstract

Bisphosphonates are osteoclast-specific inhibitors which impair bone remodelling.<sup>1</sup> Therapeutically, they are commonly used in the treatment of osteoporosis and Paget's disease, and to prevent the progression of osseous lesions associated with multiple myeloma and bony metastases.<sup>1</sup> As use of these drugs has become more widespread (five–10 years), a potentially severe complication of bisphosphonate therapy has been identified, bisphosphonate-related osteonecrosis of the jaws (BRONJ).<sup>2</sup> This complication is of particular concern in dentistry, since the osteonecrosis manifests primarily in the jaws<sup>3–6</sup>, and rarely in other bones in the body.<sup>6</sup> In approximately 50 percent of the cases, oral surgical procedures precipitated the development of BRONJ.<sup>3</sup> Furthermore, controversy exists within the dental profession regarding treatment recommendations for patients currently taking bisphosphonates, particularly for elective treatments such as dental implants.<sup>7–10</sup> The goals of this article are:

- to provide an overview of bisphosphonate therapy and thus identify the patient populations at risk of developing BRONJ;

- to discuss the patient management recommendations for those who develop BRONJ;
- to present five new cases of BRONJ including a case of a patient receiving oral bisphosphonate therapy who developed BRONJ following dental implant placement; and
- to discuss the current recommendations in terms of dental treatment for patients receiving bisphosphonate therapy.

## Introduction

Bisphosphonates are synthetic pyrophosphate-like pharmaceutical agents with a strong affinity for calcium.<sup>1,5</sup> Once absorbed, bisphosphonates are either concentrated selectively in bone or rapidly eliminated via the kidneys in an unmetabolized form.<sup>1</sup> In bone, bisphosphonates are incorporated into the extracellular matrix and accumulate over time.<sup>11</sup> When bone remodelling occurs, bisphosphonates are released and dramatically reduce bone resorption by inhibiting osteoclast activity, inducing osteoclast apoptosis and impairing angiogenesis.<sup>1,12</sup> The molecular mechanism responsible for these effects is an inhibition of farnesyl diphosphate synthase (FAS), an en-

zyme in the mevalonate pathway.<sup>1</sup> FAS modulates intracellular signalling pathways crucial for several osteoclast functions, including cytoskeletal arrangement and vesicular trafficking.<sup>13</sup> Since bisphosphonates specifically impair osteoclast function, in bisphosphonate-treated patients, osteoblast-mediated bone formation exceeds bone resorption at remodeling sites, leading to progressive gains in bone mass.

## Therapeutic Indications

Several types of bisphosphonates are currently used therapeutically, with specific types used for oral or intravenous (IV) administration (Table 1).<sup>7,14,15</sup> Bisphosphonates are among the most commonly prescribed medications, with alendronate (Fosamax) being the 19th most commonly prescribed medication.<sup>14</sup>

The primary indication for oral bisphosphonates is the treatment of osteoporosis.<sup>15</sup> Osteoporosis is a degenerative disease of bone, where dense trabecular bone is replaced by fibrous-adipotic marrow, leading to an overall decrease in bone density and greatly increased risk of fracture.<sup>15</sup> Osteoporosis primarily affects postmenopausal women, but men over 50

years are also affected.<sup>15-16</sup> An estimated 10 million people in the USA alone suffer from osteoporosis.<sup>15-16</sup> Osteoporosis-related fractures are associated with substantial morbidity, disability and mortality. **Approximately one-fifth of osteoporotic patients who experience hip fracture die within one year.**<sup>16</sup> Bisphosphonates increase bone mass and have been clinically proven to decrease the incidence of osteoporosis related fractures. Multinational clinical trials demonstrated that Fosamax reduces the incidence of hip and vertebral fractures by 48 percent and 50 percent, respectively.<sup>15</sup> Oral bisphosphonates are also used in the treatment of Paget's disease and in children with osteogenesis imperfecta.<sup>3-5,7</sup>

In addition, bisphosphonates are used intravenously and in higher doses to treat bony lesions of metastatic cancer and multiple myeloma (Table 1).<sup>3-5,7</sup> Bone metastases are commonly associated with breast, lung, prostate and renal carcinoma.<sup>1</sup> In bony metastases, cells produce excessive amounts of numerous growth factors and cytokines, which in turn

stimulate osteoclast-mediated bone resorption in an uncontrolled manner.<sup>1</sup> Multiple myeloma is characterized by the radiographic appearance of punched-out radiolucent lesions in bone.<sup>17</sup> The destruction of bone in this disease is due to both increased osteoclastic activity and impaired osteoblastic activity.<sup>3,17</sup> Bisphosphonates inhibit osteoclast function, impair the formation of osteolytic lesions characteristic in both multiple myeloma and bony metastases and improve the negative outcomes associated with these lesions, such as compression fractures of vertebrae and long bone fractures. The effectiveness of bisphosphonates in decreasing osteoclast-mediated bone lysis has been well established in clinical trials, resulting in significantly reduced patient morbidity.<sup>17</sup> Thus, the American Society of Clinical Oncology considers IV bisphosphonate therapy the standard of care for moderate to severe hypercalcemia associated with malignancy and metastatic osteolytic lesions associated with breast cancer and multiple myeloma.<sup>17</sup>

### Bisphosphonate-Related Osteonecrosis of the Jaws (BRONJ)

The therapeutic benefits of bisphosphonates in the management of patients with osteoporosis, bony metastases and multiple myeloma are clear. Recently however, a significant negative side effect of bisphosphonate therapy has been recognized to occur in some patients — osteonecrosis of the jaws.<sup>2-5,7</sup>

BRONJ presents clinically as areas of exposed yellow-white, hard bone with smooth or ragged borders (Fig. 1). It occurs in both the mandible and the maxilla.<sup>2-5,7</sup> According to the American Association of Oral & Maxillofacial Surgeons, BRONJ is a condition characterized by exposure of the bone in the mandible or maxilla, persisting for more than eight weeks in a patient who has previously taken or who is currently taking bisphosphonate, and who has no history of radiation therapy to the jaws.<sup>3,18</sup> This last caveat is crucial, since the clinical and histological appearance of BRONJ is quite similar to that of osteoradionecrosis of the jaws.

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**Table 1**

Types of bisphosphonates, primary indications and recent number of prescriptions in the US.<sup>7,14,15</sup>

Route of Administration	Bisphosphonate	Primary Indication	Relative Potency	2006 US Prescriptions
<b>Oral</b>	Alendronate (Fosamax)	Osteoporosis	1	16.7 million
	Risedronate (Actonel)	Osteoporosis	1	9.2 million
	Ibandronate (Boniva)	Osteoporosis	1	3.2 million
<b>IV</b>	Zoledronic acid (Zometa)	Bone metastases	10	650,000
	Pamidronate (Aredia)	Bone metastases	5	

**Figure 1**



- a.** Clinical appearance of a severe case of post-extraction BRONJ with a large area of exposed necrotic bone.
- b.** Radiographic appearance.

## Clinical Feature

The most commonly associated factor in patients who develop BRONJ is a history of dental extraction or trauma induced by prosthodontic appliances.<sup>3-5,7</sup> BRONJ does develop spontaneously in approximately 50 percent of cases.<sup>5</sup> The osteonecrosis ranges in severity. A mild case may involve only a small fragment of denuded, necrotic bone associated with an extraction socket,<sup>3,18</sup> whereas a severe case of BRONJ may require radical surgical resection, which then may fail to heal completely, leaving the patient with permanent facial disfigurement.<sup>18</sup>

### Treatment Recommendations for BRONJ

Current patient management recommendations are case-specific and principally conservative in nature.<sup>7,8,18</sup> Mild asymptomatic patients are best treated with systemic antibiotics such as amoxicillin, an antimicrobial mouth rinse such as chlorhexidine and close patient follow-up.<sup>7,8,18</sup> In moderate cases, the necrotic bone should be debrided as conservatively as possible, since areas of increased exposed bone may lead to further osteonecrosis.<sup>7,8,18</sup> In severe cases of BRONJ, palliative surgical resections may be necessary.<sup>18</sup> It is important for patients and clinicians to realize that a cure for severe BRONJ is not a realistic expectation and that the treatment goals are to preserve the patient's quality of life, control pain and manage infections associated with the osteonecrosis.<sup>7,8,18</sup>

### Incidence and Relative Risk of BRONJ

BRONJ arises primarily in patients treated with the higher dosage, more potent intravenous bisphosphonates, zoledronic acid (Zometa) and pamidronate (Aredia) (Table 1.); however, some cases of BRONJ have occurred in patients taking oral bisphosphonates for osteoporosis.<sup>2-5,15</sup> Since BRONJ was first recognized by Marx in 2003,<sup>2</sup> a growing number of cases have been identified, with

more than 600 cases described in the literature to date.<sup>3</sup> Originally, no potential complication of bisphosphonates related to osteonecrosis of the jaws was listed by the drug manufacturers, but with the growing volume of evidence linking bisphosphonate use to osteonecrosis of the jaws, the American Food and Drug Administration in 2005 issued a broad drug-class warning of this potential complication for all bisphosphonates.<sup>3</sup>

Depending on which study is cited, the incidence of BRONJ in patients receiving **intravenous** bisphosphonate therapy varies greatly from 0.8–12 percent.<sup>3</sup> In single-centre retrospective studies of oncologic patients, the incidence of BRONJ was noted to be between six-11 percent.<sup>4</sup> The incidence of BRONJ in patients receiving **oral** bisphosphonate therapy is much lower, with Mavrokokki *et al* reporting a frequency of between 0.01–0.04 percent.<sup>19</sup> However, if dental extractions were performed a marked increase in the frequency of BRONJ (0.09–0.34 percent) was noted in this population.<sup>19</sup>

### Oral Versus Intravenous Bisphosphonate-Treated Patients

Oral bisphosphonates differ from IV bisphosphonates in three ways as to their likelihood of causing BRONJ:

- Oral bisphosphonates are used in lower doses and are less potent, therefore, longer periods of patient exposure are necessary before bone necrosis develops;
- The amount of exposed bone and the symptoms associated with BRONJ in oral bisphosphonate patients is less severe than in IV bisphosphonate-treated patients; and
- Discontinuation of oral bisphosphonates has been shown to lead to improved healing of exposed bone in some cases.<sup>20</sup>

Thus, the incidence of BRONJ is quite different for patients receiving oral rather than IV bisphosphonate therapy (0.01 to 0.04 percent versus 0.8 to 12 percent).<sup>3,19</sup> Therefore, when determining a patient's risk of develop-

ing BRONJ these two distinct subpopulations should be considered separately. In support of this approach, a very recent study by Cartsoy *et al*, examining the medical claims of 714,217 patients receiving bisphosphonate therapy, concluded that **oral bisphosphonate therapy actually decreases the risk of adverse bone outcomes, including complications related to the jaws.**<sup>21</sup> **In contrast, IV administration of bisphosphonates significantly increased the risk of BRONJ by 4.4-fold.**<sup>21</sup>

### Dental Treatment Considerations

Interdisciplinary collaboration between dentists and physicians is necessary to decrease the likelihood of this potentially disfiguring and debilitating complication of bisphosphonate therapy. Because of increasing awareness within the medical community, more referrals for dental evaluation and treatment will likely occur in the future.

When a patient treated with IV bisphosphonates requires dental extractions, general dentists should consider referral to an oral surgeon for even the most routine extractions.<sup>7,18</sup> Expert opinion differs regarding patients treated with oral bisphosphonates. Certain specialists suggest that the risk of BRONJ in oral bisphosphonate treated patients is quite low and referral by general dentists is unnecessary; others however disagree, and still recommend referral of all bisphosphonate-treated patients requiring extractions.<sup>9,10,18</sup>

For complicated cases, the patient management strategy suggested by Marx should be considered for dental surgical treatment in bisphosphonate-treated patients. This is based on the duration and type of bisphosphonate therapy and measurement of a patient's serum C-telopeptide levels (which assesses the rate of bone remodelling).<sup>18,20</sup> Following this assessment, three-month bisphosphonate drug holidays are recommended in certain cases prior to dental surgical

treatment;<sup>18,20</sup> however, the efficacy of bisphosphonate drug holidays at reducing the risk of osteonecrosis of the jaws has not yet been established. Given the long half-life of bisphosphonates in bone (up to 10 years)<sup>1</sup>, a three-month interruption of treatment may not be of sufficient duration to decrease the risk of BRONJ.

**Five New Cases of BRONJ**

Table 2 summarizes five cases of BRONJ followed by author HL. All cases were treated with either IV bisphosphonates or oral bisphosphonates and steroids. One case included IV bisphosphonates and steroids. The intraoral location and size of the lesions was variable. In all cases the BRONJ lesion was precipitated by either an ill-fitting denture or a surgical intervention. All patients were in their sixth decade or greater and the lesions persisted for a significant period of time.

**Recommendations**

Optimal oral health and hygiene should be encouraged in patients receiving bisphosphonate therapy.<sup>7,8</sup> Restorative dentistry, periodontal maintenance and hygiene should be performed as needed.<sup>7,8</sup> When possible, less surgically invasive dental treatment such as root canal therapy should be strongly recommended in patients taking bisphosphonates, to reduce the possibility of BRONJ.<sup>7,8</sup>

A question of particular concern to general dentists with regard to bisphosphonate-treated patients is what limitations, if any, should be considered when planning an elective surgical treatment such as implants? Dental implant osseointegration failure has been seen in bisphosphonate-treated patients.<sup>20,22</sup> A retrospective clinical study evaluating the success of dental implants placed in 115 patients receiving oral bisphosphonate therapy demonstrated that in this

limited cohort none of the patients developed BRONJ.<sup>23</sup> Furthermore, implant success rates were similar for patients receiving oral bisphosphonates compared with controls.<sup>23</sup> The mean duration of oral bisphosphonate therapy in this cohort was 38 months.<sup>23</sup> Similarly, a study by Jeffcoat in 2006 of dental implant placement in osteoporotic women, 25 (50 percent) of whom were taking oral bisphosphonates for a duration of between one to four years prior, demonstrated a 100 percent implant success rate after three years with no evidence of BRONJ in any of these patients.<sup>24</sup>

**Case Report**

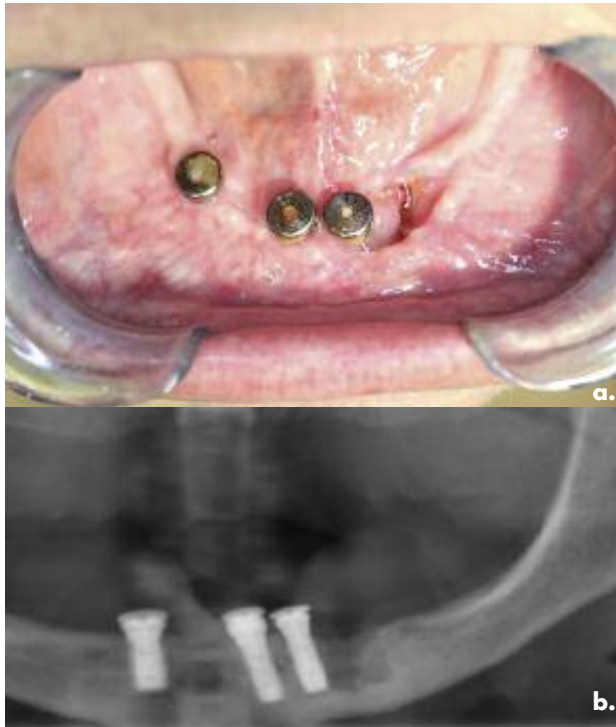
To date there are approximately 200 reported cases of BRONJ in patients taking the oral bisphosphonates alendronate (Fosamax) or risedronate (Actonel)<sup>23</sup>, none with implants and oral bisphosphonates alone for osteoporosis. We report here the case of a 73-

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**Table 2**  
Patient information for five new cases of BRONJ.

Patient	Age	Sex	Diagnosis	BP	Duration of BP Tx	Other Meds	Precipitating Event	Location	Size mm	Response to Therapy
BW	78	M	Metastatic Prostate Carcinoma	IV Zometa	19 Months	Prednisone	Extractions	Left Mandible	30 X 20	Progression
CC	73	F	Osteoporosis Rheumatoid Arthritis	Oral Fosamax	36 Months	Prednisone Methotrexate Arava Plaquenil	Implant	Anterior Mandible	10 X 10	No Change
MM	57	F	Osteoporosis Multiple Myeloma	Oral Fosamax	24 Months	Multiple N/A Smoker	Denture Rub	Anterior Maxilla	4 X 4	No Change
GK	54	M	Multiple Myeloma Hypertension	IV Pamidronate PO Clodrinatate	24 Months 90 Months	Multiple N/A	Tumour (muco-epidermoid Carcinoma) resection	Posterior Hard Palate	3 X 3	Sequestration and Healing
EW	72	M	Metastatic Prostate Carcinoma	IV Zometa	9 Months	Prednisone Smoker	Denture Rub	Left Mandible	10 X 10	No Change

## Clinical Feature



**Figure 2**

- a. Clinical appearance of implant surgery-induced BRONJ.
- b. Radiographic appearance.

year-old female treated with oral bisphosphonates for osteoporosis who developed BRONJ following dental implant placement (Fig 2.). This patient had been taking Fosamax for three years prior to implant placement. The BRONJ which this patient developed must be considered in the context of her other medical conditions and medications. In addition to Fosamax, she was also taking prednisone, methotrexate, hypdroxyquin

(Plaquenil) and leflunomide (Arava) for rheumatoid arthritis. Corticosteroid therapy affects immunity and bone homeostasis and co-treatment with corticosteroids is known to increase the likelihood of BRONJ.<sup>15,25</sup> To aid in the process of risk assessment for the development of osteonecrosis in bisphosphonate-treated patients, we have developed a table outlining factors which are known to increase the risk of BRONJ (Table 3).<sup>15,25</sup>


**Table 3**

Factors which increase the risk of developing BRONJ.<sup>15,25</sup>

1	Potency of bisphosphonate (IV vs. Oral)
2	Duration of therapy (> 6 months IV and >3 yrs oral bisphosphonate)
3	Age (>65 yrs)
4	Chronic periodontitis
5	Prosthetic appliances which irritate the oral mucosa
6	Immunosuppression (ongoing corticosteroid therapy or other)
7	Antimetabolite medications (eg. Methotrexate)
8	Anti-rejection medications (eg. Cyclosporin)

All patients considering surgical dental implant treatments should be asked about bisphosphonate and other medication use, and if they are taking bisphosphonates they should be advised of possible risk of developing BRONJ and be made aware of the nature of this condition.

### Conclusions

The management and dental treatment of patients receiving bisphosphonate therapy is complex, due to the risk of developing the potentially unresolving, debilitating complication of osteonecrosis of the jaws. The relative risk of BRONJ is distinct for patients treated with intravenous bisphosphonates compared to those treated with oral bisphosphonates. Consultation with an oral surgeon is strongly recommended prior to surgical management of patients receiving IV bisphosphonate therapy, oral bisphosphonate with corticosteroids or other immunosuppressants. The dental treatment of patients receiving oral bisphosphonate therapy carries less risk, but also requires careful informed consent with a clear presentation and full disclosure to the patient of the nature and relative risk of developing BRONJ. 

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