Tooth Extraction Protocols for Patients on Bisphosphonate Therapy: An Update

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Abstract

The aim of this review is to give an update on various tooth extraction protocols for patients on bisphosphonate therapy. Presently there is an increasing prevalence of patients receiving bisphosphonate therapy. This review has included the pathogenesis of bisphosphonate-related osteonecrosis of the jaws (BRONJ) associated with tooth extraction, its effect on alveolar bone, epithelium, variations in healing time, angiogenesis, and the risk factors associated with BRONJ development, as well as a revised staging of disease presentation for the stratification of patients. There is much heterogeneity and a lack of consensus concerning management protocols, as many recommendations lack supportive evidence-based approaches. Various regimens and treatment protocols have been reviewed for the management of patients on bisphosphonate therapy.

It is envisaged that dental practitioners working in different parts of the world will get a better understanding of bisphosphonate therapy and the complications associated with tooth extraction, so as to enable them to render care with confidence and to improve the quality of life of their patients on bisphosphonate therapy.

Key words: Bisphosphonates, pathogenesis, tooth extraction, tooth extraction protocols, prevention of BRONJ

Introduction

Oral invasive procedures, such as tooth extraction, are common dental procedures and are usually performed, among other reasons, to remove unrestorable teeth due to either caries or advanced periodontal disease (Kato *et al.,* 2013). Dentists, periodontists and oral and maxillofacial surgeons are also, however, exposed to a large group of patients in the population, especially those over the age of 55 years, who receive oral or intravenous (IV) bisphosphonate (BP) therapy. Bisphosphonates are widely used to reduce skeletally related conditions in patients with metastatic cancer, multiple myeloma, Paget's disease, osteopenia and osteoporosis (Devogelaer, 2000; Dalle *et al.,* 2010). Adverse effects of BPs include acute systemic inflammatory reactions, ocular inflammation, renal failure, nephrotic syndrome and osteonecrosis of the jaws (Tanvetyanon and Stiff, 2006). Researchers have used various nomenclatures for osteonecrosis of the jaws as related to BP therapy (*Table 1*). Bisphosphonate-related osteonecrosis of the jaws (BRONJ) is defined as a side effect of the inhibition of osteoclasts in which exposed and necrotic bone persisting for more than 8 weeks occurs in the maxillofacial region, which could be related to current or previous treatment with BPs, with no history of radiotherapy to the head and neck area (Kato *et al.,* 2013). The development of BRONJ appears to be more common with the administration of oral and IV nitrogen-containing BPs (NBPs) than with the usage of non-nitrogen-containing BPs (NNBPs; Migliorati *et al.,* 2010). The majority of osteonecrosis cases are seen in cancer patients receiving IV BPs (94%), while 6% of cases are seen in cancer patients receiving oral BP therapy (Woo *et al.,* 2006). The mandible is more likely to be involved (68.1 to 73%) than the maxilla (22.5 to 27.7%), but can occur in both jaws (4.2 to 4.5%; Rayman *et al.,* 2009; Saad *et al.,* 2012).

Tooth extraction is considered a major risk factor for the development of BRONJ (Urade *et al.,* 2011). The development of BRONJ is more related to previous tooth extractions and occurs less commonly as a spontaneous

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development (Bagan *et al.,* 2009). The risk of BRONJ among patients using oral BPs following tooth extraction is 0.5% (Kunchur *et al.,* 2009) and among cancer patients on IV BPs after tooth extraction ranges from 1.6 to 14.8% (Ruggiero *et al.,* 2009; Ruggiero *et al.,* 2014).

Table 1. Nomenclature for osteonecrosis of the jaws as related to bisphosphonate therapy.

Abbreviation	Definition
ONJ (Landesberg *et al.,* 2011a)	Osteonecrosis of the jaws
BRONJ (Malden *et al.,* 2009)	Bisphosphonate-related osteonecrosis of the jaw
BRONJ (Ruggiero *et al.,* 2009) BOJ (Kato *et al.,* 2013)	Bisphosphonate-related osteonecrosis of the jaw
MRONJ (Ruggiero *et al.,* 2014)	Medication-related osteonecrosis of the jaw
BON (ADA, 2006)	Bisphosphonate-associated osteonecrosis

Clinically, BRONJ may remain asymptomatic for weeks or months, and in some patients, the symptoms, which may mimic dental or periodontal disease, including pain in the jaws or pain at a previous extraction site (American Dental Association Council on Scientific Affairs, 2006), can occur spontaneously. The clinical presentation may include the loosening of teeth, a non-healing ulceration or extraction socket, as well as exposed jawbone with the progression to sequestrum formation, associated with a localized swelling, erythema and purulent discharge (Chiandussi *et al.,* 2006). Clinical side effects of orally administered BPs can include recurrent ulcers with a burning sensation, as well as blisters in the oral cavity (Kharazmi *et al.,* 2012).

Radiographically, there may be no initial obvious changes, but as the BRONJ lesion develops and up to 30-50% of the bone becomes demineralized (Bedogni *et al.,* 2008), evidence of bone mottling may then be seen, resembling osteomyelitis (Chiandussi *et al.,* 2006). It is therefore important to differentiate and exclude other radiographic lesions, such as periapical lesions due to pulpal infection and resulting osteomyelitis, sinusitis, primary and metastatic bone tumors and osteoradionecrosis (Sharma *et al.,* 2013).

Pathogenesis of BRONJ associated with tooth extraction

The pathogenesis of BRONJ remains unclear (Allen and Burr, 2009). BRONJ is a complex disease, and various animal models have been studied involving tooth extraction, indicating various interactions of multiple tissues and cell types with BPs, including toxicity to oral epithelium, altered wound healing, oral biofilm formation, infection and inflammation, the suppression of angiogenesis and high bone turnover of the maxilla and mandible (De Ponte *et al.,* 2016). Two different pathogenic processes leading up to BRONJ have been hypothesized: an indirect process from the oral mucosa to the bone, and a direct process from the bone to the mucosa (De Ponte *et al.,* 2013).

Effects of BPs on alveolar bone

Bisphosphonates can be classified into two classes with different mechanisms of action, based on the presence or absence of a nitrogen side chain on the pyrophosphate group (Mcleod *et al.,* 2007). Non-nitrogen-containing BPs cause a decrease in bone breakdown by means of the reduction in osteoclast cell numbers. This is accomplished by the antagonism of the cellular energy pathways within the osteoclast, leading to apoptosis. Nitrogen-containing BPs have a more complex pathway of action, including inhibition of the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase pathway. This latter pathway is imperative for the generation of hydrophobic molecules that are necessary for the maintenance of cell membranes, production of hormones, anchoring of proteins, and for *N*-glycosylation. Nitrogen-containing BP's bind and block the enzyme in the HMG-CoA reductase pathway, which is essential for connecting small proteins to the cell membrane. This disruption affects osteoclastogenesis, apoptosis and cytoskeletal dynamics, causing a loss of adherence of osteoclasts to the bone surface (Fleisch, 2002). It is known that BPs bind to the positively charged surface of bone hydroxyapatite, and as a consequence, BPs are incorporated into the bone mineral and are retained therein as a therapeutic dosage over a period of years (Cornish *et al.,* 2011), even after the drug therapy has been discontinued (Black *et al.,* 2006). After the administration of both oral and IV BPs, a large amount of the drug is sequestered in bone, although the actual amount that is deposited within the maxillofacial bones following IV administration is not known (Landesberg *et al.,* 2011a). In the jaws, the bone undergoes high turnover remodeling to maintain biomechanical competence, and this process is accelerated after tooth extractions (Malden *et al.,* 2009). The rate of bone turnover in any bone is directly related to its vulnerability to BPs (Marx *et al.,* 2007). The mandibular alveolar bone turnover rate is 10 times that of long bones, such as the tibia, thus explaining the preponderance for BRONJ to occur in the mandibular molar areas, as these areas are subjected to more active bone turnover, due to apparent occlusal or denture-related compression. This then produces a greater vulnerability to drugs that affect osteoclast function in these areas over prolonged periods (Marx *et al.,* 2007). Depending on the dose, potency, mechanism of action and the duration of therapy by BPs, the remodeling of the jaw bones can be diminished or inhibited by the decrease of bone resorption and the reduction of new bone multicellular units. This is manifested by the induction of bone matrix necrosis, which is characterized by a structural modification of the bone (Giannobile, 2008).

This modification includes a decrease in osteoblast and osteoclast recruitment, a decrease in osteoclast adhesion, the inhibition of osteoclast differentiation, osteoclast apoptosis, empty lacunae, the absence of matrix and the presence of unorganized fibrillar structures (Su *et al.,* 2015). The alveolar bone matrix has thus lost its healthy features, whereby there is the inhibition of the required regenerative ability following tooth extraction, thereby predisposing the bone to necrosis when trauma is applied (De Ponte *et al.,* 2016). This condition whereby the alveolar bone has lost its healthy features corresponds to stage 0 as is indicated in the revised staging of disease presentation, according to the American Association of Oral and Maxillofacial Surgeons (AAOMS; Ruggiero *et al.,* 2014; De Ponte *et al.,* 2016; *Table 2*). It is still unclear, however, whether BRONJ is caused by tooth extraction, or whether the process of bone necrosis has already developed by the time of tooth extraction (Allen, 2011).

Table 2. Revised staging of disease presentation for the stratification of patients as set out by the AAOMS for bisphosphonate-related osteonecrosis of the jaws (BRONJ; Ruggiero *et al.,* 2014)

BRONJ Stage	Description
At-risk category	No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates
Stage 0	No clinical evidence of necrotic bone, but nonspecific clinical findings and symptoms
Stage 1	Exposed and necrotic bone in asymptomatic patients without evidence of infection
Stage 2	Exposed and necrotic bone associated with infection as evidenced by pain and erythema in region of exposed bone with or without purulent drainage
Stage 3	Exposed and necrotic bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone, (i.e., inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extraoral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible or the sinus floor

Effects of BPs on oral epithelium

Dental extractions or other intraoral trauma may result in the release of BPs locally from adjacent injured bone, thereby exposing oral epithelial cells to the adverse effects of BPs (Marx *et al.,* 2007). This may involve direct toxic effects on the oral epithelium, including the inhibition of the proliferation of adjacent epithelial cells (Reid *et al.,* 2007). Additionally, BPs may induce epithelial modification by causing a decrease or absence of sarcoglycan and integrin transmembrane proteins, which are necessary for cell-cell and cell-matrix adhesion (Arco *et al.,* 2012). These processes can result in a delay of soft tissue healing (Reid *et al.,* 2007), thereby leading to the prolonged exposure of already compromised underlying bone, prior to the manifestation of alveolar bone necrosis (Migliorati *et al.,* 2005b; Landesberg *et al.,* 2011a). p63 is a constitutively expressed selective marker in basal cell nuclei of squamous epithelium, and is required for the initiation of epithelial stratification during the development and maintenance of basal keratinocytes (Senoo *et al.,* 2007). Bisphosphonates have been shown to decrease the number of p63-positive basal epithelial progenitor cells, thus increasing the risk of BRONJ (Scheller *et al.,* 2011). Furthermore, for the process of re-epithelization to occur, the deposition of an underlying collagen-rich granulation tissue is needed. Bisphosphonates can block collagen expression by oral fibroblasts, thereby resulting in a deficit of granulation tissue and causing a delay in oral soft tissue healing (Ravosa *et al.,* 2011). Epithelial cell apoptosis has also been shown to be promoted by BPs (Allam *et al.,* 2011). It should also be noted, however, that BPs cause a delay, but do not completely inhibit epithelial healing *in vivo* (Scheller *et al.,* 2011).

Bisphosphonates, infection and inflammation

Prolonged exposure of the underlying bone after tooth extraction may also expose the bone to oral microorganisms (Sedghizadeh *et al.,* 2008). Bacterial species such as *Actinomyces*, *Eikonella* and *Moraxella* have been indicated to be the three most commonly associated species with secondary infections in exposed bone due to BP therapy (Marx *et al.,* 2007). Co-aggregation between different bacterial species, especially *Actinomyces*, has been observed in complex biofilm formation on exposed bone, together with *Candida* species (Sedghizadeh *et al.,* 2008). *Actinomyces* species are prevalent in the oral cavity, and a statistically significant increase in *Actinomyces* colonization of exposed bone has been indicated (Kos *et al.,* 2010). It remains unclear though whether this colonization by *Actinomyces* is a primary or secondary event with BRONJ (Landesberg *et al.,* 2011a). This condition whereby exposed necrotic bone can become infected corresponds to stage 2 and 3 of the AAOMS revised staging of disease presentation (Ruggiero *et al.,* 2014; De Ponte *et al.,* 2016; *Table 2*). Pre-existing inflammatory dental disease such as periodontitis and periapical pathology are also well recognized risk factors in confounding the development of BRONJ (Tsao *et al.,* 2013), whereby clinical and radiographic apparent periodontitis has been noted to be a common dental comorbidity associated with BRONJ (Saad *et al.,* 2012).

Teeth that are extracted because of pre-existing periodontal or periapical disease are associated with both inflammation and infection, which may be sufficient to induce BRONJ (Aghaloo *et al.,* 2011). Furthermore, the degree and severity of infection prior to tooth extraction due to periodontal disease are higher as compared to extractions of carious teeth (Kato *et al.,* 2013). It has been shown that bacterial infection in periodontal tissues after tooth extraction can also induce a diminished expression of keratinocyte growth factor (KGF) in gingival fibroblasts, causing a delay in epithelial wound healing (Mawardi *et al.,* 2011). The major source of KGF is gingival fibroblasts, and KGF plays a crucial role in the promotion of epithelial wound healing. However, the combination of BPs and *Fusobacterium nucleatum*, as observed in BRONJ-related infection sites, has been shown to promote the death of gingival fibroblasts, thereby diminishing the production of KGF (Mawardi *et al.,* 2011).

Effects of BPs on angiogenesis

Angiogenesis is an essential factor in the healing of wounds, and at the same time also essential for the invasion of normal tissues by malignant cells, thus the need for the anti-angiogenic effect of BPs (Sharma *et al.,* 2013). Bisphosphonates contribute to ischemic changes associated with delayed healing of extraction sockets by means of the inhibition of angiogenesis, comprising interactions with vascular endothelial growth factors (VEGF) and the inhibition of endothelial cell function, leading to avascular necrosis (Allen, 2011). Low doses of BPs have been shown to inhibit the differentiation of endothelial progenitor cells, while high doses can induce apoptosis of these cells (Yamada *et al.,* 2009). A direct inhibitory action on endothelial cell proliferation together with the inhibition of pro-angiogenic factors, such as fibroblast-growth factor 2 (FGF2) has also been described (Ribatti *et al.,* 2008). BP's may also decrease serum levels of VEGF as well as other cytokines, such as interleukin-17, which are involved in angiogenesis (Oteri *et al.,* 2008).

Effects of BPs on healing time

As referred to earlier, the healing time (HT) of extraction sockets may also be affected. Delayed healing has shown to be statistically significantly longer in patients receiving BP therapy (median HT of 5 weeks), as compared with healthy control patients who have no history of BP exposure (median HT of 2 weeks) (Migliorati *et al.,* 2013). The HT in patients receiving BP therapy is not influenced by the type or potency of BPs received, or by the duration of BP therapy. Furthermore, delayed healing in patients receiving oral versus IV BP therapy may not be statistically different (Migliorati *et al.,* 2013). Healing time after tooth extractions performed due to periodontal diseases may be longer (median HT of 32 days) than those performed due to caries (median HT of 24 days; Kato *et al.,* 2013). This can be ascribed to a higher degree and severity of infection prior to tooth extraction due to periodontal disease, whereby periodontal disease is considered to be a factor for delayed HT (Kato *et al.,* 2013).

Risk factors associated with BRONJ-related tooth extraction

Any patient on BP therapy carries the risk of spontaneous BRONJ development (Malden *et al.,* 2009). However, as shown in an Australian study, patients receiving BP therapy can be up to seven times more likely at risk to develop BRONJ when undergoing tooth extractions (Mavrokokki *et al.,* 2007). Numerous case studies, as well as a limited number of retrospective and prospective studies have been done on the development of BRONJ; however, the majority of suspected risk factors for such development have not been scientifically validated (Landesberg *et al.,* 2011a). Although tooth extraction per se is considered to be a major risk factor for BRONJ development (Urade *et al.,* 2011), mention should be made of related risk factors concerning tooth extraction in patients receiving BPs.

Dosage, administration and potency of BPs

The risk and severity of BRONJ development can be influenced by drug-related factors, such as the dose, duration, route of administration, frequency and potency of administered BPs (Marx *et al.,* 2005; Landesberg *et al.,* 2011b). Orally administered BPs usually cause less extensive osteonecrosis and are more responsive to treatment than IV administered BPs, as IV BPs accumulate in bone much faster, causing a more rapid and insidious bone turnover suppression (Marx *et al.,* 2007). *Table 3* lists the type of BPs prescribed, their potency, administration routes and the main indications for their usage (Sharma *et al.,* 2013). Both NNBPs and NBPs are anti-resorptive drugs, but the NNBPs are less potent and mainly used for treating osteoporosis, whereas the NBPs are more potent and are used in severe bone resorption cases, as in malignancies (Sharma *et al.,* 2013). Worldwide, the majority of patients receiving BP therapy for the treatment of osteoporosis initially place them in a low-risk group, as lower potency oral preparations are usually used for treating osteoporosis. High-risk patients, being fewer in number, are those usually being treated for malignancies, whereby high dose, high potency IV NBPs are usually administered (Malden *et al.,* 2009). However, high dose, high potency BPs can also be administered orally for the management of oncology patients, and the same drug can be prescribed at a lower dosage for the treatment of osteoporosis (American Dental Association Council on Scientific Affairs, 2006).

Table 3. Bisphosphonates (BPs): Type, potency, administration routes and main indications (Sharma *et al.,* 2013)

Type of BPs	Potency	Administration	Main Indications
NNBPs			
Etidronate	1	Oral	Osteoporosis, Paget's disease of bone
Clodronate	10	Oral/intravenous	Osteoporosis, Paget's disease of bone
Tiludronate	10	Oral	Paget's disease of bone
NBPs			
Pamidronate	100	Intravenous	Osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma, Paget's disease of bone
Alendronate	500	Oral	Osteoporosis, Paget's disease of bone
Ibandronate	1000	Oral/intravenous	Osteoporosis
Risedronate	2000	Oral/intravenous	Osteoporosis, Paget's disease of bone, osteolytic lesions of multiple myeloma, hypercalcemia of malignancy
Zoledronate	10000	Intravenous	Osteolytic lesions of multiple myeloma and metastases from solid tumors, hypercalcemia of malignancy

Duration of BP therapy

The duration of exposure to BPs, regardless of the indications for therapy, is considered a risk factor for BRONJ development (Landesberg *et al.,* 2011b; Ruggiero *et al.,* 2014). The prevalence of BRONJ in patients receiving oral BPs increases over a period after 4 years or more, from near 0 at baseline to 0.21% (Lo *et al.,* 2010). The incidence of BRONJ can increase from 0.5% to 1.8% over a 3-year period for cancer patients on IV BP therapy (Henry *et al.,* 2011; Saad *et al.,* 2012) Bone healing may thus be uncomplicated in patients having a history of oral BP therapy of less than 3 to 4 years, presenting with an associated small risk for osteoporosis (Marx *et al.,* 2007; Carlson and Basile, 2009).

Concomitant corticosteroid therapy

A well recognized side effect of corticosteroids is the inhibition of wound healing, as well as osteonecrosis secondary to both oral and IV administered corticosteroids (Landesberg *et al.,* 2011b). Patients taking the equivalent of 7.5 mg prednisolone daily for more than 3 months are subject to general skeletal osteoporosis, whereby the concurrent usage of BPs may be prescribed so as to counteract the osteoporotic effects of corticosteroid therapy (Tsao *et al.,* 2013). The jaws are not usually considered as being at risk for corticosteroid-associated osteonecrosis (Sarin *et al.,* 2008); however, corticosteroid therapy may be emerging as a significant co-risk factor in the development of post-extraction BRONJ when used in combination with BPs (Tsao *et al.,* 2013). This can be ascribed to specific molecular mechanisms of corticosteroid action, including the direct suppression of osteoblasts, apoptosis of osteoclasts, osteoblasts and osteocytes, and the increase of the bio-availability of concurrently used BPs (Patschan *et al.,* 2001).

Other risk factors

Patients are placed in a high-risk group who have a history of previously diagnosed BRONJ (Malden *et al.,* 2009). Anti-angiogenic agents in addition to BP therapy are associated with an increased risk of BRONJ (Saad *et al.,* 2012). Co-morbid conditions, such as poor oral hygiene, osteomyelitis, anemia, diabetes and cancer type are also considered as associated risk factors (Landesberg *et al.,* 2011b; Saad *et al.,* 2012; Qi *et al.,* 2014). Inconsistencies have been reported among various authors as to tobacco use as a risk factor for BRONJ (Ruggiero *et al.,* 2014). However, the deleterious effects of carbon monoxide, hydrogen cyanide, nicotine and tissue hypoxia on the healing of traumatized tissues are well known (Bergstrom, 2006). Genetic factors can also be involved, whereby a single nucleotide polymorphism in the RBMS3 gene, which is associated with bone density, bone turnover and collagen formation, can make patients 5.8 times more likely to develop BRONJ (Nicoletti *et al.,* 2012).

Tooth extraction protocols for the management of patients receiving BP therapy

It is of paramount importance that patients with osteoporosis requiring tooth extraction are provided with comprehensive care that will not compromise the long-term management of their osteoporosis, including minimizing the risks of developing BRONJ (Marx *et al.,* 2007). Such comprehensive care should be focused on the preservation of quality of life of these patients, this being done by means of patient education and reassurance, the control of pain, the control of secondary infection, the prevention of extension of BRONJ lesions, as well as preventing the development of new areas of necrosis (Ruggiero *et al.,* 2014). Many studies have produced tooth extraction protocols for patients undergoing BP therapy that entail the recommendations of panels of experts on this issue (Rayman *et al.,* 2009).

There is, however, a lack of prospective studies providing evidence of scientific validation for the various guidelines presented. There is a clear association between BRONJ and poor dental and oral health, and the best treatment approach has been described to be prevention (Migliorati *et al.,* 2005a). Retrospective studies describing a connection between BRONJ and oral surgery have initiated the development of prevention-oriented management protocols, whereby the establishment of good oral health prior to the initiation of BP therapy is envisaged (Mozzati *et al.,* 2013). Ideally, a dramatic reduction in the incidence of BRONJ can be achieved when dental screening and appropriate preventive dental treatment is performed prior to the initiation of BP therapy, as such an approach has been shown to reduce the incidence rate of developing BRONJ by 50% in patients who are to undergo IV BP therapy (Vandone *et al.,* 2012). Such preventive dental treatment, if systemic conditions permit, may include the extraction of non-restorable teeth and those teeth with a poor prognosis, as well as other necessary elective dentoalveolar surgery. Bisphosphonate therapy may then be initiated after healing of the extraction site (14-21 days), entailing adequate osseous healing and epithelialization of the extraction wound (Ruggiero *et al.,* 2014). Concerning patients already on BP therapy for osteoporosis, other authors have suggested preventive treatment protocols. An Australian study (Kunchur and Goss, 2008) has suggested scaling, oral hygiene instructions, endodontics, the extraction of teeth that cannot be saved, and including the administration of pre-extraction antibiotics, together with minimal trauma and the suturing of extraction sockets. Ruggiero *et al.* (2014) have developed a revised staging of disease presentation for patients already on oral and IV BP therapy (*Table* 2), whereby suggested treatment protocols include patient education, antibacterial mouth rinses, pain control, systemic antibiotic therapy and surgical debridement (*Table 4*). Recommendations concerning specific tooth extraction protocols by various authors can be categorized into non-surgical and surgical protocols (*Table 4*). Non-surgical protocols include the assessment of risk associated with BP therapy, the reduction of risk factors prior to tooth extraction, the implementation of a BP drug holiday, the reduction/cessation of corticosteroid therapy, the improvement of oral hygiene and periodontal health, and the prevention and treatment of infection. Surgical protocols in the literature for tooth extraction are limited and often inconsistent (Mozzati *et al.,* 2013). Various surgical tooth extraction protocols may include intrasulcular incisions with or without detachment of full-thickness flaps, surgical debridement/resection, the usage of vascularized bone, and allowing for healing via primary or secondary intention (Marx *et al.,* 2007; Malden *et al.,* 2009; Seth *et al.,* 2010; Mozzati *et al.,* 2013; Ruggiero *et al.,* 2014). In other prospective and case-controlled surgical studies, it has been hypothesized that oncology patients on IV BP therapy who are to undergo tooth extractions should be treated with plasma-rich growth factors, so as to accelerate the healing process by means of promoting angiogenesis, bone and mucosal wound healing (Mozzati *et al.,* 2011; Scoletta *et al.,* 2013). *Table 4* illustrates the various non-surgical and surgical tooth extraction protocols for patients on oral and IV BP therapies, as recommended by various researchers.

Conclusions and recommendations

A patient's vulnerability to BRONJ development resulting from tooth extraction is subject to the compromised healing status of the hard and soft tissues of the jaws, and is also determined by significant risk factors, such as oral hygiene status, periodontal disease and systemic conditions. Until any pre-operative valid risk assessment is available, a thorough clinical examination should be done to determine and evaluate the risk status of the patient, including the need for antibiotic prophylaxis and therapy. This includes the importance of imperative consultation with the patient and the patient's physician. Accordingly, this will enable the dental practitioner to judiciously plan and perform tooth extractions on patients undergoing BP therapy.

Conflicts of interest

The authors report no conflicts of interest.

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Table 4. Tooth extraction protocols for the management of patients receiving bisphosphonate (BP) therapy as recommended by various authors

Tooth Extraction Protocol:	Protocol Recommendations by Various Authors:
Non-surgical	
Assessment of risk associated with BP therapy	The number and significance of risk factors should be assessed, thereby placing patients in low-, medium- and high-risk categories (Malden *et al.,* 2009). Patients receiving BPs for osteoporosis are in a low-risk group category, and those with additional systemic and local risk factors can move them into a medium-risk group category. Patients receiving BPs for the management of primary or secondary malignancies affecting the skeleton are in a high-risk group category (Malden *et al.,* 2009). A proposed predictive index for ONJ risk assessment, namely the University of Connecticut OsteoNecrosis Numerical Scale (UCONNS) includes specific risk factors, such as oral and IV BP's, oral and maxillofacial surgical procedures, oral health, medical conditions and various comorbidities (Landesberg *et al.,* 2011b). Low-risk group asymptomatic patients receiving oral BPs have a much lesser degree of risk than those on IV therapy (Malden *et al.,* 2009; Lo *et al.,* 2010). For low-risk group patients on oral BPs for less than 4 years with no clinical risk factors, elective dentoalveolar surgery is not considered to be contraindicated (Henry *et al.,* 2011). High-risk group oncology patients receiving monthly IV BPs have an increased risk for BRONJ development following tooth extraction, and such procedures should thus be avoided if possible (Damm and Jones, 2013).
Reduction of risk factors prior to tooth extraction	The avoidance or delaying of tooth extractions is considered as risk reduction, including a coronectomy procedure of unrestorable teeth, whereby endodontically treated retained roots may be kept in the dental arch (ADA, 2006). This treatment concept can be applicable to patients who are asymptomatic undergoing both oral and IV BP therapy (Ruggiero *et al.,* 2014). However, such treatment should be appropriate and each case should be considered on its own merits (Malden *et al.,* 2009).
Implementation of a BP drug holiday	There are limited informative data available to support any evidence of benefits of discontinuing BP therapy (Ruggiero *et al.,* 2014). The benefits versus risks of BP therapy discontinuation should be done in consultation with the patient and the treating physician. (Malden *et al.,* 2009). If systemic conditions permit, for asymptomatic patients on oral BPs for more than 4 years, a drug holiday of 2 months prior to, and 3 months following tooth extractions can be implemented (Damm and Jones, 2013). A drug holiday of at least 2 to 3 months prior to oral surgery can be considered for patients on oral BP therapy for less than 4 years with concomitant corticosteroids, as well as for those taking oral BPs for more than 4 years, with or without concomitant corticosteroid therapy. BPs should then not be restarted until osseous healing has occurred (Damm and Jones, 2013). A drug holiday of 4 to 6 months for patients on oral BP therapy has also been suggested (Marx *et al.,* 2007).
Reduction/cessation of corticosteroid therapy	Delaying tooth extractions until such time as the corticosteroid dose is less than the equivalent of 7.5 mg per day should be considered, due to the dose and potency of corticosteroids having a direct and immediate effect on the risk of tooth extraction-related BRONJ development (Patschan *et al.,* 2001).
Improvement of oral hygiene and periodontal health	The risk of development of BRONJ after tooth extraction can be greatly reduced if patients who are presently receiving BP therapy undergo pre-extraction dental care, such as plaque control and the elimination of periodontal and other active dental diseases (Lodi *et al.,* 2010; Migliorati *et al.,* 2013).
Prevention and treatment of infection	Antibacterial mouth rinses should be used in patients presenting with BRONJ stages 1, 2 and 3 (AAOMS; Ruggiero *et al.,* 2014). Chlorhexidine mouthwash should be used pre-operatively (Migliorati *et al.,* 2013) and post-operatively until healing of the extraction wound is observed (ADA, 2006). Systemic antibiotic therapy should be administered in patients presenting with BRONJ stages 0, 2 and 3; the penicillin group of antibiotics is recommended. For patients who are allergic to penicillin, then the alternative usage of quinolones, metronidazole, clindamycin, doxycycline and erythromycin is indicated. Antibiotic regimens should also be adjusted according to analyses of microbial cultures (Ruggiero *et al.,* 2014). Furthermore, in the event of failure of systemic antibiotic therapy in cases due to biofilm formation on the surface of exposed bone, then operative therapy including the reduction of the volume of colonized necrotic bone may be a beneficial adjunct to antibiotic therapy (Ruggiero *et al.,* 2014). The risk:benefit equation of surgical antibiotic prophylaxis in low-risk group patients should be considered in light of the known risk and severity of reactions to penicillin-based and other prescribed antibiotics (Malden *et al.,* 2009). However, in high-risk group patients the routine use of such prophylaxis is recommended. In light of the most common pathogens associated with BRONJ (Marx *et al.,* 2007), penicillin V-K 500 mg four times per day, and for patients allergic to penicillin the second line of choice is levofloxacin 500 mg once daily, followed by doxycycline 100 mg once daily and this regimen to be used for 14 days (Marx *et al.,* 2007). Patients who are refractory to the latter antibiotics should be administered metronidazole 200 to 500 mg three times daily (Marx *et al.,* 2007; Malden *et al.,* 2009). Amoxycillin and clindamycin are not considered as first line drugs for prophylaxis (Khosla *et al.,* 2007). Furthermore, to ensure effective antibiotic blood levels during surgical procedures, oral antibiotics should be administered one hour pre-operatively (Malden *et al.,* 2009).

table 4 continued overleaf...

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Surgical	
Extraction and wound debridement	Tooth extraction should be performed with the least trauma, with removal of sharp socket wall margins and/or inter-radicular bone, without lifting the periosteum from the bone. One tooth at a time should be dealt with, or there can be a sextant-by-sextant approach. Primary closure of extraction wounds may not be considered imperative (Malden *et al.,* 2009). Mozzati *et al.* (2013) have suggested that extractions in osteoporotic patients taking oral BP's be performed without the detachment of full-thickness flaps, and that sockets should be filled with absorbable gelatin sponge haemostatic, including suture placement, so as to allow wound healing via secondary intention. Oncology patients receiving IV BP's may also receive plasma-rich growth factors during tooth extraction to promote a shortened healing time (Mozzati *et al.* (2013; Scoletta *et al.,* 2013). Patients being treated with oral BP's for osteoporosis presenting with exposed and necrotic bone, with no evidence of infection and who are asymptomatic (thus corresponding to BRONJ stage 1), should not receive any initial debridement, but should be treated with antibacterial mouth rinses (Marx *et al.,* 2007; Ruggiero *et al.,* 2014). Debridement to relieve soft tissue irritation and for infection control should be done in patients with BRONJ stage 2, and surgical debridement/ resection for longer term palliation of infection and pain should be done for patients with BRONJ stage 3 (Ruggiero *et al.,* 2014). Symptomatic patients with stage 3 disease may require resection and immediate reconstruction with a plate or an obturator (Ruggiero *et al.,* 2014), as well as including the usage of vascularized bone (Seth *et al.,* 2010). Ruggiero *et al.* (2014) have furthermore indicated that mobile bony sequestra should be removed so as to facilitate soft tissue healing, regardless of the disease stage. Also, symptomatic teeth within exposed necrotic bone should be extracted, as the extraction procedure is unlikely to exacerbate an established necrotic process. Resected bone specimens should also be histologically analyzed for possible metastatic cancer (Ruggiero *et al.,* 2014).

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