Bisphosphonates and Osteonecrosis of the Jaws

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Abstract: Bisphosphonates are important drugs that are increasingly prescribed to reduce the morbidity associated with osteoclast-mediated bone diseases. Shortly after the turn of the century, a variety of case reports described a necrosis of the jaw bone in patients using bisphosphonates. Currently, an exposed area of necrotic jaw bone present for at least eight weeks in patients using bisphosphonates has been defined as a bisphosphonate-associated osteonecrosis (BON) by the American Dental Association. BON may occur spontaneously but is more frequently associated with local trauma to the jaw. At this time, a causal relationship between BON and bisphosphonates has not been demonstrated. This review will evaluate current data related to the occurrence, risk, prevention, treatment, and management of BON.

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Life consists in penetrating the unknown, and fashioning our actions in accord with the new knowledge thus acquired.
—Leo Tolstoy

It has a name but no one knows for sure what to call it (e.g., ONJ, BION,[1] BIONJ,[2] BON,[3] BRONJ[4]); it is an osteonecrosis of the jaw, but the natural course and spectrum of clinical outcomes remain a mystery; though there have been numerous reports in the literature about it, the incidence and prevalence in the general population remain uncertain; it has been reported to occur in patients taking a specific drug yet the etiology is unclear; and, finally, since we don't know what causes it, we are naïve about how best to prevent it and, when it does occur, naïve about how best to adequately treat it. This malady that has caught the attention of dentists worldwide is an osteonecrosis of the jaws that appears to be associated with patients using bisphosphonates.

Osteonecrosis of the jaw (ONJ) has been documented in the literature for over 150 years and has been characterized by bone death as a consequence of a wide variety of systemic and local factors that compromise bone blood flow. ONJ has been associated with environmental pollutants, pre-existing diseases, and radiotherapy, as well as many popular medications. Prior to the advent of antibiotics, ONJ was a familiar outcome[5] that was characterized by infection, inflammation, and thrombosis.[6] In the early twentieth century, when antibiotics were used for the treatment of acute bone destruction, the incidence of massive necrotizing bone infections ceased to be a commonplace occurrence. However, in the new millennium of preventive dental and periodontal care, improved diagnostics, zealous use of systemic antibiotics, and minimally invasive dental care, the occurrence of ONJ secondary to bisphosphonate therapy has received clinical recognition as a result of a growing literature base. In spite of this information cascade, prevailing uncertainties remain about the etiology, early diagnosis, incidence, and management of this condition.

Although our information about ONJ in patients using bisphosphonates continues to increase, the conventional wisdom about the dental management of individuals using bisphosphonates is a combination of art and science mixed with ignorance. We all know of the fearful dentist who refuses to treat any patient taking bisphosphonates and the fearless dentist who sees no problem with providing any treatment requested by patients using these drugs. This review, using an evidence-based approach, will attempt to answer some of the important questions related to the occurrence, risk factors, prevention, treatment, and management of jaw osteonecrosis associated with bisphosphonates. With the amount of material on this subject being introduced to the literature weekly, it would be prudent to consider that additional information to further clarify this disease will soon become available.

Before we begin to examine the issues as we currently understand them, it is important to discuss what bisphosphonates are, what they are used for, and how they work. In this article, bisphosphonate-asso-

ciated osteonecrosis or BON will be the terms used to describe an osteonecrosis of the jaws secondary to bisphosphonate therapy. Please know that BON is no better or worse a term than the others that have found their way into the literature, but it is the name adopted by the American Dental Association,[3] the organization that represents all dentists in the United States.

Bisphosphonates: What Are They and What Do They Do?

In the mid-1960s, inorganic pyrophosphates were found to prevent calcification in body fluid by binding to hydroxyapatite crystals.[7] This discovery led investigators to find stable analogs of inorganic pyrophosphates, which are now called bisphosphonates. As a family of pyrophosphate analogs, bisphosphonates contain a common chemical configuration: two phosphate groups attached to a central carbon atom that forms a three-dimensional structure (Figure 1).[8] This molecular construct enables the molecule to attach to bone[8] and disrupts osteoclast function.[9,10] In addition to the effects on bone, bisphosphonates also have anti-invasive,[11] anti-angiogenic,[12] and anti-proliferative[13] properties.

In regard to pharmacokinetics, bisphosphonates are highly polar compounds and as a result are poorly absorbed after oral ingestion.[14] More specifically, the bioavailability of the drug is less than 5 percent after oral administration.[15] Because food can reduce absorption, timing of meals is important to enhance the bioavailability of the drug.[14] To increase the amount of bisphosphonates introduced to bone, drug delivery can be accomplished via intravenous administration.[14] Once in the bloodstream, almost all of the dose is either absorbed by the bone or eliminated in urine.[8] As a result of their negative charge and chemical structure, bisphosphonates can be retained by the bone for as long as ten years.[16] When bone remodeling does occur, bisphosphonates are released into the acidic environment of the resorption lacunae where they impede osteoclast action by either inhibit-

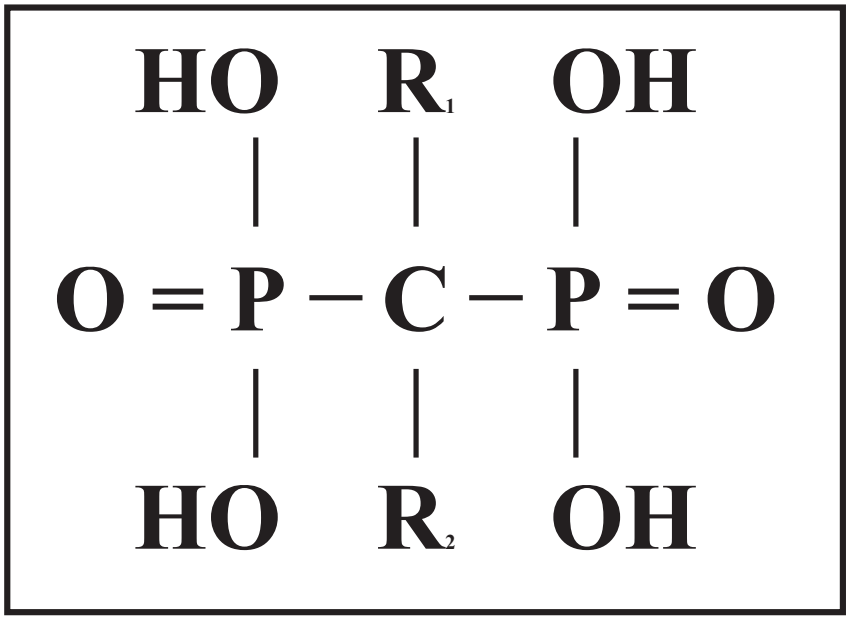

Figure 1. Chemical structure of bisphosphonates

The germinal carbon atom is flanked by two phosphate groups. This core configuration is essential for skeletal bioavailability. Adding a hydroxyl group to R_1 increases binding to hydroxyapatite. Addition of functional groups to R_2 increases potency of compound.

ing cholesterol biosynthetic pathways, accelerating apoptosis,[8] or disrupting the cell cycle.[10]

Over time, bisphosphonate structure has been modified to increase efficacy[17] (Table 1). First generation bisphosphonates (e.g., etidronate) had minimally modified side chains of the pyrophosphage molecule or contained a chlorphenyl group. With the addition of a nitrogen group in the side chain, second generation bisphosphonate (e.g., alendronate) potency increased by ten- to a hundred-fold. Third generation bisphosphonate (e.g., risedronate) potency increased by 10,000 times when a heterocyclic ring containing nitrogen was inserted into the drug molecule.

The value of bisphosphonates resides in their ability to inhibit bone resorption. These drugs are employed for the treatment of osteoclast-mediated bone diseases, which include osteoporosis, steroid-induced osteoporosis, Paget's disease, tumor-associated osteolysis, multiple myeloma, and malignancies associated with hypercalcemia.[17] In regard to the prevention of bone metastases, bisphosphonates are important adjuncts commonly used in patients with many types of neoplasms, especially breast and prostate cancer. In dentistry, they have been shown to prevent dental calculus formation[18] and are beneficial in modulating host responses in the management of periodontal diseases.[19,20] Bisphosphonates can also have toxic properties; some of the adverse effects include osteomalacia, esophagitis, mild fever, muscle aches, and renal toxicity.

Does BON Exist?

At this time, there are no controlled, randomized, prospective, double-blinded studies to support a causal relationship between bisphosphonates and the presence of exposed bone in the jaw; however, there are data that suggest that some sort of association exists between ONJ and bisphosphonates. These data include the following: 1) the perceived higher prevalence of ONJ in bisphosphonate users versus nonusers; 2) a sequential relationship requiring bisphosphonate administration prior to the onset of clinical signs; 3) a reported dose response effect of the drug; 4) the consistency of numerous reports from a variety of investigators from different institutions regarding BON; and 5) biologically plausible explanations regarding the cause of a bisphosphonate-induced bone lesion.[21,22]

To be sure, there are skeptics. These clinicians view the effects of bisphosphonates as stressors of bone health and argue that this particular agent is not very different from other drugs, such as glucocorticoids or estrogens, that have caused similar events in the jaw.[23] Further, they point to the use of bisphosphonates for the treatment of osteonecrotic conditions, such as the traumatic osteonecrosis of the femoral head,[24] and steroid-associated osteonecrosis in young patients treated for acute lymphoblastic leukemia.[25] Whatever your position, the current trend, until more data are available, is to view bisphosphonates as a risk predictor for an osteonecrosis of the jaw (Table 2).

What Is BON, and Who Gets It?

The first peer-reviewed report of an ONJ associated with a bisphosphonate was reported in 2004.[26] Since that time, the absence of a universally accepted case definition, combined with missing historical or clinical patient information, has reduced the quality of many case reports in the literature concerning BON. Presently, a confirmed case of BON has a clinical presentation that includes soft tissue swelling and exposed, necrotic bone that has persisted for more than eight weeks[4,27] (Figure 2). It is important to

Table 1. Antiresorptive potency of bisphosphonates currently on the U.S. market

Generic Name	Trade Name	Manufacturer	Side Chain	Relative Potency	Administered
Etidronate	Didronel	Procter & Gamble	Short alkyl or halide	1	Orally/Intravenously
Tiludronate	Skelide	Sanofi-Aventis	Cyclic chloro	10	Orally
Pamidronate	Aredia	Novartis	Aminoterminal	100	Intravenously
Alendronate	Fosamax	Merck	Aminoterminal	100–1,000	Orally
Risedronate	Actonel	Procter & Gamble	Cyclic nitrogen	1,000–10,000	Orally
Ibandronate	Boniva	Roche	Cyclic nitrogen	1,000–10,000	Orally
Zoledronic acid	Zometa	Novartis	Cyclic nitrogen	≥10,000	Intravenously

note that the eight-week duration of exposed bone in the jaw is necessary to distinguish BON from other conditions that exhibit a delayed healing response. To further distinguish BON from other maladies, the patient must have taken or be currently using bisphosphonates, while other potential confounding conditions (e.g., radiotherapy to the jaws, alcoholism, heavy metal accumulation, heritable prothrombotic

Table 2. Definitions of risk assessment

Type of Risk Assessment	Definition
Risk Factor	An environmental, behavioral, or biologic factor confirmed by a temporal sequence that directly increases the probability of the disease occurring and, if removed, decreases the probability of the disease occurring. Risk factors are part of the causal chain or expose the host to the causal chain. Identifying risk factors can be useful in identifying interventions.
Risk Indicator	Probable or putative risk factor. Usually identified in cross-sectional studies but has not been confirmed in longitudinal studies.
Risk Predictor	A characteristic associated with elevated risk for disease but may not be a component of the causal chain. Predictors can identify those at risk but should not be used to identify interventions.
Prognostic Factor	An environmental, behavioral, or biologic factor that directly affects the probability for a positive therapeutic outcome.

Source: Genco RJ, Jeffcoat M, Caton J, Papapanou P, Armitage G, Grossi S, et al. Consensus report. Periodontal diseases: epidemiology and diagnosis. Ann Periodontol 1996;1(1):216–22.

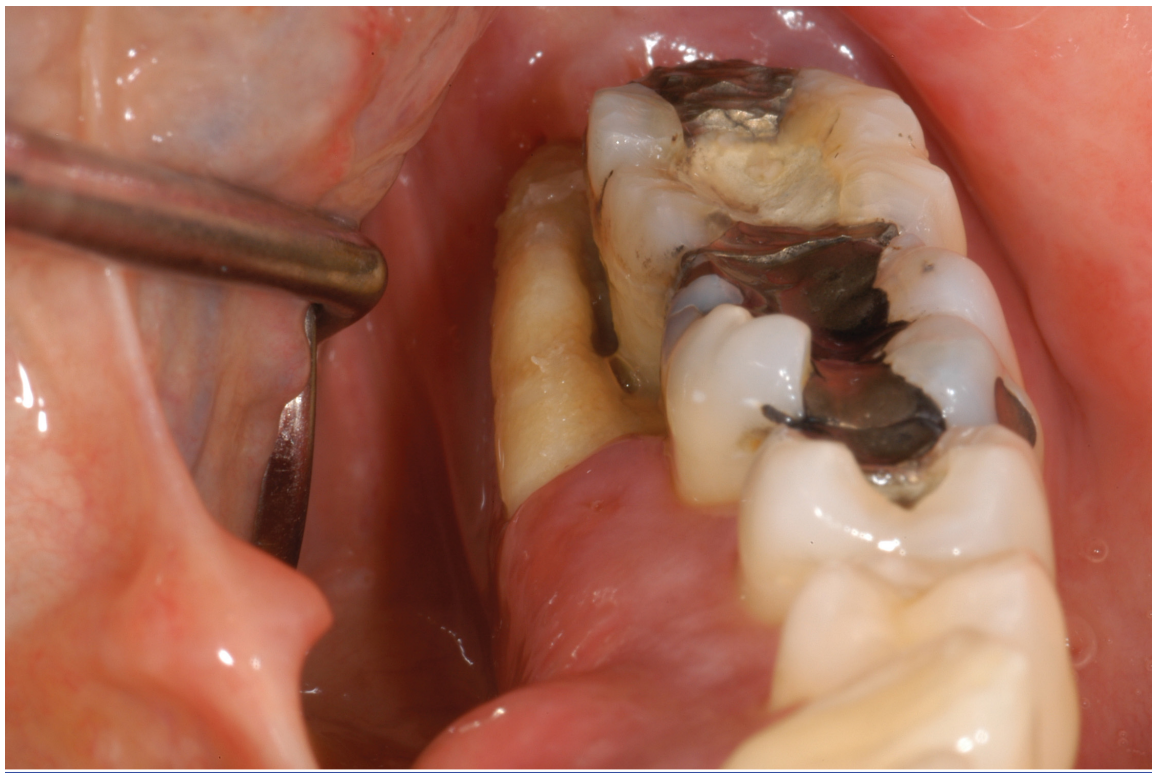

Figure 2. Clinical characteristics of BON

Photo courtesy of Dr. John Kalmar.

tendencies, corticosteroids, etc.) should be eliminated (Table 3). Although BON may remain asymptomatic for months, it can be associated with localized pain in the affected area.[27] Reported cases are more often identified only in the mandible (65 percent), while bone exposure in the maxilla only (26 percent) or the maxilla and mandible (9 percent) is less common.[22] In the mandible, most lesions were found on the posterior lingual side near the mylohyoid ridge.[22] A female sex predilection (3:2) has been reported.[22] However, this may be a consequence of the number of women currently using this drug.

It has been estimated that over thirty million prescriptions of bisphosphonates are prescribed annually in the United States, yet the incidence of, and who is at risk for, BON is not well understood. There are several putative factors that may place the patient at risk for BON (Table 4). These factors include pharmacokinetic and pharmacodynamic factors associated with bisphosphonates, comorbid medical conditions (e.g., diabetes, coagulopathy, blood dyscrasias, malignancy), dental factors (e.g., dentoalveolar surgery, trauma, periodontal disease, poor oral hygiene), age, environmental factors (e.g., alcohol and tobacco use), concomitant medications (e.g., glucocorticoids, estrogens), and skeletal factors (e.g., low bone mineral density).[3,4,22,28] Three of these risk factors pertinent to dental care are discussed in more detail below.

Pharmacokinetics and Pharmacodynamics of Bisphosphonates

Even though the incidence of BON is not known, there seems to be a difference in the prevalence depending on the mode and frequency of administration, drug potency, and the duration of treatment. Intravenous administration provides greater drug bioavailablilty for the bone, and combined with the recommended oncologic doses (up to twelve times greater than for non-oncologic purposes), the prevalence of BON has been estimated to range between 1 percent and 10 percent.[22,28] Drug potency also appears to have an effect (Figure 3). For example, the average time for onset of BON in patients receiving zoledronic acid (relative potency is 10,000 times etidronate) for oncologic motives was eighteen months, whereas the onset in patients taking pamidronate (relative potency is 100 times etidronate) was thirty-nine to seventy-two months.[29,30] Furthermore, the cumulative hazard for zoledronic acid was 1 percent in the first year and 21 percent at three years, whereas pamidronate had a cumulative hazard of 0 percent in the first year and 4 percent at three years.[31] Moreover, it appears that the cumulative dose and potency of bisphosphonates may substantially increase the incidence of BON.[32]

The incidence of BON in patients taking enteral forms of these agents has also been difficult to ascertain, and the collected data are somewhat confusing. One estimate provided by a global pharmaceutical company (Merck & Co.) reported the spontaneous incidence of BON to be approximately 0.7 cases per

Table 3. Conditions that may present with exposed maxillary or mandibular bone

Infections leading to osteomyelitis
Osteoradionecrosis
Neuralgia-inducing cavitational osteonecrosis (NICO)
Bone tumors or metastases
Trauma
Herpes zoster infection-associated osteonecrosis
Benign sequestration of the lingual plate
Necrotizing ulcerative periodontitis
Excessive absorption of heavy metals

Table 4. Putative risk factors for BON

Drug/Disease/Demographic Factors	Dental Factors
Route of administration (intravenous)	Intraoral trauma
Potency of bisphosphonate	Dentoalveolar surgery
Duration of treatment	Periodontal diseases
Co-morbid conditions (i.e., malignancy)	Poor oral hygiene
Age	Poorly fitting dentures
Cancer and anticancer therapy	Anatomical (mandibular lingual ridge, mylohyoid ridge, tori)
Tobacco and alcohol use	
Glucocorticoid and estrogen therapy	
Diabetes mellitus	

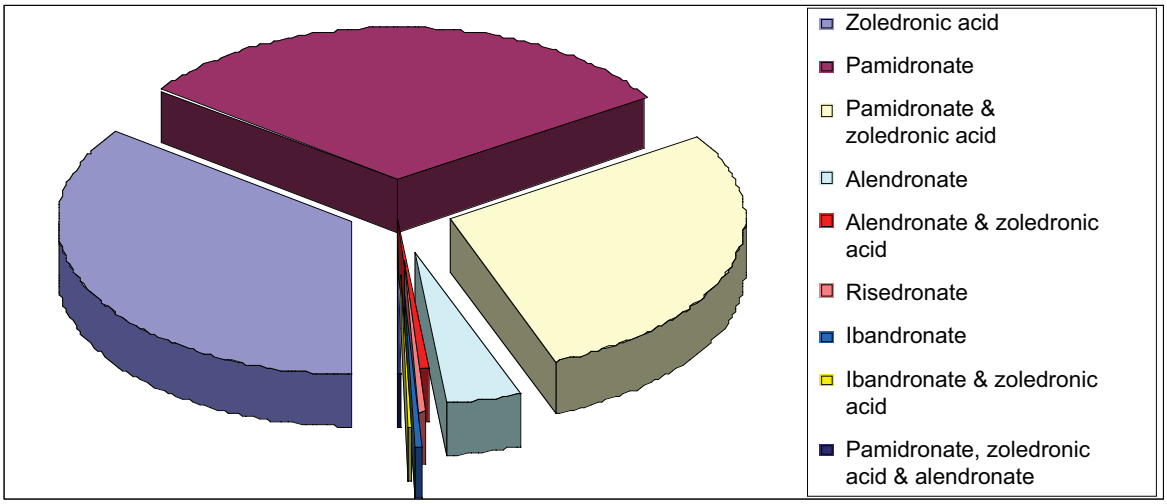

Figure 3. Frequency of BON in patients using various bisphosphonate formulations

Adapted from Woo S-B, Hellstein JW, Kalmar JR. Systematic review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med 2006;144(10):753–61.

100,000 person-years exposure,[3] while a clinical study in Germany also identified a relatively similar, low prevalence (less than one in 250,000 subjects).[28] In stark contrast to these reports are data from Australia that indicate the prevalence of BON is one case in from 2,260 to 8,470 persons.[33] These data are at least twenty-fold higher than what had been previously reported. At this point, the differences for these estimates of prevalence are difficult to explain, but reinforce our awareness that the prevalence of BON in patients who orally administer bisphosphonate is relatively low.

Comorbidity

Reports of BON cases have been identified at a higher frequency in patients with existing bone disease (Figure 4). Considering that BON occurred most frequently in patients taking intravenous bisphosphonate therapy for multiple myeloma (46.5 percent) and metastatic breast cancer (38.8 percent), there has been some consideration that these diseases many contribute to BON. Presently, it is not clear if osteoclast-mediated diseases exist independently of BON or whether an osteoclast-mediated disease causes or exacerbates BON. Furthermore, there are no data to make a coherent statement regarding any of the other suspected systemic diseases (diabetes mellitus, etc.) that have been proposed to affect BON. Finally, there is no information regarding how to consolidate any comorbid condition into a single predictive variable that measures BON.

Dental Factors

In approximately 60 percent of patients, the instigating factor for BON involved bone necrosis at a dentoalveolar surgical site, and most often this involved a dental extraction.[22] It seems logical to concur that if dental extractions can elicit BON, then other surgical procedures (periodontal surgery, periapical surgery, preparation of osteotomy site for dental implants, etc.) should produce a similar effect; however, this assumption may be incorrect. For example, a recent study evaluating implant placement in forty-three patients who had been orally taking alendronate or risedronate for at least three years did not observe the presence of BON immediately postoperatively or during the follow-up period.[34] In considering these clinical data, the route of administration and duration of treatment with bisphosphonates, as well as the type of clinical procedure, offer important clues

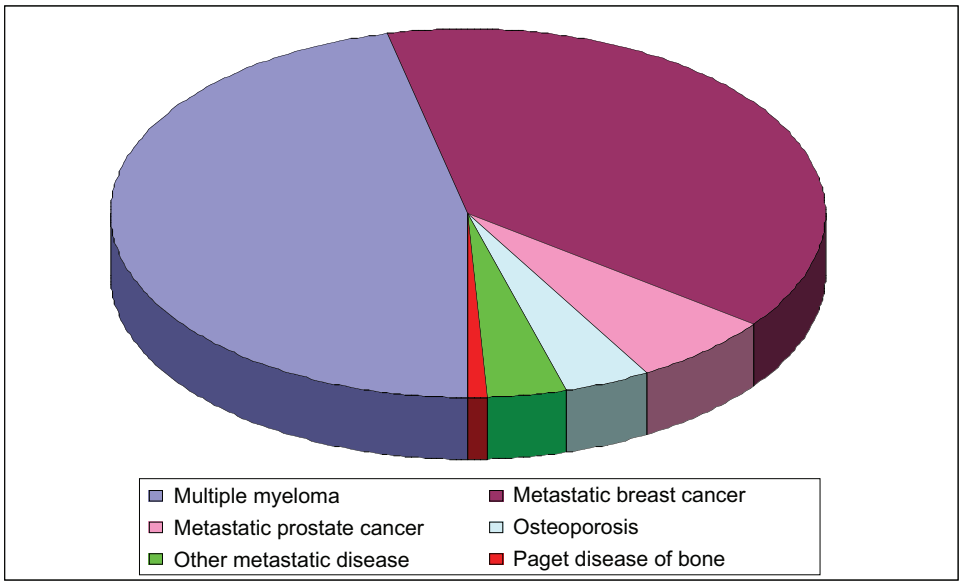

Figure 4. Frequency of BON in patients using various types of bisphosphonates to treat bone diseases

Adapted from Woo S-B, Hellstein JW, Kalmar JR. Systematic review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med 2006;144(10):753–61.

regarding patient management, but also point to the necessity for more information concerning the effects of periodontal, periapical, and implant surgery in patients using bisphosphonates.

In regard to dental infections, dental plaque and periodontal diseases have been vaguely defined as risk factors for jaw osteonecrosis in patients using bisphosphonates. A study at the University of Texas M.D. Anderson Cancer Center suggested that periodontal disease was a significant factor in patients with BON,[35] but the methods to ascertain periodontal disease were not described, appeared to be crudely measured, and therefore were subject to error. Another study claimed that "active" periodontitis was found in 84 percent of patients with BON. However, the authors failed to provide any data or information as to how the "active" periodontal disease was measured in this cohort.[36] At this time, the association between dental plaque or periodontal diseases with BON may be purely coincidental because of their ubiquitous nature in the oral cavity. In other words, the association between plaque or periodontal diseases with BON may not represent a causal relationship. Future clinical studies on the effects of dental plaque and periodontal disease need to be conducted to determine if they are important factors in the induction and/or exacerbation of BON.

How Can a Dentist Manage a Patient Using Bisphosphonates?

Currently, there is no way to predict which patients who are taking bisphosphonates are at greatest risk for BON, nor are there reliable diagnostic tests that can forecast jaw osteonecrosis. The task force of the American Society for Bone and Mineral Research reviewed various imaging methods for BON and has suggested that the most promising modality to detect patients with BON is to image bone and soft tissue in individuals using contrast agents combined with magnetic resonance imaging.[28] The future evaluation of this modality will need to prove if this is an effective approach, especially in identifying early cases of BON. There has also been a recom-

mendation to monitor the levels of bone resorption markers in serum, especially C-terminal telopeptide (CTX), to ascertain when an individual is at risk for BON.[37] Presently, the sensitivity and specificity of CTX for predicting BON have not been determined, and controlled, randomized clinical trials will be necessary to corroborate the efficacy of this test in detecting BON.

Protocols for the management of patients using bisphosphonates have been outlined by task forces from the American Dental Association,[3] the American Association of Oral and Maxillofacial Surgeons,[4] the American Society for Bone and Mineral Research,[28] and the American Academy of Oral Medicine.[27] Presently, the outcomes for treatment and long-term assessment of treatment and prevention programs from these task forces have not been determined. As a result, many of the suggestions for patient management have been dependent on anecdotal observations and expert opinion.

All patients who are going to begin treatment with bisphosphonates should receive a dental examination and be informed about the potential adverse oral effects of these drugs.[3,4,22,27] Patient management should be directed at reducing future needs of dentoalveolar surgery.[3,4,22,27] This means eliminating active sites of infection by periodontal, prosthodontic, and/or endodontic treatment or with appropriate dental extractions. It is also very important to establish meticulous preventive dental regimens for patients.[3,4,22,27] Each preventive dental regimen should be customized to patient needs. In general, these regimens should include patient education, oral hygiene home care routines to reduce dental caries and periodontal disease, elimination of habits that can increase dental disease (smoking, alcohol, etc.), and a schedule for routine visits to a dentist. Delaying initiation of bisphosphonate therapy until dental treatment is completed is probably not necessary since there appears to be a three-month window prior to when the first oral pathological outcomes of bisphosphonates were observed.[22]

Patients without BON but who are receiving bisphosphonate therapy should continue to receive dental examinations or receive an examination if they have not previously been seen by a dentist prior to the onset of treatment. Information about the potential for adverse oral outcomes needs to be provided, and meticulous preventive dental strategies must continue to be executed. Dental treatment that does not affect the orofacial bone can be executed at any time; however, appropriate nonsurgical and pharmacologic management of dental disease that affects the bone should be attempted prior to dentoalveolar surgery.[3] If dentoalveolar surgery is necessary, conservative surgical techniques with primary tissue closure should be a prime goal of the dentist.[3] Postoperative care should include the use of appropriate oral hygiene methods using FDA-approved antimicrobial toothpastes and rinses.[3]

Controversy exists regarding the need to discontinue bisphosphonate therapy (i.e., a drug holiday) for three months in patients with a putative risk factor or for those who have been on the drug for more than three years. The rationale for the drug holiday is that these patient groups are at higher risk for BON and that removal of the drug will potentially lower the chance of inducing BON, facilitate soft tissue healing, and therefore improve outcomes when dentoalveolar surgery is done.[22,37] Presently, there are no data to support or oppose improved dental outcomes with a drug holiday.[22,28] Considering the extended skeletal half-life of these drugs, it is optimistic to consider a significant recovery of bone turnover following such a short period of time without the drug.[22,28] In addition to anecdotal reports of improved outcome with a drug holiday, clinical studies are needed to ascertain if drug discontinuation is valuable and to determine the optimal length of a warranted drug withdrawal.

Patients with BON who are receiving bisphosphonate therapy have been categorized into three stages that progress from asymptomatic patients with exposed bone and no infection (stage one), to symptomatic patients with exposed bone, infection, and possible purulent drainage (stage two), to symptomatic patients with exposed bone, infection, fracture, extra-oral fistula, or osteolysis extending to the inferior border (stage three)[4] (Table 5). Unless patients are in stage 3, surgical debridement of BON has not been encouraged[4,38,39] because it is difficult to find viable bone margins given the broad effects of bisphosphonates in the jaw. When surgical intervention has been attempted, fistulae may develop around flap edges,[39] and enlargement of the necrotic area can occur.[27] Symptomatic relief can be obtained with antibiotic therapy and antimicrobial mouth rinses, but this effect appears to be transitory.[38] Removal of bony sequestrum that is mobile and does not impinge on unaffected bone and

Table 5. Staging of BON

Stage	Description
1	Exposed bone in patients who are asymptomatic combined with no observable infection.
2	Exposed bone with infection, pain, erythemia. Purulent exudates may be present.
3	Exposed bone with infection, pain, and at least one of the following: pathologic fracture, extra-oral fistula, osteolysis extending to the inferior border of mandible.

Source: American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. Approved by the Board of Trustees, September 25, 2006. J Oral Maxillofac Surg 2007;65(3):369–76.

extraction of symptomatic teeth that are in exposed, necrotic bone should be considered.[4] Although a drug holiday has been proposed for those patients who might have to undergo surgical revision of the necrotic site,[4] there is scant documentation to support drug withdrawal.[22,28]

What Messages Can Dentists Take Away from This?

Bisphosphonates are important drugs that reduce the morbidity and mortality in patients with diseases that affect bone. Oral bisphosphonates are the drugs of choice for osteoporosis, and intravenous bisphosphonates are commonly prescribed for osteoclast-mediated bone diseases as well as for metastatic bone cancers. Patients who are on intravenously administered bisphosphonates for oncologic reasons appear to have the greatest risk for BON (between 1 percent and 10 percent prevalence). The prevalence of orally administered bisphosphonates is dramatically lower (between 0.00007 percent and 0.04 percent). When BON does occur, it appears as an exposed area of jaw bone that has been present for at least eight weeks in patients taking a bisphosphonate. BON may appear spontaneously but is more frequently associated with local trauma to the jaw, especially following tooth extraction.

Currently, the spectrum of clinical signs and symptoms, etiology, preventive measures, and effect of the disruption of bisphosphonate therapy, as well as prognostic indicators for BON, remains to be defined. Further, the effective and efficient management of patients with BON has not been adequately characterized. Presently, the management of BON usually involves simple measures that include local antimicrobial rinses, antibiotic therapy, and improved oral home care. Even though surgical debridement and wound closure can exacerbate BON, surgical treatment may be necessary when pathologic features continue to expose the jaw to further destruction. In patients taking bisphosphonates who do not exhibit BON, prevention is the preferred method for patient management and involves the establishment of a customized oral home care program that emphasizes meticulous and routine oral hygiene practices. Furthermore, prior to bisphosphonate therapy, preventative treatment that involves periodontal, prosthetic, and endodontic therapy, combined with suitable dental extractions, should be instituted to reduce the amount of dentoalveolar surgery once bisphosphonate treatment is initiated. Finally, during bisphosphonate therapy, patient education, regular periodontal maintenance, and review of oral hygiene practices are important methods to reduce invasive dental treatment and the possible appearance of BON.

Bisphosphonates are the drugs of choice for many life-threatening diseases. For the patient who is taking a bisphosphonate, the benefits of this agent far exceed the risks. Therefore, patients must maintain their prescribed drug regimen. As more and more of these types of drugs are used in the future, it is imperative that high-quality clinical research be implemented to ascertain the risk of BON as well as proper dental management of the BON patient.

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