

**Dental Management of Patients Receiving Oral Bisphosphonate Therapy—Expert
Panel Recommendations**

Report of the Council on Scientific Affairs

American Dental Association

July, 2008

ACKNOWLEDGEMENTS

Expert Panel Members

Beatrice J. Edwards, MD, FACP

Department of Medicine and Orthopaedic Surgery.

Feinberg School of Medicine, Northwestern University

John W. Hellstein, DDS, MS

Department of Oral Pathology, Radiology/Medicine

University of Iowa

Peter L. Jacobsen, PhD, DDS

Department of Pathology and Medicine

Arthur A. Dugoni School of Dentistry

University of the Pacific

Steven Kaltman, DMD, MD

Department of Oral Surgery

Nova Southeastern University College of Dental Medicine

Angelo Mariotti, DDS, PhD

Department of Periodontology

Ohio State University College of Dentistry

Cesar A. Migliorati, DDS, MS, PhD

Department of Diagnostic Sciences – Oral Medicine Nova Southeastern University

College of Dental Medicine

Contributors

Dennis W. Raisch, PhD, RPh

Associate Center Director, Scientific Affairs

Veterans Affairs Cooperative Studies Program

Clinical Research Pharmacy Coordinating Center

Albuquerque, NM

Charles L. Bennett, MD, PhD

Professor, Division of Hematology/Oncology

Northwestern University

VA Chicago Healthcare Systems

VA Center for Management of Complex Chronic Care

Robert H. Lurie Comprehensive Cancer Center

Chicago, IL

1 *Introduction*

1.1 Nomenclature

Osteonecrosis is defined by Dorland's Medical Dictionary as necrosis of bone due to obstruction of its blood supply. Osteonecrosis of the jaw (ONJ) can result from radiation therapy of the head and neck, chronic corticosteroids therapy, herpes zoster virus infection in immunocompromised patients, uncontrolled infections and major trauma. The various etiologic agents resulting in ONJ determine case nomenclature, such as radiation osteonecrosis, steroids osteonecrosis and viral osteonecrosis. The term bisphosphonate-associated osteonecrosis (BON) originated in a paper published in the *Journal of the American Dental Association*.¹ Differences in the nomenclature used to identify osteonecrosis associated with a bisphosphonate include ONJ, bisphosphonate-related osteonecrosis of the jaw (BRONJ), bisphosphonate-induced osteonecrosis of the jaw (BIONJ), and bisphosphonate-associated osteonecrosis of the jaw (BONJ). To remove naming ambiguity and promote international uniformity, the expert panel proposes a standardized nomenclature for the diagnosis of bisphosphonate-associated osteonecrosis, or BON.

1.2 Background

Since 2003 reports of BON associated with the use of zoledronic acid (Zometa) and pamidronate (Aredia) have appeared in the literature.^{2,3} Zoledronic acid and pamidronate are intravenous bisphosphonates administered every three to four weeks to treat certain cancers (primarily multiple myeloma and metastatic bone, breast or prostate cancer) and Paget's disease of bone. Yearly and quarterly intravenous bisphosphonate infusions have recently been approved for the treatment of osteoporosis. More cases of bisphosphonate-

associated osteonecrosis of the jaw (BON) were diagnosed following an invasive dental procedure like tooth extraction. Also, but less noted, BON appears to spontaneously occur in patients taking these drugs.⁴

The risk for developing BON remains unknown despite attempts to quantify it. Study limitations such as retrospective design, inadequate study durations, and issues associated with voluntary reporting of cases have limited estimates of incidence in the general population. The studies that have attempted to estimate the risk for BON are summarized below.

An approximate frequency of 1 in 140,000 person-life years of exposure associated with the orally administered drugs was originally based on BON cases reported to pharmaceutical companies.^{5,6,7} Since 2006, Mavrokokki prospectively studied the occurrence of BON in Australia. Cases were identified by the presence of exposed bone in the mandible/maxilla for at least six weeks. This case series, which included verifying drug prescriptions, estimated the incidence associated with oral alendronate use to be from 1 in 8,470 to 2,260 cases (0.01 percent to 0.04 percent). The risk of developing BON increased more than four-fold when individuals underwent a dental extraction. The median time of alendronate use was two years prior to onset of BON.⁸

Novartis sponsored a randomized controlled trial that studied the effect of once yearly zoledronate administered intravenously for treatment of osteoporosis in 7,714 postmenopausal subjects. Study results demonstrated clinical efficacy in preventing vertebral and hip fractures. In the three-year study, no BON cases were reported. However, a retrospective search of the adverse events database identified two possible

cases of osteonecrosis of the jaw (defined as the presence of exposed bone for more than six weeks), one case in the treatment and one incidence in the placebo group.^{9,10}

Currently, there are insufficient data to determine the risk for BON associated with yearly zoledronate infusion for treating osteoporosis.

The few studies on the risk of developing BON suggest the risk is low. A German study reported three cases of BON among 780,000 patients who received oral bisphosphonate treatment for osteoporosis.¹¹ This study may be limited because the authors used case reports provided to the German Central Register of necrosis of the jaw to the Charité Hospital. Because physicians voluntarily provide these case reports, the number of BON cases may be underreported.

The authors of a Canadian study¹² used a risk ratio to describe the probability of aseptic osteonecrosis (AON) occurring in patients taking oral bisphosphonates as compared with patients not taking oral bisphosphonates. That study, which utilized the administrative health databases of 87,837 patients, reported a risk ratio of 2.87 (95 percent confidence interval 1.17-5.05) for AON in past or present users of alendronate, etidronate and risedronate. Another study, which analyzed the United States medical claims data of 714,217 patients,¹³ found an increased risk of inflammatory conditions and surgical procedures of the jaw for users of intravenous bisphosphonates related to cancer therapy, but not for users of oral bisphosphonates. Both these studies are limited by their use of medical claims information, which can pose methodological challenges for accurate data reporting. The Canadian study also may be limited because the authors lacked a specific International Statistical Classification of Diseases and Related Health Problems (ICD) code for BON. Instead, relegated to using the AON code, the authors

probably included other cases of osteonecrosis (e.g. avascular necrosis of the hip). In the U.S. study, it is possible that the less severe lesions associated with the oral form of the drug were managed by non-institutional dentists who tend not to report claims using ICD-9 and CPT codes; while the more severe lesions associated with intravenous bisphosphonates related to cancer therapy were managed at institutions that use ICD-9 and CPT codes.

Osteonecrosis of the jaw was not reported in large, randomized clinical trials and 7 to 10 year safety studies with risedronate and alendronate.¹⁴ However, it is not uncommon for rare adverse drug reactions to be uncovered during post marketing surveillance.

Table 1. Summary of published studies estimating BON in oral bisphosphonate users

| Study | Data collection | Findings | Estimates of BON in oral bisphosphonate users |
|---|--|--|--|
| Felsenberg D, Hoffmeister B, Amling M. Bisphosphonattherapie assoziierte Kiefernekrosen Deutsches Arzteblatt 2006;46:A3078-A3080. | Reports to the German Central Register of Necrosis of the Jaw to the Charité Hospital | 3 reports of BON out of 780,000 patients taking oral bisphosphonates | 1 out of 263,158 (0.00038%) |
| Mavrokokki T, Cheng A, Stein B, Goss A. Nature and Frequency of Bisphosphonate-Associated Osteonecrosis of the Jaws in Australia. J Oral Maxillofac Surg 2007;65:415-23. | Survey sent to all members of the Australian and New Zealand Association of Oral and Maxillofacial Surgeons Case definition – area of exposed bone in the jaw area that fails to heal in 6 weeks in patients on a bisphosphonate for bone disease Total number of prescriptions was obtained from Medicare Australia | 1 case of BON in every 8,470 to 2,260 patients on oral alendronate If extractions were carried out the frequency increased to 1 in 1,130 to 296 | No tooth extraction 1 out of 8,470 to 2,260 (0.01% to 0.04%) Tooth extraction 1 out of 1,130 to 296 (0.09% to 0.34%) |
| Black DM et al. HORIZON Pivotal Fracture Trial. Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis. N Engl J Med 2007;356(18):1809-22. | Randomized controlled trial with once yearly infusion of zoledronate for osteoporosis therapy | No spontaneous reports of BON during the study | 0 |
| Grbic JT et al. Incidence of Osteonecrosis of the Jaw in Women with Postmenopausal Osteoporosis in the Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly Pivotal Fracture Trial. J Am Dent Assoc 2008;139:32-40. | Three year follow-up of 7,714 women who received either 5 mg intravenous zoledronate or placebo in HORIZON Pivotal Fracture Trial | A retrospective review of the database identified 2 possible cases of BON. One in the zoledronate group and one in the control group | 0 |
| Etminan M, Aminzadeh K, Matthew IR, Brophy JM. Use of Oral Bisphosphonates and the Risk of Aseptic Osteonecrosis: A Nested Case-Control Study. J Rheumatol 2008;35:1-5. | Administrative health database of 87,837 patients Includes all cases of aseptic osteonecrosis | 267 cases per million person-years exposure Risk ratio equals 2.87 (95% confidence interval 1.17 – 5.05) | 1 out of 3,745 |
| Cartsos VM, Zhu S, Zavras AI. Bisphosphonate Use and the Risk of Adverse Jaw Outcomes. J Am Dent Assoc 2008;139:23-40. | U.S. medical claims data of 714,217 patients | Increased risk of inflammatory conditions and surgical procedures of the jaw for users of intravenous bisphosphonates, but no increased risk for users of oral bisphosphonates | 0 |

Though it is early in the investigative stage, the relationship between bisphosphonate exposure and the occurrence of osteonecrosis of the jaw appears to be consistent with Bradford Hill's criteria for causality:¹⁵ *strength of association*, i.e., individuals on bisphosphonate therapy appear to present a higher incidence of BON than nonusers; *temporal association*, i.e., bisphosphonate exposure precedes the occurrence of BON; a *biological gradient*, with higher doses of bisphosphonates resulting in more rapid and serious presentations of BON;^{16,17,18} *consistency*, i.e., the effect (BON) has been observed by several investigators;^{19,20,21,22,23,24} *specificity*, ie, BON is seen in cancer and bone and mineral metabolism disease (osteoporosis and Paget's disease of the bone); and *biologic plausibility*, i.e., the event is defined by the mechanism of action of the drug.

Although bisphosphonates offer benefit in the short-term treatment (fewer than six months) of periodontal disease and avascular necrosis of the hip,^{25,26,27,28} the median time to onset of BON in patients taking alendronate reportedly is more than two years. Also, two of the studies reporting a benefit examined the effect of bisphosphonates administered locally. Recent animal studies (rodent models) provided preliminary results that alendronate and zoledronate use produced impaired angiogenesis and delayed bone formation, resulting in reduced healing after dental extraction.^{29,30} Prolonged bisphosphonate use in humans (more than three years) may cause development of poorly functional, highly multinucleated osteoclasts with nuclear condensation and poor adhesion to bone surface.³¹ A recent study in dogs found that three years of daily oral bisphosphonate treatment significantly reduced bone turnover and increased the incidence of matrix necrosis in the mandible.³²

Table 2. Oral and Intravenous Bisphosphonates

| Brand Name | Manufacturer | Generic Name |
|--|---------------------------------------|--|
| Oral Formulations | | |
| Actonel | Procter & Gamble Pharmaceuticals | risedronate |
| Bonefos | Micromedex | clodronate (not commercially available in the U.S.) |
| Boniva | Roche/GlaxoSmithKline Pharmaceuticals | ibandronate |
| Didronel | Procter & Gamble Pharmaceuticals | etidronate |
| Fosamax | Merck & Co. | alendronate |
| Fosamax Plus D | Merck & Co. | alendronate |
| Skelid | Sanofi-aventis | tiludronate |
| Intravenous Formulations | | |
| Aredia (cancer therapy) | Novartis | pamidronate |
| Bonefos (cancer therapy) | Schering AG | clodronate |
| Boniva IV (quarterly infusion for osteoporosis) | Roche/GlaxoSmithKline | ibandronate |
| Reclast (yearly infusion for osteoporosis) | Novartis | zoledronic acid |
| Zometa (cancer therapy) | Novartis | zoledronic acid |

Possible risk factors and comorbidities reported in the literature are: corticosteroid use,^{33,34} diabetes mellitus,³⁵ clinically and radiographically apparent periodontitis, tooth extractions³⁶ and smoking.³⁷ Alendronate users who develop BON may present as soon as 22 months after the initiation of therapy, although most cases have occurred after prolonged therapy (more than five years). Because the incidence of BON and its concomitant risk factors are relatively unknown, dentists are understandably concerned

about how to appropriately manage patients receiving oral bisphosphonate therapy. This expert panel was convened to develop clinical recommendations for dentists treating this patient population.

1.3 Incorporating expert panel recommendations into clinical decision making

These recommendations are intended as a resource for dentists, to complement their own professional judgment, data obtained from the dental and medical literature, and information from the patient's treating physician. The recommendations should be balanced with the practitioner's professional judgment and the individual patient's preferences and needs.

1.4 Expert panel

Panelists were selected by the American Dental Association Council on Scientific Affairs based on their expertise in the relevant subject matter and on their respective dental or medical specialties. All panelists were required to sign a disclosure stating that neither the panelist nor his or her spouse or dependent children had a significant financial interest that would reasonably appear to affect the development of these recommendations.

1.5 Rationale for developing expert panel recommendations for the dental management of patients on oral bisphosphonate therapy

In 2005 Novartis and the FDA issued drug precautions regarding ONJ, a condition observed in cancer patients receiving intravenous bisphosphonate treatment.³⁸ The precautions also raised concerns about patients who receive invasive dental treatment while taking oral bisphosphonates for osteopenia, osteoporosis and Paget's disease of bone.

It is important to reiterate that, based on the current literature and on the cases reported so far, a patient's risk for developing BON is minute with oral bisphosphonate therapy as compared to intravenous bisphosphonate therapy in cancer patients. Accordingly, the majority of reported BON cases have occurred in patients taking the drugs intravenously for cancer therapy. At present there are no studies that adequately address the incidence of BON. Studies have estimated that BON occurs in about 20 percent of patients receiving bisphosphonates intravenously for cancer therapy (after extended use of zoledronate) and from zero to 0.34 percent of patients orally taking the drug.^{8,Error! Bookmark not defined.,36} Although total U.S. prescriptions for oral bisphosphonates in 2006 exceeded 30 million,³⁹ fewer than 10 percent of BON cases are associated with patients taking orally administered bisphosphonate drugs.^{4,8} In BON cases associated with oral formulation of the drugs, there were not only fewer cases reported, but in those cases documented in a single, small study, the clinical features appeared to be less severe and all resolved with treatment.

The pathophysiological link between bisphosphonates and the development of BON remains unknown. It has been suggested that the effect may be partially mediated by an inhibition in angiogenesis and bone formation after dental extraction. More confirmatory studies are needed to support that hypothesis. It is worth noting that in some situations the clinical signs and symptoms presenting as dental pathology could indicate that the process of osteonecrosis is already active. As such, extractions may be the end result, but not necessarily a discrete causative factor in this scenario. There also is speculation that bone-accumulated bisphosphonates are directly toxic to overlying tissue.⁴⁰ Intravenous doses used to treat cancer, which can be 10 times higher than doses

used to treat osteoporosis, are associated with a higher incidence of BON. These higher doses also are associated with more severe cases, perhaps resulting from both higher doses of the drug and increased bioavailability through intravenous dosing. Less than one percent of the dose of an oral bisphosphonate is absorbed by the gastrointestinal tract, whereas more than 50 percent of the dose of an intravenous bisphosphonate is bioavailable for incorporation into the bone matrix.^{41,42}

Based on the information available, the risk for developing BON is much higher for cancer patients on intravenous bisphosphonate therapy than for patients on oral bisphosphonate therapy. Therefore, clinical recommendations are specific to the type of bisphosphonate therapy administered. Recommendations for cancer patients on intravenous therapy were developed by an expert panel in 2004.⁴³ Since then, the American Academy of Oral Medicine has published a position paper on managing the care of patients with BON. The American Academy of Oral and Maxillofacial Pathology, the American Association of Oral and Maxillofacial Surgeons and the American Society for Bone and Mineral Research also have published papers on BON.^{44,45,46} *Readers should refer to these documents to obtain recommendations for the management of cancer patients on intravenous bisphosphonate therapy and patients with BON.* The American Society of Bone and Mineral Research,⁴⁷ the National Osteoporosis Foundation,⁴⁸ the American Association of Endodontists⁴⁹ and the American College of Rheumatology⁵⁰ also have addressed these issues.

1.6 Osteoporosis and bisphosphonate therapy

Osteoporosis is a major cause of morbidity, functional dependence and institutionalization in older Americans. In 2004, the U.S. Surgeon General's Report on Bone Health and Osteoporosis highlighted the public health imperative to address osteoporosis and prevent its health-related consequences. One out of every two women will sustain an osteoporosis-related fracture (such as wrist, spine or hip) in her lifetime.

More than 10 million Americans over age 50 have osteoporosis, while another 34 million are at risk for the disease. By 2020, it is estimated that more than 60 million Americans will suffer from low bone mass or osteoporosis.⁵¹ Because the loss of bone density weakens the bone, the risk of fracture in patients with osteoporosis rises significantly. Each year, the bone disease accounts for 1.5 million new fractures. Of these fractures, 250,000 are hip fractures resulting in mortality rates exceeding 20 percent in women and 30 percent in men, recurrent hospitalizations, increased office visits and often the need for care at extended treatment facilities. In individuals who have hip fractures, less than 25 percent of them regain full function.^{52,53} Vertebral fractures, which are more prevalent than hip fractures, cause back pain, restrictive lung disease and pneumonia-related mortality.

The cost of osteoporosis is \$17 billion annually in the United States. As the population ages, the number of hip fractures and associated expenditures in the United States both could triple by 2020. It is estimated that oral bisphosphonates will prevent 50 percent of all vertebral (250,000) and 35 to 50 percent of non-vertebral fractures (i.e. 350,000 to 500,000 hip and extremity fractures) each year.

Given the risks associated with osteoporosis and the proven benefits of oral bisphosphonate therapy, the physician and patient should fully discuss any decision to alter the use of these medications.

1.7 Clinical presentation of BON

AAOMS uses the following case definition to describe bisphosphonate-related osteonecrosis of the jaw: exposed, necrotic bone in the maxillofacial region persisting for more than eight weeks in a patient who is taking, or has taken, a bisphosphonate and has not had radiation therapy to the head and neck.⁴⁶

The clinical presentation of BON typically includes variable reports of pain, lack of pain, soft-tissue swelling and infection, loosening of teeth, drainage, and exposed bone. Symptoms spontaneously may occur in the bone; or, more commonly, at the site of a tooth extraction. In some cases, osteonecrosis may be present but not clinically visible. The asymptomatic patient with BON unknowingly can have the disease for weeks, even months, until examination reveals exposed bone in the patient's jaw. The symptoms of BON can mimic dental or periodontal disease, as well. A patient may seek care because of oral pain. Infection may not be present. The symptoms of BON do not resolve with routine dental and periodontal treatment. In such a case, if the patient is known to be receiving bisphosphonate therapy, BON must be considered as a differential diagnosis, even in the absence of exposed bone.

If a practitioner suspects a patient to have BON, they should contact the FDA's MedWatch program at www.fda.gov/MedWatch/report.htm or 800-FDA-1088.

2 Panel conclusions

Based on a review of the available scientific literature and expert opinion, the panel reached these conclusions:

A patient's risk of developing BON while on oral bisphosphonate appears to be low. At present there are no studies that adequately address the incidence. The few studies to date use a wide range of methods, all with potential shortcomings, and come to varied estimates. Without good information on the incidence of BON it is difficult to predict a patient's risk, estimates range from zero to 1 one in 2,260 cases of BON for oral bisphosphonate users (Table 1).

BON can occur spontaneously, but is more commonly associated with specific medical and dental conditions, including dental procedures or conditions that increase the risk for bone trauma. Most commonly, BON is associated with invasive bone procedures like dental extractions.^{3,4} Older age (over 65 years), periodontitis, corticosteroid use for chronic conditions, prolonged use of bisphosphonates (more than two years), smoking and diabetes have been associated with an increased risk for BON.^{8,23,35,37} One recent study (that controlled for the effects of several known or potential confounders) found that smoking and obesity were risk factors for developing BON in cancer patients receiving intravenous zoledronic acid.⁵⁴

3 Panel recommendations for the dental management of patients receiving oral bisphosphonate therapy

These recommendations focus on conservative surgical procedures, proper sterile technique, appropriate use of oral disinfectants and the principles of effective antibiotic

therapy. Because of a paucity of clinical data on the dental management of patients on oral bisphosphonate therapy, these recommendations primarily are based on expert opinion.

These recommendations are intended to help dentists make clinical decisions. These recommendations should be considered with the practitioner's professional judgment and the patient's preferences. Dentists are encouraged to visit www.ada.org/prof/resources/topics/osteonecrosis.asp before treating patients taking oral bisphosphonates. As new information becomes available, these recommendations will be updated, as appropriate.

3.1 General recommendations

Routine dental treatment generally should not be modified solely due to use of oral bisphosphonates.

All patients should receive routine dental examinations. Patients who are prescribed oral bisphosphonates and are not receiving regular dental care would likely benefit from a comprehensive oral examination before or early during their bisphosphonate therapeutic regime.

All patients taking the drug should be informed that:

- Oral bisphosphonate use places them at very low risk for developing BON. The actual incidence is unknown with estimates ranging from zero to 1 one in 2,260 cases for oral bisphosphonate users (Table 1).
- The low risk for developing BON may be minimized but not eliminated.

- An oral health program consisting of sound oral hygiene practices and regular dental care may be the optimal approach for lowering the risk for developing BON.
- There is no validated diagnostic technique currently available to determine if patients are at increased risk for developing BON.
- Discontinuing bisphosphonate therapy may not eliminate any risk for developing BON.

The patient also should be informed of the dental treatment needed, alternative treatments, how any treatment relates to the risk of BON, other risks associated with various treatment options, and the risk of foregoing treatment, even temporarily. The patient should be encouraged to consult with his/her physician about health risks associated with discontinuation of bisphosphonate treatment. All decisions with respect to utilization of drugs prescribed for medical conditions should be discussed with the prescribing physician.

BON can occur spontaneously, due to dental disease or secondary to dental therapy. Therefore, patients taking oral bisphosphonates should be instructed to contact their dentist if any problem develops in the oral cavity.

A major goal in the prevention of BON is to limit the possibility of extensive or multifocal involvement. Although there is no evidence to support a conservative clinical approach, it may be prudent to proceed conservatively in some cases. This may allow the practitioner to gain some insight into how a patient will heal in a relatively small region before putting multiple quadrants at risk. Common scenarios include, but are not limited to, a patient needing “full mouth” extractions for dentures or a patient needing full mouth

periodontal surgery. It may be beneficial to assess the patient's capacity for bone healing, using a conservative and individualized approach. For example, initially single tooth extraction or one sextant of alveolar surgery could be accomplished while treating the patient with chlorhexidine. Patient healing response may be assumed to be adequate once normal healing of the surgical site(s) is observed. Chlorhexidine may be used longer if the area remains inflamed, irritated or erythematous. After establishing the patient's apparent adequate healing response a more accelerated surgical treatment plan involving multiple sextants at a single appointment could be considered.

Periapical pathoses, sinus tracts, purulent periodontal pockets, severe periodontitis and active abscesses that already involve the medullary bone all may exacerbate osteonecrosis. These areas should be treated immediately. When dental pathoses are not evident, the trial sextant approach may be applicable. The sextant by sextant approach does not apply to emergency cases, even if multiple quadrants are involved.

Patients should have all their questions answered to the extent possible. The dentist should consider documenting the discussion of risks, benefits and treatment options with the patient (see discussion above) and obtaining the patient's written acknowledgment of that discussion and consent for the chosen course of treatment. The dentist should retain in his/her file the acknowledgment and [consent for the treatment](#).

3.2 Management of periodontal diseases

Bisphosphonate users who have active periodontal diseases should receive appropriate forms of non-surgical therapy, which should be combined with the commonly recommended reevaluation at four to six weeks. If the disease fails to resolve, the goal of

surgical treatment should be to obtain access to root surfaces. When necessary, modest bone recontouring techniques should be used. At this time, there is no evidence that periodontal procedures such as guided tissue regeneration or bone replacement grafts increase or decrease the risk for BON or success of implant treatment. Use of such techniques should be judiciously considered based on patient need. Primary soft tissue closure following periodontal surgical procedures is desirable, when feasible.

Patients without periodontal disease should receive preventive therapy for periodontal disease. Patients should be regularly monitored.

3.3 Implant placement and maintenance

There is a paucity of data on the effects of implant placement in patients taking oral bisphosphonates.^{55,56} One study found no adverse effects associated with implant placement and bisphosphonates. In a subsequent review of this study⁵⁷ limitations were noted regarding the total number of subjects enrolled and duration of the study.

Because implant placement requires the preparation of the osteotomy site, treatment plans should be carefully considered. The patient may be at increased risk for BON when extensive implant placement or guided bone regeneration is necessary to augment the deficient alveolar ridge prior to implant placement. Before implant placement, the dentist and the patient should discuss the risks, benefits and treatment alternatives, which may include, but are not limited to, periodontal, endodontic or non-implant prosthetic treatments. As stated above, this discussion should be documented and the patient's written acknowledgement of that discussion and consent for the elected course of treatment should be obtained.

Maintenance of implants should follow accepted mechanical and pharmaceutical methods to prevent peri-implantitis, with regular monitoring of the patient. Appropriate forms of non-surgical therapy combined with a prolonged phase of initial therapy should be considered for patients with peri-implantitis. If the disease does not resolve, surgical revision of soft tissues around the implant(s) may be appropriate; when necessary, modest bone recontouring also may be considered.

3.4 Oral and maxillofacial surgery

When treatment of dental and/or periodontal diseases has failed, surgical intervention may be the best alternative. Patients receiving oral bisphosphonates who are undergoing invasive surgical procedures should be informed of the risk, although small, of developing BON. Alternative treatment plans should be discussed with the patient, which include: endodontics (including endodontic treatment followed by removal of the clinical crown), allowing the roots to exfoliate (instead of extraction), bridges and partial dentures (instead of implant placement). (See sections 3.2 and 3.3 regarding discussion and documentation of risks, benefits and alternative treatments.)

If extractions or bone surgery are necessary, conservative surgical technique with primary tissue closure, when feasible, should be considered. In addition, immediately before and after any surgical procedures involving bone, the patient should gently rinse with a chlorhexidine containing rinse until healed. The regimen may be extended based on the patient's healing progress. Prophylactic antibiotics after a surgical procedure should be based on the risk of an infection and NOT because the patient is taking a bisphosphonate. There is no evidence that the use of antibiotics is effective in preventing BON.

3.5 Endodontics

Endodontic treatment is preferable to surgical manipulation if a tooth is salvageable. Routine endodontic technique should be used. Manipulation beyond the apex is not recommended. In some situations, depending on risk, endodontic treatment of nonrestored teeth after removal of the clinical crown, which allows passive exfoliation of the root tip, may be considered. Endodontic surgical procedures should be guided by the same recommendation as is used for any oral and maxillofacial surgical procedure described above.

3.6 Restorative dentistry and prosthodontics

There is no evidence that malocclusion or masticatory forces increase the risk for BON. All routine restorative procedures may be conducted. Prosthodontic appliances in patients should be promptly adjusted for fit in order to avoid ulceration and possible bone exposure.

3.7 Orthodontics

There are no published studies examining the effect of bisphosphonates on orthodontia. Case reports have recounted inhibited tooth movement in patients taking bisphosphonates.^{58,59} Patients should be advised of this potential complication.

3.8 CTX testing and drug holidays

Recently, the use of serum levels of the collagen breakdown product, C-terminal cross-linking telopeptide of type I collagen (CTX), has been advocated as a risk predictor for developing BON. Serum CTX and urinary N telopeptide of type I collagen (NTX) are considered markers for bone resorption. Higher levels of these markers are associated with active bone turnover. Reports suggest that dental treatment decisions should be

based on the results of serum CTX/NTX levels.^{60,61} These recommendations are derived from clinical observations at one institution that have not been validated. It remains to be seen if these recommendations will be corroborated by well-controlled, randomized clinical trials. Therefore, while this expert panel recognizes the value of predicting and mitigating the risk for developing BON in individual patients, until objective research studies document and correlate specificity, predictive value and reliability of such tests, no recommendations can be made.

4 Recommendation for research

Based on the current literature on BON pathophysiology and based on the lack of knowledge of the factors that place patients at risk for developing BON, the panel recommends that research be conducted on the following topics:

4.1 Basic research

- Basic research should aim to discover the molecular mechanisms that lead to the formation of BON, and the role of bisphosphonates in the alteration of bone remodeling and its effect on BON. Research on the pharmacogenetics that place patients at risk for BON may be helpful for the detection of patients at increased risk.

4.2 Clinical research

- The effect of routine dental therapy in patients taking oral bisphosphonates.
- The effect of placing dental implants in patients taking oral bisphosphonates.
- The effect of orthodontic treatment in patients taking oral bisphosphonates.
- The effect of tooth extraction in patients taking oral bisphosphonates.

- Risk factors for BON.
- Studies relevant to managing patients with BON.
- Development of a national registry to allow systematic study of cases of BON and the effect of co-morbidities and concurrent therapies.
- Collaboration with bone specialists in order to establish whether BON is a localized or systemic condition. Bone biopsy and histomorphometric assessment will provide insights into the underlying bone pathology.
- Assessment of the effect of discontinuation of bisphosphonate therapy and its relevance to healing.
- Assessment of surrogate bone markers relative to the risk for and treatment of BON.
- Screening and diagnostic tests.

5 *References*

-
- ¹ [Migliorati CA, Casiglia J, Epstein J, Jacobsen PL, Siegel MA, Woo S-K](#). Managing the care of patients with bisphosphonate-associated osteonecrosis. *JADA* 2005;136:1658-68.
- ² [Marx RE](#). Pamidronate (Aredia) and zoledronic acid (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 2003;61:1115-7.
- ³ [Migliorati CA](#). Bisphosphonates and oral cavity avascular bone necrosis. *J Clin Oncol* 2003;21:4253-4.
- ⁴ [Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL](#). Osteonecrosis of the jaws associated with the use of bisphosphonates: A review of 63 cases. *J Oral Maxillofac Surg* 2004;62:527-34.
- ⁵ Procter and Gamble Pharmaceuticals. Incidence rates of osteonecrosis of the jaw with risedronate. In: Edwards BJ, ed. Chicago; 2006.
- ⁶ Roche Pharmaceuticals. Incidence of osteonecrosis of the jaw with Ibandronate. In: Edwards BJ, ed. Chicago; 2006
- ⁷ Merck Pharmaceuticals. Incidence rates of osteonecrosis of the jaw with alendronate. In: Edwards BJ, ed. Chicago; 2006.

-
- ⁸ [Mavrokokki T, Cheng A, Stein B, Goss A](#). Nature and Frequency of Bisphosphonate-Associated Osteonecrosis of the Jaws in Australia. *J Oral Maxillofac Surg* 2007;65:415-23.
- ⁹ [Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu H, Caminis J, Tong K, Rosario-Jansen T, Krasnow J, Hue TF, Sellmeyer D, Eriksen EF, Cummings SR](#); HORIZON Pivotal Fracture Trial. Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis. *N Engl J Med* 2007;356(18):1809-22.
- ¹⁰ [Grbic JT, Landesberg R, Lin S-Q, Mesenbrink P, Reid IR, Leung P-C, Casas N, Recknor CP, Hua Y, Delmas PD, Eriksen EF](#). Incidence of osteonecrosis of the jaw in women with postmenopausal osteoporosis in the Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly Pivotal Fracture Trial. *J Am Dent Assoc* 2008;139:32-40.
- ¹¹ Felsenberg D, Hoffmeister B, Amling M. Bisphosphonattherapie assoziierte. Kiefernekrosen *Deutsches Arzteblatt* 2006;46:A3078-A3080.
- ¹² [Etminan M, Aminzadeh K, Matthew IR, Brophy JM](#). Use of Oral Bisphosphonates and the Risk of Aseptic Osteonecrosis: A Nested Case-Control Study. *J Rheumatol* 2008;35:1-5.
- ¹³ [Cartsos VM, Zhu S, Zavras AI](#). Bisphosphonate use and the risk of adverse jaw outcomes *J Am Dent Assoc* 2008;139:23-40.
- ¹⁴ [Bilezikian JP](#). Osteonecrosis of the Jaw – Do Bisphosphonate Pose a Risk? *N Engl J Med* 2006;355(22): 2278-81.
- ¹⁵ Bradford Hill A. The Environment and Disease: Association or Causation? *Proc Royal Soc Medicine* 1965;58:295-300.
- ¹⁶ [Dimopoulos MA, Kastritis E, Anagnostopoulos A, Melakopoulos I, Gika D, Moulopoulos LA, Bamia C, Terpos E, Tsioukas K, Bamias A](#). Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: evidence of increased risk after treatment with zoledronic acid. *Hematologica*. 2006;91:968-971.
- ¹⁷ [Bamias A, Kastritis E, Bamia C, Moulopoulos LA, Melakopoulos I, Bozas G, Koutsoukou V, Gika D, Anagnostopoulos A, Papadimitriou C, Terpos E, Dimopoulos MA](#). Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. *J Clin Oncol*. 2005;23:8580-8587.
- ¹⁸ [Badros A, Weikel D, Salama A, Goloubeva O, Schneider A, Rapoport A, Fenton R, Gahres N, Sausville E, Ord R, Meiller T](#). Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors. *J Clin Oncol*. 2006;20:945-952.
- ¹⁹ [Bagan JV, Jimenez Y, Murillo J, Hernandez S, Poveda R, Sanchis JM, Diaz JM, Scully C](#). Jaw osteonecrosis associated with bisphosphonates: Multiple exposed areas and its relationship to teeth extractions. Study of 20 cases. *Oral Oncol* 2006;42:327-9.
- ²⁰ [Wang J, Goodger NM, Pogrel MA](#). Osteonecrosis of the jaws associated with cancer chemotherapy. *J Oral Maxillofac Surg*. 2003;61:1104-1107.
- ²¹ [Migliorati CA](#). Bisphosphonates and oral cavity avascular bone necrosis. *J Clin Oncol*. 2003;21:4253-4254.

-
- ²² [Ruggiero SL, Bhoomi M, Rosenberg TJ, Engroff SL](#). Osteonecrosis of the Jaws Associated With the Use of Bisphosphonates: A Review of 63 Cases. *J Oral Maxillofac Surg*. 2004;62:527-534.
- ²³ [Marx RE, Sawatari Y, Fortin M, Broumand V](#). Bisphosphonate-Induced Exposed Bone (Osteonecrosis/Osteopetrosis) of the Jaws: Risk Factors, Recognition, Prevention, and Treatment. *J Oral Maxillofac Surg*. 2005;63:1567-1575.
- ²⁴ [Bagan JV, Murillo J, Jimenez Y, Poveda R, Milian MA, Sanchis JM, Silvestre FJ, Scully C](#). Avascular jaw osteonecrosis in association with cancer chemotherapy: series of 10 cases. *J Oral Pathol Med*. 2005;34:120-3.
- ²⁵ [Adachi H, Igarashi K, Mitani H, Shinoda H](#). Effects of topical administration of a bisphosphonate (risedronate) on orthodontic tooth movements in rats. *J Dent Res*. 1994;73:148-184.
- ²⁶ [Liu L, Igarashi K, Haruyama N, Seeki S, Shinoda H, Mitani H](#). Effects of local administration of clodronate on orthodontic tooth movement and root resorption in rats. *Eur J Orthod*. 2004;26:469-473.
- ²⁷ [Reddy MS, Weatherford TW, Smith CA 3rd, West BD, Jeffcoat MK, Jacks TM](#). Aledronate treatment of naturally occurring periodontitis in beagle dogs. *J Periodontol*. 1995;66:211-217.
- ²⁸ [Little DG, McDonald M, Sharpe IT, Williams P, McEvoy T](#). Zoledronic acid improves femoral head sphericity in a rat model of perthes disease. *J Orthop Res*. 2005;23:862-868.
- ²⁹ Aguirre JI, Vanegas SM, Altman MK, Franz SE, Leal ME, Wronski TJ. Alendronate impairs angiogenesis and bone formation during early stage stage of bone healing in animal model for osteonecrosis of the jaw. American Society of Bone and Mineral Research. Honolulu; 2007.
- ³⁰ Kobayashi Y, Hiraga T, Ueda A, Nishimura R, Yatani H, Yoneda T. Zoledronic acid delayed the wound healing of tooth extraction socket but failed to cause osteonecrosis of the jaw in mice. American Society of Bone and Mineral Research. Honolulu; 2007.
- ³¹ Weinstein RS, Chambers TM, Hogan EA, Webb WW, Wicker CA, Manolagos SC. Giant osteoclast formation after long term oral aminobisphosphonate therapy for postmenopausal osteoporosis. American Society of Bone and Mineral Research. Honolulu, Hawaii; 2007.
- ³² [Allen MR, Burr DB](#). Mandible matrix necrosis in beagle dogs after 3 years of daily oral bisphosphonate treatment. *J Oral Maxillofac Surg* 2008;66:987-94.
- ³³ [Marx RE, Sawatari Y, Fortin M, Broumand V](#). Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. *J Oral Maxillofac Surg* 2005;63:1567-75.
- ³⁴ [Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY](#). Severely suppressed bone turnover: a potential complication of alendronate therapy. *J Clin Endocrinol Metabolism* 2005;90:1294-301.
- ³⁵ [Khamaisi M, Regev E, Yarom N, Avni B, Leitersdorf E, Raz I, Elad S](#). Possible association between diabetes and bisphosphonate-related jaw osteonecrosis. *J Clin Endocrinol Metabolism* 2007;92(3):1172-5.

-
- ³⁶ [Boonyapakorn T, Schirmer I, Reichart PA, Sturm I, Massenkeil G](#). Bisphosphonate-induced osteonecrosis of the jaws: Prospective study of 80 patients with multiple myeloma and other malignancies. *Oral Oncol* 2008 Feb 15 [Epub ahead of print].
- ³⁷ [Yarom N, Yahalom R, Shoshani Y, Hamed W, Regev E, Elad S](#). Osteonecrosis of the jaw induced by orally administered bisphosphonates: incidence, clinical features, predisposing factors and treatment outcome. *Osteoporos Int*. 2007;June 28 (Epub ahead of print).
- ³⁸ U.S. Food and Drug Administration. MedWatch 2005 Safety Alerts. (<http://www.fda.gov/medwatch/SAFETY/2005/safety05.htm#zometa2>, accessed March 27, 2006).
- ³⁹ Drug Topics. Top 200 Brand-Name Drugs by Units in 2006. <http://www.drugtopics.com/drugtopics/Pharmacy+Facts+And+Figures/Top-200-brand-name-drugs-by-units-in-2006/ArticleStandard/Article/detail/407649?contextCategoryId=7604> (Accessed Sept. 12, 2007).
- ⁴⁰ [Reid IR, Bolland MJ, Grey AB](#). Is bisphosphonate-associated osteonecrosis of the jaw caused by soft tissue toxicity? *Bone* 2007;41:318-20.
- ⁴¹ [Ezra A, Golomb G](#). Administration routes and delivery systems of bisphosphonates for the treatment of bone resorption. *Adv Drug Deliv Rev*. 2000;42:175-95.
- ⁴² [Berenson JR, Rosen L, Vescio R, Lau HS, Woo M, Sioufi A, Kowalski MO, Knight RD, Seaman JJ](#). Pharmacokinetics of pamidronate disodium in patients with cancer with normal or impaired renal function. *J Clin Pharmacol*. 1997;37:285-90.
- ⁴³ [Ruggiero S, Gralow J, Marx RE, Hoff AO, Schubert MM, Huryn JM, Toth B, Damato K, Valero V](#). Practical Guidelines for the Prevention, Diagnosis, and Treatment of Osteonecrosis of the Jaw in Patients With Cancer. *J Oncol Prac* 2006;2:7-14.
- ⁴⁴ [Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, Gagel RF, Gilsanz V, Guise T, Koka S, McCauley LK, McGowan J, McKee MD, Mohla S, Pendrys DG, Raisz LG, Ruggiero SL, Shafer DM, Shum L, Silverman SL, Van Poznak CH, Watts N, Woo SB, Shane E](#). Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. 2007;22:1479-91.
- ⁴⁵ [Woo SB, Hellstein JW, Kalmar J](#). Bisphosphonates and Osteonecrosis of the Jaws. *Ann Intern Med* 2006;144:753-61.
- ⁴⁶ [American Association of Oral and Maxillofacial Surgery. Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaw](#). *J Oral Maxillofac Surg* 2007;65:369-76.
- ⁴⁷ [Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, Gagel RF, Gilsanz V, Guise T, Koka S, McCauley LK, McGowan J, McKee MD, Mohla S, Pendrys DG, Raisz LG, Ruggiero SL, Shafer DM, Shum L, Silverman SL, Van Poznak CH, Watts N, Woo SB, Shane E](#). Bisphosphonate-associated osteonecrosis of the jaw: Report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2007 July 30;(epub ahead of print).
- ⁴⁸ National Osteoporosis Foundation. Osteonecrosis of the Jaw. <http://www.nof.org/patientinfo/osteonecrosis.htm> (Accessed August 22, 2007).
- ⁴⁹ American Association of Endodontists Position Statement. Endodontic Implications of Bisphosphonate-associated Osteonecrosis of the Jaw.

<http://www.aae.org/ManagedFiles/pub/0/Pulp/bisphosonatesstatement.pdf> (Accessed September 10, 2007).

- ⁵⁰ Clarke B, Koka S. Hotline: Bisphosphonate-associated osteonecrosis of the jaw. <http://www.rheumatology.org/publications/hotline/0606onj.asp> (Accessed August 22, 2007).
- ⁵¹ U.S. Department of Health and Human Services. Bone Health and Osteoporosis: A Report of the Surgeon General (2004) <http://www.surgeongeneral.gov/library/bonehealth/content.html> (accessed March 27, 2006).
- ⁵² [Palmer RM](#), [Saywell RM Jr](#), [Zollinger TW](#), [Erner BK](#), [LaBov AD](#), [Freund DA](#), [Garber JE](#), [Misamore GW](#), [Throop FB](#). The impact of prospective payment system on the treatment of hip fractures in the elderly. *Arch Intern Med.* 1989;149:2237-41.
- ⁵³ [Cummings SR](#), [Melton LJ](#). Epidemiology and outcomes of osteoporotic fractures. *Lancet.* 2002;359(9319):1761-7.
- ⁵⁴ [Wessel JH](#), [Dodson TB](#), [Zavras AI](#). Zoledronate, Smoking, and Obesity are Strong Risk Factors for Osteonecrosis of the Jaw: A Case-Control Study. *J Oral Maxillofac Surg* 2008;66:625-31.
- ⁵⁵ [Jeffcoat MK](#). Safety of oral bisphosphonates: controlled studies on alveolar bone. *Int J Oral Maxillofac Implants* 2006;21(3):349-53.
- ⁵⁶ [Wang HY](#), [Weber D](#), [McCauley LK](#). Effect of Long-Term Oral Bisphosphonates on Implant Wound Healing: literature Review and a case report. *J Periodontol* 2007;78(3):584-94.
- ⁵⁷ [Migliorati CA](#), [Hujoel P](#). Osteonecrosis of the Jaw May Not Be a Common Acute Side-Effect of Oral Bisphosphonates. *J Evid Base Dent Pract* 2007;7:77-8.
- ⁵⁸ [Schwartz JE](#). Ask us: Some drugs affect tooth movement. *Am J Orthod Dentofacial Orthop* 2005;127:644.
- ⁵⁹ [Rinchuse DJ](#), [Rinchuse DJ](#), [Sosovicka MF](#), [Robison JM](#), [Pendleton R](#). Orthodontic treatment of patients using bisphosphonates: A report of 2 cases. *Am J Orthod Dentofacial Orthop* 2007;131:321-6.
- ⁶⁰ Marx RE. Oral & Intravenous Bisphosphonate–Induced Osteonecrosis of the Jaws: History, Etiology, Prevention, and Treatment. Hanover Park, IL: Quintessence; 2006.
- ⁶¹ [Marx RE](#), [Cillo JE](#), [Ulloa JJ](#). Oral Bisphosphonate-Induced Osteonecrosis: Risk Factors, Prediction of Risk Using Serum CTX Testing, Prevention, and Treatment. *J Oral Maxillofac Surg* 2007;65:2397-410.