University of Miami Division or Oral and Maxillofacial Surgery Position Paper on
Drug Induced Osteonecrosis of the Jaws
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Introduction: From its first discovery in 2002[1] and the first few publications in the scientific literature[2, 3, 4] exposed alveolar bone in the jaws representing osteonecrosis has adversely affected the health of numerous individuals and has been one of the most published diseases in the world since that time.[5,6,7,8,9,10] What began as a strong relationship to the bisphosphonate class of drugs has now gone on to a definitive proof of causation and has expanded to a strong relationship and cause from the monoclonal antibody denosumab,[11,12] the anti-angiogenic drug bevacizumab[13,14] and the tyrosine kinase inhibitor Sunitinib.[15,16] Therefore, what was once termed by various names such as bisphosphonate induced osteonecrosis, bisphosphonate related osteonecrosis, bisphosphonate associated osteonecrosis and chemonecrosis has been replaced by Drug Induced Osteonecrosis of the jaws (DIONJ) by the American Medical Association and has the site specific ICD-10 code of M87.10.[17] Additionally, some of the new names advanced by certain organizations are scientifically incorrect Antiresorptive Related Osteonecrosis (ARONJ) is incorrect because neither bevacizumab and sunitinib are antiresorptive drugs. Medicine Related Osteonecrosis (MRONJ) is also incorrect because the related is not defined. These drugs actually cause (induce) the exposed bone. Moreover, our patients go to pharmacies and drug stores not "medicine stores". The term drug reinforces the reality thah these chemicals interfere with normal cellular functions and therefore have side effects.

General Purpose: The purpose of this position paper is to relate the most up to date knowledge and experience to prevent, manage, or when possible to cure DIONJ. The authors feel that the position papers currently available from the major organizations of dentistry and

medicine are either now out dated or have substantial mis-assessments and have not adequately addressed the new drugs causing DIONJ or the vast knowledge and experience gained in understanding the mechanism and dynamics of this disease.[7,18,19,20] Additionally, current position papers have not reviewed a differential diagnosis of exposed bone nor have they definitively addressed causation, outcomes of preventative measures and treatment measures. Many have published staging systems that are variable and misleading due to the incorrect incorporation of the subjective assessment of pain.

Specific Purposes:

1. Provide a knowledge base to assess the different risks of developing DIONJ from each drug.
2. To separate and compare the pharmacodynamics of each drug as to how they create DIONJ and how this relates to prevention and treatment
3. Review the clinical differential diagnosis of patients presenting with exposed bone and guide clinicians as to the workup and distinguishing features of the diseases considered in a reasonable differential diagnosis.
4. To guide the clinician and pathologist as to the distinguishing histopathologic characteristics of the common differential diagnosis considerations and to distinguish between primary and secondary infections.
5. Provide evidence and experienced based data guiding the clinician in prevention strategies, management measures, and specific surgeries aimed at controlling or curing DIONJ.

The Offending Drugs Therapeutic Uses:

1. **Bisphosphonates:** The main cellular effect of bisphosphonates is osteoclastic death (apoptosis) at the resorption site.[21, 22] Therefore, they are termed anti-resorption drugs.[21, 22] As intravenous drugs, they are FDA approved to resist bone resorption from metastatic cancer deposits in bone and reduce hypercalcemia of malignancy.[23] This is accomplished by reducing osteoclast numbers and/or their response to the stimulatory signaling effects of the cancer secretions of Reactor Activator of Nuclear Kappa-b Ligand (RANKL) on osteoclasts which would result in resorption cavities in bone.[24] Secondary cellular effects which are a less prominent are a pro-inflammatory effect[25] and an inhibition of capillary synthesis.[26] Although these secondary effects have been suggested to produce an anti-tumor effect, no bisphosphonate has shown definitive antitumor

effects and they are not approved as an anticancer drug.[27] However, these two secondary mechanisms may contribute to the loss of overlying soft tissue and therefore also contribute to bone exposure.[28]

As an oral drug bisphosphonates are FDA approved to treat osteoporosis and prevent osteoporosis.[29] This is accomplished by the same osteoclast cellular kill reducing bone resorption. However, this strategy retains old bone because it suppresses bone turnover which would otherwise synthesize new more elastic bone.[30] Over time, this action results in a more brittle bone.[31] This is sometimes seen as subtrochanteric (mid-shaft) fractures of the femur actually caused rather than prevented by Alendronate and reported in the literature as caused by Fosamax.[32,33,34] as well as some other bisphosphonates.[R]

It should be noted that bisphosphonates mainly kill functionally resorbing osteoclasts at peripheral resorption sites. They also to a lesser extend reduce osteoclast development in the bone marrow.[9,35]

2. Denosumab: The two denosumab preparations marketed as Xgeva and Prolia are inhibitors of RANKL.[35,36] Therefore, they not only inhibit bone resorption by disabling or killing osteoclasts at resorption sites, but they also do this by arresting the development and maturation of osteoclasts in bone marrow. This negative affect on osteoclasts in every stage of its development has translated into a more rapid emergence and greater extent of DIONJ from these drugs. RANKL inhibitors do not irreversibly bind to the mineral matrix in bone. Therefore, current data has indicated that denosumab has a half life effect in bone of 26 days[37] as compared to bisphosphonates which is 11 years.[38]

3. Bevacizumab (Avastin): Bevacizumab is a monoclonal antibody that blocks the action of the protein known as vascular endothelial growth factor (VEGF) which in both normal cells and cancer cells produces new capillaries and small blood vessels to replace aged or injured ones.[39,40] Therefore, VEGF like the growth factors of bone morphogeneic protein (BMP) and insulin like growth factors 1, 2, (ILG1 and 2) released by normal osteoclastic bone resorption serves to renew and maintain bone integrity, VEGF maintains tissue vascularity. The strategy in Bevacizumab use is to inhibit the growth of new blood vessels that feed cancer cells.[41] In individuals more sensitive to the actions of

Bevacizumab or when used at higher doses for longer periods its effects on normal endothelial cell renewal can in some instances result in exposed bone.[13]

4. Sunitinib (Sutent): Sunitinib is an inhibitor of several tyrosine kinase receptors such as those for PDGF and VEGF.[42] Disabling such receptors down regulates their promotion on cellular replication and other proliferative and synthetic cellular capabilities thus slowing the growth of cancer cells.[43] Such effects on cellular turnover and vascular regeneration may also affect normal tissues and may be the mechanism explaining the reports of DIONJ linked to this drug.[15,16]

When bisphosphonates were the only known drug to directly produce ONJ the stratification was based on the route of administration, i.e.: oral versus intravenous. Since intravenous bisphosphonates are used today in different dosing schedules to treat osteoporosis as well as a cancer metastasis and denosumab drugs are used at different dosing schedules via a subcutaneous route to treat osteoporosis or metastatic cancer in bone and now two direct anticancer drugs have caused ONJ cases, it is better to stratify these drugs according to their treatment indications.

TABLE 1

I. Osteoporosis Drugs *

Drug	Classification	Action	Dose	Route	% of Reported Cases *
Alendronate (Fosamax Generic)	Bisphosphonate	Osteoclast Toxicity	70 mg/wk	Oral	82%
Residronate (Actonel Atelvia)	Bisphosphonate	Osteoclast Toxicity	35 mg/wk	Oral	1%
Ibandronate (Boniva)	Bisphosphonate	Osteoclast Toxicity	150 mg/mos	Oral IV	1%
Zoledronate (Reclast)	Bisphosphonate	Osteoclast Toxicity	5 mg/yr	IV	6%
Denosumab	Monoclonal Antibody	Osteoclast Impairment	60 mg/6 mos	Subcutaneous	10%

*Data from University of Miami Division of Oral and Maxillofacial Surgery as of July 1, 2016.

TABLE 2

II. Drugs in Treatment of Cancer Complications and Metastasis *

Drug	Classification	Action	Dose	Route	% of Reported * Cases **
Zoledronate (Zometa)	Bisphosphonate	Osteoclast Toxicity	4 mg/mo	IV	67%
Pamidronate (Aredia)	Bisphosphonate	Osteoclast Toxicity	90 mg/mo	IV	18%
Bevacizumab (Avastin)	Monoclonal Antibody	VEGF Inhibitor	100-400 mg/ 14 days	IV	<1%
Sunitinib (Sutent)	Tyrosine Kinase Inhibitor	Osteoclast Toxicity	5 mg/yr	IV	<1%
Denosumab (Xgeva)	Monoclonal Antibody	Osteoclast Inhibitor	120 mg/mo	IV	15%

*Data from University of Miami Division of Oral and Maxillofacial Surgery as of July 1, 2016.
** Percentages are anticipated to change as the newer drugs are more frequently used.

Risks of Drug Therapy to Cause DIONJ: Risks of developing DIONJ cannot be accurately produced or predicted due to the fact that DIONJ initiation is due to variable factors the most significant of which is dose over time. This among other reasons is why no warnings about ONJ development were included in product labeling when the bisphosphonate drugs were first prescribed to the public and why only Dear Doctor letters and the first mention of DIONJ in the product labeling was in the post marketing observation section rather than the warning section.[44] This is further exampled by the early incidence reports concerning DIONJ caused by IV bisphosphonates in cancer patients of only 0.8%[45] reported in drug company sponsored studies which also expanded to 12% to 18%[46] as researchers began to incorporate dental trained individuals in their reviews. Researchers also learned what to look for, and patients began appearing who had a longer time of exposure. Therefore, incidence studies must be looked at as the minimal incidence due to missed and subtle cases and that the absence of exposed bone at the time of the study does not insure that DIONJ did not occur with further treatment or at a later time.

Causality from Bisphosphonates: Although causation of DIONJ from bisphosphonates is underscored by the tens of thousands of cases experienced by the dental and medical professions from both oral and intravenous bisphosphonates where no other plausible cause existed, some have demanded a more epidemiologic proof. There are three epidemiologic studies that indeed confirm causation. The first two are the actual randomized prospective double blind studies accomplished by the drug manufacturer in patients with metastatic breast

cancer and prostate cancer.[44] In their study groups that received a bisphosphonate, cases of DIONJ emerged during and after the study despite their naivety about the possibility of DIONJ. In their control group were patients without metastatic deposits that received the same chemotherapy and other treatments for the primary cancer but did not receive a bisphosphonate, a zero incidence of DIONJ occurred. The second epidemiology study comes from the University of Miami Division of Oral and Maxillofacial Surgery database, In this study of over 800 total patients, four cohort groups were compared: Group I; those that received a bisphosphonate and developed DIONJ. Group II; those that received a bisphosphonate but did not develop DIONJ. Group III; those that developed DIONJ that never received a bisphosphonate. Group IV; those that never received a bisphosphonate and also did not develop DIONJ. The results indicated that no causative correlation to any other drug, disease, or external agent other than the taking of a bisphosphonate was apparent. Only the bisphosphonate in this study was the cause of the exposed bone.

Causality from Denosumab: Denosumab is a sufficiently new drug that causation studies have not yet been done. However, the relatively rapid identification of DIONJ cases where no other plausible cause coincided as well as a common mechanism to bisphosphonates establishes a compelling and highly probable causation to Denosumab.[11,12,36,37]

Causality from Bevacizumab and Sunitinib: Both of these drugs have too few cases and a seemingly low incidence of developing DIONJ as to make causation arguments for or against a moot discussion at this time. A plausible mechanism exists and causation via a similar mechanism to each other but one that is substantially different from the mechanism for bisphosphonates and denosumab is likely.[39,41]

DIONJ: Differential Diagnosis:

There are a limited number of pathologies that result in exposed nonhealing bone in the jaws that presents over time. Therefore, the definition of DIONJ must include characteristics which will allow the clinician to rule out this small number of other conditions in a differential diagnosis and arrive at a reliable diagnosis of DIONJ. These conditions are:

1. Herpes Zoster: Herpes zoster may result in exposed bone but usually does not. When it does, it can be distinguished from DIONJ by its accompanying distinctive painful

crusting skin lesions over a distinct nerve distribution that exhibits an abrupt cut off at the midline.[47] Additionally, the exposed bone covers over with healing.[47]

2. Osteoradionecrosis: Osteoradionecrosis results in exposed bone that frequently becomes secondarily infected thus mimicking DIONJ and osteomyelitis. It is distinguished by the known history of direct radiation area of the jaw and the characteristics of xerostomia, radiation fibrosis, radiation telangiectasis, trismus, radiation caries and others which may be variable present.[48,49,50] Histologically, one finds nonviable bone and significant marrow fibrosis that is hypocellular and hypovascular. Cases where secondary infection has occurred may show some inflammatory cells but retains a background of marrow fibrosis.
3. Suppurative Osteomyelitis. A primary osteomyelitis uncommonly results in exposed bone (4%).[51] Like osteoradionecrosis DIONJ frequently becomes secondarily infected which has led to pathology reports incorrectly diagnosing either one as an osteomyelitis. If known, a precise history will identify that the primary osteomyelitis infection began within the medullary component of the bone with obvious signs, symptoms, and characteristic radiographs long before exposed bone appeared. Radiographic clues and histologic clues also aid in distinguishing an osteomyelitis from DIONJ. Radiographically, a suppurative osteomyelitis will show little if any osteosclerosis about the area of exposed bone and none in other parts of the jaw. Histopathologically, a representative central core specimen will show inflammatory cells in the marrow space and uniform, healthy osteoclasts resorbing bone in well defined Howship's lacunae.[51]
4. Osteopetrosis: Osteopetrosis will result in exposed bone that will strongly mimic DIONJ and is most always secondarily infected as well.[52, 53] It can usually be distinguished from DIONJ by the already established diagnosis of osteopetrosis. If not, genetic testing will identify one of the eight genetic variants of osteoclast dysregulation or maldevelopment.[52, 53] Radiographically, osteopetrosis will show prominent sclerosis in nearly all other bones as well as the jaws.[52]
5. Cemento-osseous Dysplasia: Only 10% of cases result in exposed bone.[54] However, since this condition is limited to the jaws and starts in the alveolar bone as does DIONJ, it can mimic DIONJ. However, this condition is limited to women of Black African heritage and usually develops in the age range between 30-50 years of age.[54,55]

DIONJ Definition: Patients can be diagnosed with DIONJ if all of the following four conditions have been met:

1. Current or previous treatment with a systemic drug with a plausible mechanism that affects bone homeostasis (bone health).
2. Exposed alveolar bone in the jaws that persists for more than eight weeks with or without nonsurgical therapy
3. No history of radiotherapy to the jaws
4. No known diagnosis of osteopetrosis or cemento-osseous dysplasia or either ruled out by history, clinical examination, imaging, or genetic testing.
   *Note: DIONJ remains a history based clinical diagnosis. Imaging, laboratory tests and histopathology may only add to the diagnosis.
   **Exposed bone may be subtle and not readily visible to the naked eye. Exposed bone may be identified by probing a fistula or a periodontal defect or by reflecting granulation tissue covering over unhealed exposed bone.
   ***Pure central bone specimens of DIONJ cases caused by bisphosphonates or denosumab will show nonviable bone with empty Howship's Lacunae and an absence of inflammatory cells in the marrow space. Such cases that become secondarily infected may indeed show inflammatory cells in the marrow space but will show empty Howship's lacunae and or dying osteoclasts rather than the healthy osteoclasts working in groups that are seen in a primary osteomyelitis.

Risk Factors for DIONJ: The only risk factor for DIONJ is the offending drug itself. What has been misinterpreted as risk factors in previous position papers are initiating events, vulnerable anatomic sites, and comorbidities.

The risk factors for developing DIONJ are related to the potency of the drug, its route of administration, its dose, its frequency of administration and the length of time the offending drug has been used and the length of the drugs half life in bone i.e. bisphosphonates half life 11 years,[38] denosumab 26 days,[37] Bevacizumab 50 days,[58] Sunitinib 4.6 days.[56,57]

The most important risk factor for the bisphosphonate class of drugs is the route of administration. The intravenous route loads the bone 140 times more and sooner than the oral route.[58] The second most significant risk factor is the drugs potency. Table -23 presents the relative potencies of the bisphosphonate class of drugs based on the first bisphosphonate to appear in the market which placed Etidronate as 1 and each related to their FDA approved dose and frequency.

TABLE-3

Drug	Route	Dose	Frequency	Relative Potency
Etidronate	Oral	300-700 mg	Daily x 6 month	1
Alendronate	Oral	70 mg	Weekly	1,000
Residronate	Oral	35 mg	Weekly	1,000
Ibandronate	Oral IV	150 mg 3 mg	Monthly Every 3 Months	1,000
Pamidronate	IV	90 mg	Monthly	5,000
Zolendronate	IV	4 mg 5 mg	Monthly Yearly	10,000+

For denosumab, the most significant risk factor is the dose as both indications for denosumab are the same subcutaneous route of administration and the same potency. Denosumab as Prolia for osteoporosis is FDA approved for 60 mg subcutaneous every six months where as denosumab as Xgeva for cancer metastasis and hypercalcemia of malignancy is FDA approved for 120 mg subcutaneous monthly. NOTE, Xgeva is not approved for use in patients with multiple myeloma.

Therefore, for both bisphosphonates and denosumab in general, the cancer patients receiving each drug develop DIONJ sooner, a more extensive form and one more refractory to nonsurgical management which more frequently requires a more aggressive surgery not so much related to the effects of their cancer but to the greater drug dose they received. It should also be noted that a physician's well meaning effort to switch to denosumab after an initial treatment sequence of a bisphosphonate has resulted in a rapid development of extensive expose bone. It seems that reducing the bone marrows repopulation of osteoclasts that are needed to resorb bone already loaded sub clinically with a bisphosphonate pushes the compromised bone remodeling/renewal cycle toward bone death.

Initiating Events: Approximately 29% of cases develop exposed bone spontaneously without any initiating insult to the alveolar bone. These are related to the risk factors of dose, potency, length of time on the drug, frequency of administration and route of administration. The following have been recognized as initiating events in order of frequency:

1. Extractions 61.6%
2. Periodontal osseous surgery 5.6%
3. Dental implant surgery 2.2%
4. Bone biopsy 1.1%

5. Periapical surgery 0.5%
6. Spontaneous 29.0%

*Data derived from 478 patients in the University of Miami Division of Oral and Maxillofacial Surgery database.

Anatomic Vulnerable Sites: The foremost vulnerable anatomic site is the alveolar bone. Nearly all DIONJ by the definitions of all dental and medical organizations begins in the alveolar bone. Affected bone may often be seen by observing sclerosis of the lamina dura or radiographic identification of a more diffuse sclerosis mostly in the alveolar bone as well as elsewhere supporting the fact that tooth extractions are the most common initiating event. Other vulnerable anatomic sites are the lingual cortex in the molar region of the mandible due to the distribution of greater occlusal loading to this area and the surface of tori due to the increased remodeling rate of their surface bone. It should also be noted that the cases of subtrochanteric fractures of the femur due to alendronate are in the midshaft area. This is the bending moment of this bone during function which is the second most active remodeling site in the adult skeleton after the alveolar bone in the jaws.

Co-Morbidities: Comorbidities are concomitant diseases, medical conditions, other drugs, age, and genetics etc which by themselves are not noted to result in exposed bone in the jaws but may make DIONJ appear sooner and become more extensive in someone exposed to one of the known offending drugs.

To date, the cancer itself, a host of chemotherapeutic drugs, diabetes, immune based diseases, anemia, age, smoking, obesity, renal dialysis among many others are noted as comorbidities.[59,60,61] While gender and race are not considered to be comorbidities by themselves, the prudent clinician should understand that osteoporosis prevention and treatment with bisphosphonates and denosumab is more than 90% focused on women over the age of 50 years and that osteoporosis is more common in white Caucasian women and Asian women.

Certainly genetics plays a role in DIONJ vulnerability as it does in most other diseases and some studies have implied such.[62] However, specific genetic profiles identifying certain genetic types more likely to develop DIONJ or more sensitive to the same dose have not been identified as it has for radiation tissue injury.[63]

Prevention Strategies:

General: Transcending all drugs know or suspected to cause DIONJ now and in the future is the best preventative measure: **stable oral health**. Classic preventative dentistry such as eliminating periodontal inflammation, treating caries, removing unsalvageable teeth before an offending drug is prescribed reduces many of the initiating events that result in DIONJ.

Specific Prevention Strategies: Osteoporosis Treated Patients.

Beyond stable oral health maintenance, prevention strategies for those treated for osteoporosis depend mostly on the half lives of the oral bisphosphonates, subcutaneous denosumab, and the IV bisphosphonates approved for osteoporosis. However, related to gaining and maintaining oral health it should be noted and passed on to the nonsurgical specialties of dentistry that neither the bisphosphonates nor the denosumab drugs enter or become incorporated into developed teeth. Therefore, dental prophylaxis, restorations, crowns, bridges, nonsurgical root canal treatments, and non surgical periodontal treatments and even well made partial and full dentures that do not place excessive pressure on the ridges are safe at all times and are recommended.

For the oral bisphosphonates alendronate (Fosamax), residronate (Actonel, Atelvia) and Ibandronate (Boniva) several studies have validated the usefulness of the morning fasting serum C-terminal telopeptide (CTX) test values above 150 pg/ml to support alveolar bone healing provided the test is not invalidated by cancer (the values are too high), the recent or current use of a steroid or methotrexate (values are too low). If the CTX is invalidated by either of these or the clinician prefers not to use the CTX test, experienced based data identifies that a nine month drug holiday supports clinically normal healing. After any dentoalveolar surgery using either the CTX value of > 150 pg/ml with or without a drug holiday or the nine month presurgical drug holiday and follow up three month drug holiday, normal bone regeneration and maturity can be anticipated including osseointegration of dental implants.

Note: Drug holidays from bisphosphonates or denosumab should be initiated by the prescribing physician. Oral and maxillofacial surgeons should request the drug holiday and not initiate it independently. On only rare occasions will the prescribing physician be reluctant to cooperate with a drug holiday. In such cases, it is recommended to refer the physician to the Landmark

multicenter double blinded prospective study by Black, Ensrud et al that appeared in JAMA Dec 2006.[67] This study clearly showed that drug holidays of even five years had no increased fracture risk for the treated osteoporotic patient. Moreover, the 2011 official FDA statement for osteoporosis treatment with bisphosphonates related that women treated for 3 years require osteoporosis re-testing and that no one needs to take a bisphosphonate for more than five years. There statement is based on the drub companies database which identified no benefit beyond three years and a sharp increase in side effects i.e. DIONJ and femur fractures.[71]

Non-bisphosphonate and non-denosumab alternatives may be suggested and used during a drug holiday if it is preferred. Such alternatives are Vitamin D3 and calcium to prevent and treat mild osteoporosis, Raloxifene (Evista)[68] for mild to moderate osteoporosis and rhPTH1-34 (Forteo)[69] to treat severe osteoporosis. It should be noted that subcutaneous or nasal spray Calcitonin is no longer recommended for more than three months and is therefore not a good choice as an alternative. This is due to a statistically higher incidence of cancer as compared to population background rates with longer term use.[70]

It is also recommended that oral and maxillofacial surgeons be aware of the Sept 2011 FDA published document concerning the length of osteoporosis treatment using a bisphosphonate.[71]

For those osteoporosis patients receiving Zoledronate 5 mg IV once yearly (Reclast) our data indicates that a significant risk factor begins with the fourth yearly dose due to the 11 year half life of the drug and its accumulation effect. Therefore, elective alveolar bone surgeries are best deferred until nine months after the most recent dose and three months before the next planned dose. For such cases, the morning fasting serum CTX test is useful.

The clinician should be particularly aware of the patient switched to Reclast after having taken an oral bisphosphonate for several years. These individuals have a higher risk for DIONJ due to the gradual but significant accumulation from the oral bisphosphonate that is rapidly added to by the IV bisphosphonate which loads the bone rapidly with 140 times the amount of a single dose of an oral bisphosphonate. The appropriate length of a drug holiday in these patients has not been adequately studied. It is likely to be somewhat longer than nine months and guidance from CTX results may help.

Use of these guidelines for drug holidays and/or CTX testing allows todays clinicians to treat patients with full and comprehensive treatment plans including indicated tooth extractions, osseos periodontal surgery and dental implants.

Treatment Strategies for Those Patients who Develop DIONJ from Drugs Used to Treat Osteoporosis: Before treating DIONJ in either osteoporotic patients or cancer patients from any of the drugs discussed it is recommended to stage the disease. Unfortunately past staging systems incorrectly included pain in the staging levels and thusly created an overly complicated and changing stage that did not correlate to the severity or extent of the disease. Since pain is subjective and is actually caused by inflammation from secondary bacterial colonization or infection rather than the amount or extension of necrotic bone, it should not be part of the staging system. Other disease staging systems such as those for oral cancer, osteoradionecrosis, lymphoma, etc, do not do not include pain for these same reasons. Therefore, it has been eliminated in the following simplified staging system applicable to all causes of DIONJ:

Stage 0:	Clinical or radiographic evidence of drug toxicity in the jaws (i.e. sclerosis of the lamina dura, widening of the periodontal ligament space, tooth mobility or pain not explained by a more obvious cause.)
Stage I:	Exposed bone limited to one quadrant
Stage II:	Exposed bone involving two quadrants
Stage III:	Exposed bone involving three or four quadrants, or the presence of a cutaneous fistula, or osteolysis to the inferior border, or a pathologic fracture or if in the maxilla, extension into the maxillary sinus.

DIONJ caused by an oral bisphosphonate or denosumab can be effectively managed with a 0.12% chlorhexidine and intermittent course of antibiotics and in most cases resolved with the use of a drug holiday alone or followed by surgery. The University of Miami data base identifies a 50% spontaneous resolution rate with a drug holiday of nine months alone. Another 40% required an alveolar debridement/local alveolar resection after either a CTX value rose to > 150 pg/ml or a nine month drug holiday. However, 10% required a continuity resection of the mandible or a partial submucosal maxillary resection and a Sinusotomy after the same CTX/nine month drug holiday considerations.

While the drug holiday progresses, effective control of secondary infection and therefore pain can be obtained in one of two ways. In the asymptomatic patient, 0.12% chlorhexidine (Peridex) oral mouth rinse 15 ml swish and spit works well to reduce bacterial colonization and infection of the exposed bone. In those patients who are symptomatic with pain and/or have soft tissue inflammation or a suppurative exudate, antibiotics are often necessary. Several studies have identified that the most common microorganism is Actinomyces. Therefore, penicillin is the drug of choice. Since many of these patients require either long courses of penicillin or repeated courses, phenoxymethyl penicillin 500 mg q.i.d or amoxicillin 500 mg t.i.d. is preferred over amoxicillin with clavulanate which can produce gastrointestinal side effects with extended use. In penicillin allergic patients doxycycline 100 mg q.d. is a good second choice and also can be used in an extended course or repeatedly with minimal side effects.

In those patients that experience a less than adequate response to either penicillin or doxycycline adding a limited 10 day course of metronidiazole 500 mg t.i.d to these antibiotics usually controls the infection.

Note: Due to a much shorter half life for denosumab (Prolia) a shorter drug holiday of three months is adequate. Additionally, there is insufficient CTX data for patients on Prolia at this time. Therefore, the use of an arbitrary three month drug holiday is preferred.

Once DIONJ in noncancer patients treated for osteoporosis with either a bisphosphonate or denosumab (Prolia) is resolved, dental implant osseointegration can be expected as long as the drug holiday is continued for at least three months after the implants are placed.

Specific Prevention Strategies: Cancer Patients

A. <u>Before The Patient Begins Treatment:</u>

It is ideal and recommended that patients be referred to and seen by dental professionals before beginning treatment with any of the known drugs that have caused DIONJ. This requires a close working relationship between dental professionals and medical oncologists.

The goal of pretreatment dental care is to accomplish any necessary procedures to reduce the need for invasive oral surgical procedures after treatment begins which may initiate DIONJ and to achieve stable oral health. In order of urgency:

1. Accomplish necessary tooth extractions and request a two month postponement of drug therapy.
   Note, partially bony impactions that represent a risk for pericoronitis are best removed. Fully covered impacted teeth by healthy soft tissue or bone are best left unless there is radiographic evidence of a pathology
2. Accomplish necessary osseous periodontal surgery
3. Dental prophylaxis and non osseous periodontal care
4. Caries controls and occlusal adjustments
5. Root canal therapy
6. Prosthetic appliances
   Note: Most medical oncologists will defer commencing with such drug therapy for two months. However, if they feel it is imperative to begin sooner, it is well to remember that the cancer control is a higher priority than DIONJ prevention or treatment. However, it is also well to remember that the risk factor sharply increases with the fourth dose allowing much of the required invasive procedures to be accomplished with a reduced risk profile within the early portion of that time period.

B. <u>During Drug Therapy</u>

The goal during drug therapy is to reduce the need for surgical trauma (i.e. tooth extractions, osseous periodontal surgery, root resection etc) and to balance the occlusion. These represent the most common initiating factors of DIONJ. Recommended treatments may include.

1. Root canal therapy that may require crown coverage or crown amputation leaving the treated root/roots in place
2. Splinting mobile teeth
3. Occlusal adjustments
4. Operculectomy
5. Caries control and restorative dentistry
6. Non-osseous periodontal procedures
7. The full spectrum of prosthetic appliances,
   Note, Obviously, abscessed teeth and fractures of teeth that extend into the roots and other necessary surgical procedures may be required during drug therapy. In such cases it is best to provide written informed consent concerning the relative risk for DIONJ based upon the drug, the dose, its frequency, the length of time the patient took the drug and the degree of surgery required.

Note: While dental implants are a relative contraindication rather than an absolute contraindication in this group of patients, surgeons should use extreme caution before placing dental implants. Observing bone remodeling in extraction sockets and a long drug holiday of more than one to two years should be incorporated into the decision process. A cautionary and specific informed consent is recommended in the rare cases where dental implants are considered.

Management strategies and treatment options for DIONJ are focused on control or resolution of the exposed bone and therefore the secondary infection and pain without significantly interfering with the cancer treatment and allow patients to live with minimal impact on their daily lives.

Although resective surgery may be required in many cases, it should be reserved only for those with strong and clear indications for a resection. This is due to the following factors:

1. Many of these patients are a significant anesthetic/surgical risk
2. Reconstruction of such patients may not be possible due to metastatic disease in donor bone sites and an absolute contraindication for the use of rhBMP-2/ACS in patients with active cancer.[72] This relegates most mandibular reconstructions to be limited to a rigid titanium plate.
3. The amount of bone affected by the DIONJ is often extensive. A resection may create the need for a tracheostomy or a gastrostomy tube etc and often results in parasthesias, speech and swallowing compromise as well as deformity.

In the University of Miami database, 60% of cancer patients with DIONJ have been effectively managed to an infection controlled and a pain free state with continued exposed bone but with adequate oral function using the 0.12% chlorhexidine and antibiotic regimens as outlined for the DIONJ caused by drugs in the treatment for osteoporosis. The remaining 40% required a resection using the following clear indications:

1. Symptomatic cases refractory to the nonsurgical management with 0.12% chlorhexidine and antibiotics
2. Progressive osteolysis to the inferior border of the mandible
3. A pathologic fracture
4. Direct maxillary sinus involvement with radiographic evidence of sinusitis

Experience Based Evidence Related to Resections for DIONJ in Cancer Patients:

1. General Considerations: Due to the 11 year half life of bisphosphonates in bone, general considerations identify that drug holidays are not required but will assist the healing of any bony surgery although by only a small measure. It will however reduce the possibility of a second site of bone exposure. Nevertheless the position of the oral and maxillofacial surgeon should be one where the control of the cancer is a priority over control or cure of DIONJ. If there remains a cancer related therapeutic gain for the patient to continue a DIONJ causing drug, then there is no reason to discontinue it. However, if the oncologist feels that there is little or no further benefit from the drug, then it should be discontinued as any medication which has exhausted its therapeutic benefit.

2. The Maxilla: Submucosal resections of the posterior maxilla with complete debridement of the mucoceles and inflamed sinus membrane (Sinusotomy) has been one of the most curable procedures for DIONJ. This has largely been due to advancing the buccal fat pad with its robust blood supply and mesenchymal stem cell population into the defect and extensive undermining of the labial mucosa to cover the sinus with a two layer closure.

   Resections of the anterior maxilla usually do not require a resection of the nasal floor. This is due to the fact that the alveolar bone is the target of DIONJ and in only rare instances does the necrotic bone extend into the heavily vascular nasal floor. Therefore, alveolar resections and primary closure have an excellent track record with the defect being capable of undergoing reconstruction with routine nonimplant supported appliances. In those rare cases that do involve the nasal floor the resection must remove the necrotic bone of the nasal floor committing the patient to an obturator prosthesis.

3. The Mandible: While most DIONJ cases meeting the indication for a resection require a continuity resection, some are limited to alveolar bone but have been refractory to antibiotic control. In these cases, an alveolectomy and a primary closure usually resolves the DIONJ. The adequacy of the alveolectomy may be guided by observing residual vascular marrow at the alveolectomy margins.

Continuity resections for DIONJ of the mandible are more commonly needed than alveolectomy. The margins of such resections should be guided by the radiographic appearance (a cone beam CT scan is advantageous). The fact that the ramus is not alveolar bone and is less involved unless the DIONJ has extended from the alveolar bone areas, often recommends the resection be carried to the ramus. Additionally, the observation of residual vascular marrow at the resection margins usually indicates sufficient viability to heal. The resultant defect is most often reconstructed with a rigid titanium plate that is placed with the intent of long term stability. To gain this it is recommended to use the thickest and strongest plate made by the respective manufacturer and use four to eight bicortical locking screws on each remaining segment if possible. Reconstruction using autogenous cancellous marrow or free vascular fibula grafts may be used in rare selective cases provided that the benefits outweigh the risks and morbidity of the graft procedure and that the donor bone is documented to be free of metastatic cancer.

Vigilance and Future Research: The lessons learned from DIONJ underscores the need for clinicians to be vigilant observers and reporters of drug complication. Like Vioxx[73] and Fen Phen[74] before, the complications from bisphosphonates, denosumab, Bevacizumab, and Sunitinib were not either thought to be looked for or adequately warned by the drug companies. Therefore, the stewardship of patient safety falls to us providers as the final safety net. No doubt extremely potent generalized toxic drugs and disease targeted drugs are in the Pharma pipelines currently. Only the naïve would think that we have seen the last of oral drug complications.

It is incumbent on independent scientists and clinicians to continue data collection, retrospective reviews, and clinical trials to further our knowledge about the mechanism of DIONJ related to each drug and to explore, debate, and test novel prevention and treatment modalities.

Disclaimer: The Division of Oral and Maxillofacial Surgery at the University Of Miami Miller School Of Medicine provides this position paper based on the equally valid data from evidenced based and experienced based studies. It is not associated with any other position paper or meant to be in competition or critical of other position papers by any organization. It remains an independent resource for clinicians.

It is intended to be a resource for practitioners in all specialties of dentistry and medicine, as well as patients, industry, and other interested parties.

This position paper is not intended to be a standard of care or an algorithm for either prevention or treatment but rather only an informational document for the reader to devise individual management or treatment plans to optimize patient care on a case by case basis. As already stated this position paper represents the best independent evidence and experience related to DIONJ at the time of its development. Most assuredly new data and new drugs will come about that may modify and add to this paper. The Division of Oral and Maxillofacial Surgery at the University Of Miami Miller School Of Medicine or its authors make no expressed or implied warranty regarding the content, accuracy, completeness, reliability, probability or legality of the information continued within this position paper. This includes without limitation, the warranties of merchantability, fitness for any particular purpose and non-infringements or proprietary rights. However, the authors attest that no conflict of interest exists and that no outside industrial, legal or academic interests influenced the clinical science contained in the this paper. In no event shall the University of Miami be liable to the reader or user of this position paper or anyone else for any decision made or action taken by him or her in reliance in such information.

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