Presented by the American Association of Oral and Maxillofacial Surgeons

Osteonecrosis of the Jaws: Bisphosphonates, Diagnosis, Management and Future Research

This important educational program is offered by the AAOMS at no charge as a public health initiative to the dental and medical communities through an unrestricted educational grant from Merck & Co., Inc., Novartis Pharmaceuticals and Procter & Gamble.

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Welcome

W. Mark Tucker, DDS, President

American Association of Oral and Maxillofacial Surgeons

Chief, Oral and Maxillofacial Surgery
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Faculty Disclosure

- **W. Mark Tucker, DDS** has no financial interest/arrangements that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

- *Safeguard:* This presentation has been peer reviewed to ensure an evidence-based presentation free of bias.

Bisphosphonate-Related Osteonecrosis of the Jaws (BRONJ) on the Rise

- Growing number of patients exhibiting symptoms of BRONJ
- Characterized by exposed, necrotic bone in the maxillofacial region
- Investigation revealed link between IV and oral bisphosphonate drug treatment

Our Purpose Today

- **Alert dental and medical professionals most likely to encounter patients in the early stages of BRONJ**
  - Make appropriate diagnosis and referral for treatment
- **Educate dental professionals on the significant health problems caused by osteoporosis**
  - Many patients will seek your guidance
  - Need for a study to gather better information on the prevalence and incidence of BRONJ

Our Panel of Experts Will Discuss

- **Osteoporosis and its management**
- **How to identify and counsel patients who present with or may be at risk for BRONJ**
- **Current management for those patients diagnosed with BRONJ**

Commercial Support

- **Supported by unrestricted educational grants from Merck & Co., Inc., Novartis Pharmaceuticals, and Procter & Gamble**

Accreditation Statements

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Salvatore Ruggiero, DMD, MD

- **Former chief of the Division of Oral and Maxillofacial Surgery**
  - Long Island Jewish Medical Center, New Hyde Park, NY
- **One of the first OMSs to recognize a potential osteoporosis/BRONJ link**
- **Has treated almost 200 BRONJ patients**

Overview

Salvatore Ruggiero, DMD, MD
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Department of Oral & Maxillofacial Surgery
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Faculty Disclosure

- **Salvatore Ruggiero, DMD, MD** has a financial interest/arrangement with the following companies that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation:
  - Paid Consultantship: Amgen Inc.

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At the completion of this session, the participants should be able to:

- **Describe bone metabolism and the pathophysiology of osteoporosis**
- **Describe the role of bisphosphonates in the treatment of osteoporosis including their mechanism of action and how long they stay in the bone**
- **Describe the pathophysiology of bisphosphonate-related osteonecrosis of the jaws (BRONJ) and define its presentation characteristics**

At the completion of this session, the participants should be able to:

- **Identify patients presenting with BRONJ or the potential for developing BRONJ**
- **Recognize the approaches for the management of BRONJ and describe**
  - How to address the patient
  - The general dentist's role in diagnosis and management
  - The oral & maxillofacial surgeon's role in diagnosis and management

The Role of Bisphosphonates in Osteoporosis

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Providence Portland Medical Center
Director, Oregon Osteoporosis Center
Portland, Oregon

Faculty Disclosure

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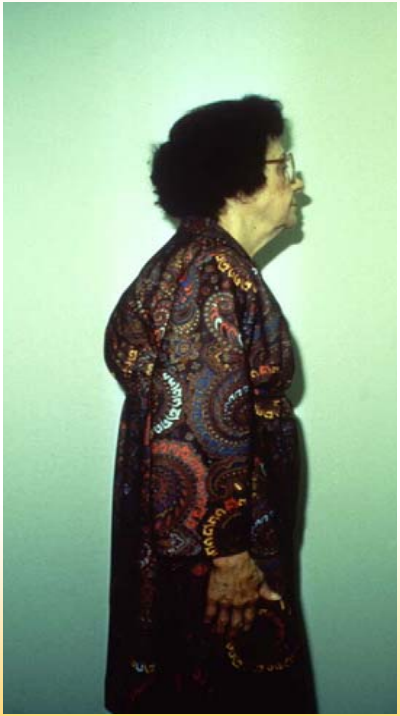
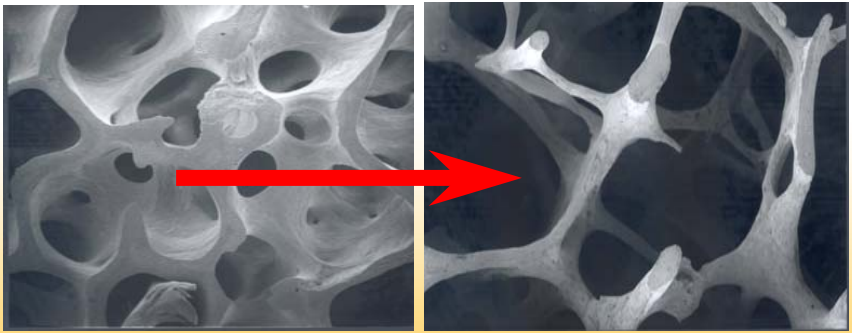
Osteoporosis: The Definition

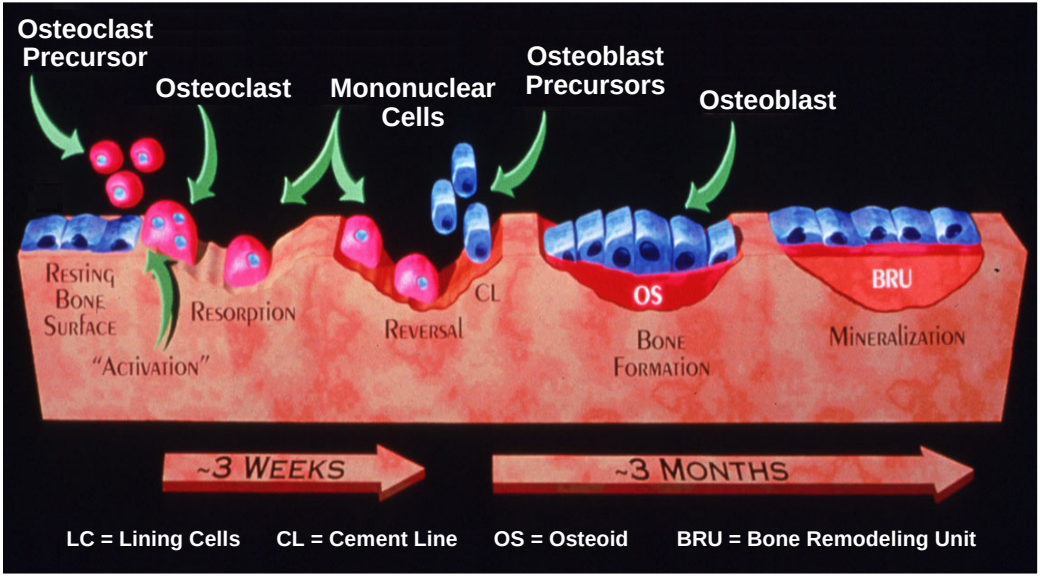


- **Impaired bone strength**
  - Low Bone Mineral Density
  - Poor bone quality
- **Increased fracture risk**
  - Due to bone loss



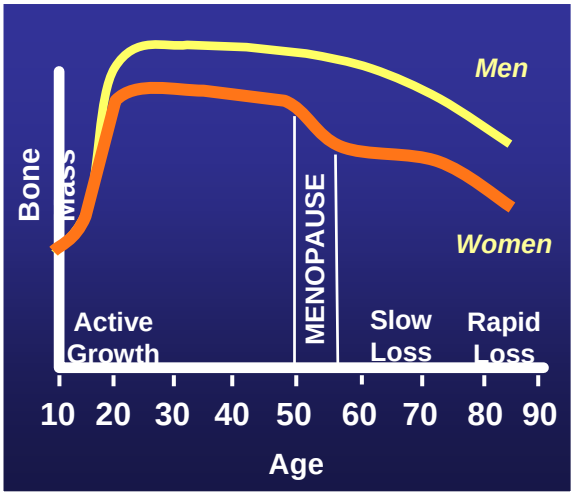
Bone images courtesy of by Dr. David Dempster

Bone Remodeling is a Dynamic Process



Bone Mineral Density Over the Lifespan

- **Minimal in healthy young men and premenopausal women**
- **Accelerates at menopause due to estrogen deficiency**
- **Continues throughout life**
- **Increases in old age**
- **Influenced by other factors—nutrition, diseases, medications, activity, etc**



Adapted from Wasnich RD, et al. *Osteoporosis: Critique and Practicum*. Honolulu, Banyan Press, 1989:179-213. Recker R, et al. *J Bone Miner Res*. 2000;15:1965-1973.

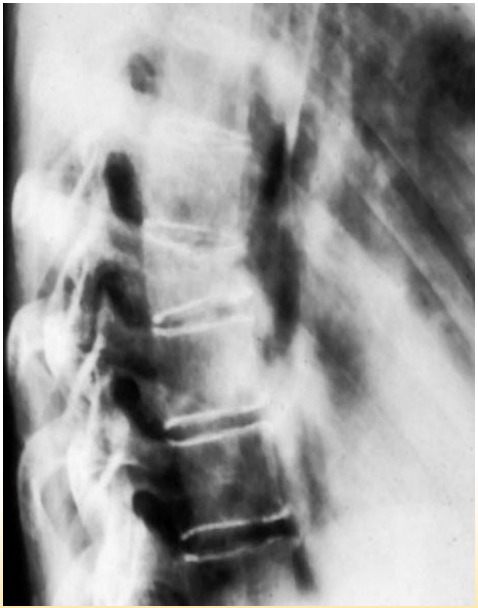
Fracture Incidence and Cost

- **Direct cost is at least $17 billion/year[1]**
- **Lifetime risk of any fracture at age 50**
- **53% for Caucasian women[2]**
  - More common than breast cancer[3]
- **21% for Caucasian men[2]**
  - More common than prostate cancer[3]
- **Fractures are expected to triple in 50 years and costs to rise substantially[4]**

[1] Gabriel SE et al. *Osteoporosis Int*. 2002;13:323.
[2] Van Staa T et al. *Bone*. 2001;29:517.
[3] American Cancer Society. *Cancer Facts & Figures.* 1996.
[4] *Bone Health and Osteoporosis: A Report of the Surgeon General.* 2004 www.surgeongeneral.gov/library/bonehealth

Vertebral Fracture–Consequences

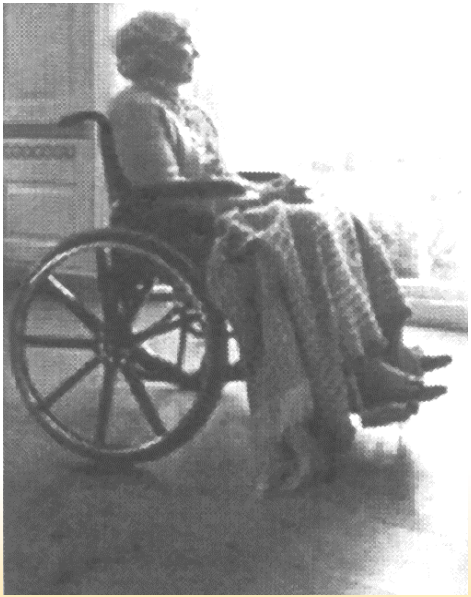
- Most common fracture
- Frequently unrecognized
- Acute and chronic pain
- Kyphosis and height loss
- Impaired function
- Increased mortality
- Increased fracture risk



Silverman SL, et al. *Arthritis Rheum*. 2001;44:2611-2619.

Hip Fracture–Consequences

- **200,000 women and 100,000 men with hip fractures every year**
- **Average age = 84**
- **Increased morbidity**
- **Major reason for nursing home admission**
- **30% of patients do not regain their pre-ambulatory status**
- **15%-20% excess mortality**

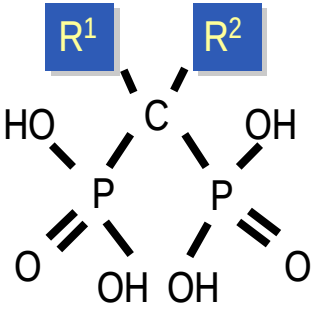


Stevens JA, et al. *MMWR Recomm Rep*. 2000;49(RR-2):3-12.
National Osteoporosis Foundation Physicians' Guide, Washington, DC: 2003.
Accessed at: http://www.nof.org/physguide/impact_and_overview.htm

Drugs to Treat Osteoporosis

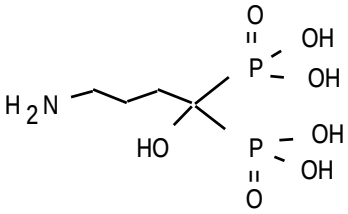
- ***Antiresorptive Agents***
  - **Estrogen**
  - **Calcitonin (Miacalcin®)**
  - **Selective estrogen receptor modulator**
    - Raloxifene (Evista®)
  - **Bisphosphonates**
    - Alendronate (Fosamax®)
    - Risedronate (Actonel®)
    - Ibandronate (Boniva®)
- ***Anabolic Agents***
  - **Teriparatide (Forteo®)**

Bisphosphonates

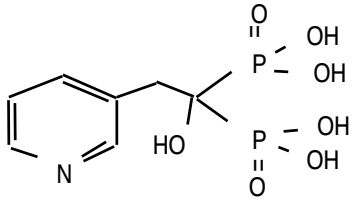


- Non-metabolized analogues of pyrophosphate
- Bind tightly to bone mineral
- Incorporated into osteoclasts
- Interfere with intracellular processes
- Reduce bone resorption
- Reduce fracture risk

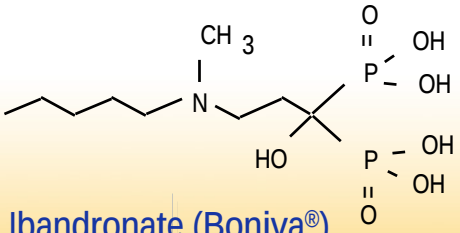
N-containing Bisphosphonates



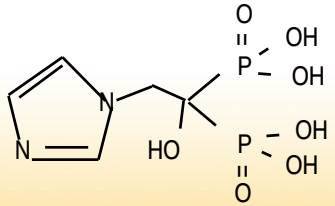
Alendronate (Fosamax®)



Risedronate (Actonel®)



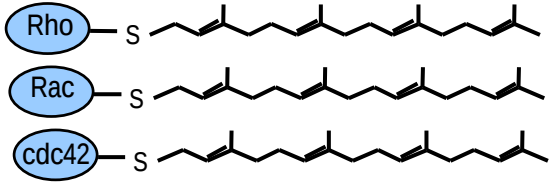
Ibandronate (Boniva®)



Zoledronic Acid (Zometa®)

Mechanisms of Action for N-containing Bisphosphonates

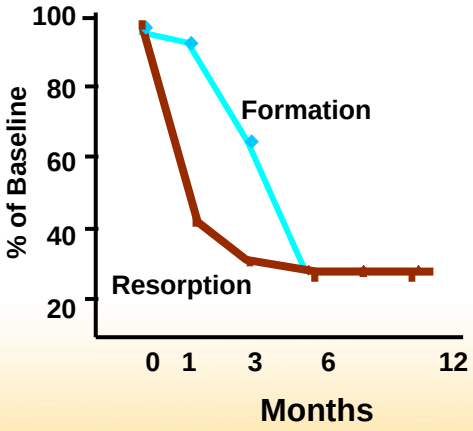
- **Inhibit the prenylation and function of GTP-binding proteins required for osteoclast formation, function, and survival**



- **Reduce proliferation and action of osteoclasts**
- **Reduce bone resorption**
- **Indirectly reduce bone formation**

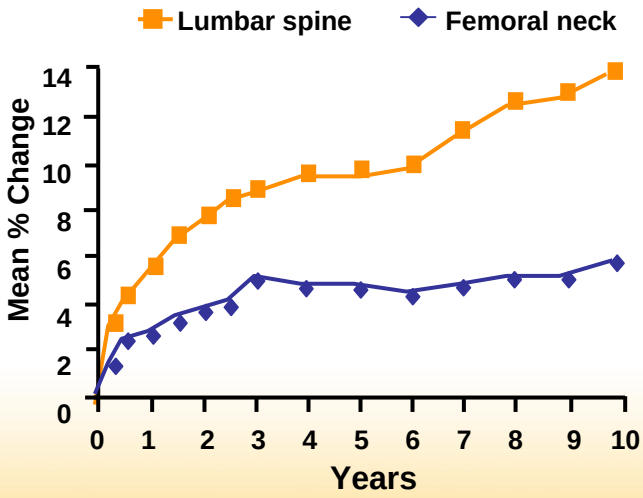
Effects of Alendronate Therapy on Bone Turnover and Bone Density

Bone Turnover



Chesnut CH, et al. *Am J Med.* 1995;99:144.

Bone Mineral Density



Bone HG, et al. *N Engl J Med*. 2004;350:1189.

Bisphosphonate Therapy and Fracture Risk

Fracture	Relative Risk Reduction
Vertebral fractures	40%-65%
Multiple vertebral fractures	75%-95%
Non-vertebral fractures	30%-40%
Hip fracture	40%-50%
Spine fracture in patients on glucocorticoids	70%

- Risk reduction occurs as early as 6 months
- No evidence of waning of effect out to 10 years

Bisphosphonates in Oncology

- **Intravenous pamidronate (Aredia®) and zoledronic acid (Zometa®) are commonly used to treat patients with hypercalcemia of malignancy, multiple myeloma, and skeletal metastases, especially from breast and prostate**
- **Therapy may be additive with chemotherapy agents[1]**
- **Skeletal-related events are significantly reduced[2]**
- **Complications include**
  - Hypocalcemia
  - Flu-like syndrome after initial injection
  - Nephrotoxicity

[1] Budman DR, Calabro A. *Oncology*. 2006;70:147-153.
[2] Body JJ. *Support Care Cancer*. 2006;14:408-418.

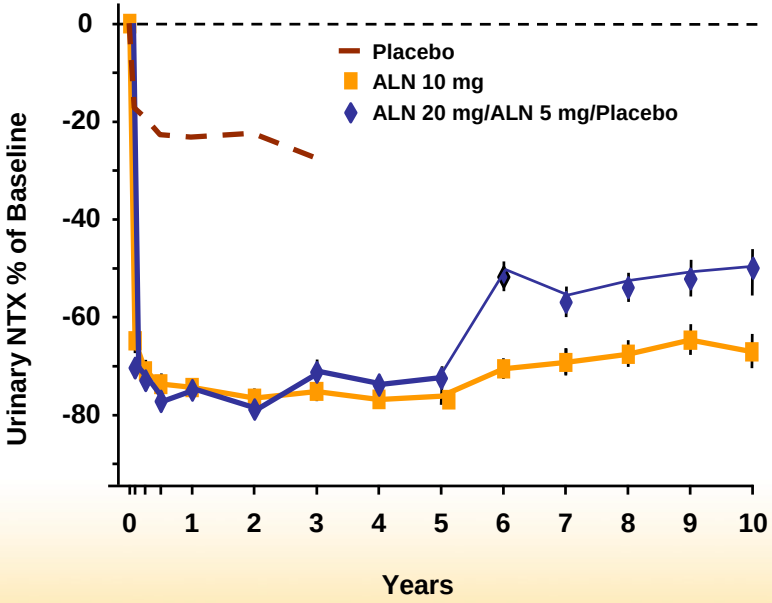
Bisphosphonates in Bone Tissue

- **Initially deposited on bone surface**
  - Half-life on surface is a few weeks (may differ among drugs)
- **Then buried in bone tissue**
  - In tissue, half-life is many years
- **Some recycling of stored drug**

Bisphosphonates: Long-term Effects in Humans

- Two studies (N=850) with alendronate followed for 10 years
- One study (N=83) with risedronate for 7 years
- Persistent but not progressive inhibition of bone turnover
- Bone biopsies demonstrate persistent bone turnover and no abnormal bone histology
- Fracture rates remain decreased
- No different adverse effects seen with long-term therapy

Discontinuing Alendronate Therapy



Bone HG, et al. *N Engl J Med.* 2004;350:1189.

Bisphosphonates and Osteoporosis

- **Bisphosphonates are the main treatment for patients with osteoporosis**
- **Treatment restores bone remodeling balance and effectively reduces fracture risk in adults with osteoporosis**
- **Long-term effectiveness has been demonstrated**
- **Therapy is well tolerated**
- **Benefits of treatment outweigh risks in patients at moderate or high risk for fracture**

Addressing the Patient With or At Risk for Bisphosphonate Related Osteonecrosis of the Jaws

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Faculty Disclosure

- **Thomas B. Dodson, DMD, MPH,** has a financial interest/arrangement with the following that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
  - *Paid Consultantship:* Spriggs & Hollingsworth

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Bisphosphonate Related Osteonecrosis of the Jaws: Working Definitions

- ***American Dental Association (ADA)*** **—Typical clinical presentation includes pain, soft-tissue swelling and infection, loosening of teeth, drainage, and exposed bone**
- ***American Society for Bone and Mineral Research (ASBMR)*** **— Typically appears as an area of exposed alveolar bone in the mandible or the maxilla. May or may not be painful. May or may not be associated with infection or local trauma. Most often develops after a recent tooth extraction or oral contusion/abrasion**
- ***American Association of Oral and Maxillofacial Surgeons (AAOMS)*** **—Exposed bone in the maxillofacial region that has persisted for >8 wks in the presence of current or previous treatment with bisphosphonates and absence of radiation treatment to the jaws**

How Common is BRONJ?

- **Among cancer patients exposed to IV bisphosphonates**
  - 0.8%–12%
- **May be more than 5000 cases nationwide[1]**
- **Among noncancer patients with osteoporosis taking oral bisphosphonates**
  - 0.7 cases per 100,000 patient years' exposure[2] to 0.34%[3]

1. AAOMS Survey launched 12/5/05
2. Merck & Co. data
3. Personal communication, Alastair Goss, DDS

Drug-Related Risk Factors

- **IV bisphosphonates >> oral**
  - Zoledronate > pamidronate >> oral bisphosphonates[1]
- **Duration of therapy appears to be associated with increased risk of BRONJ**
  - IV bisphosphonates: cases increase with number of doses and duration of follow-up[2]
  - Oral bisphosphonates: most cases described after 3 years of therapy[3]

1. Durie et al. *N Engl J Med*. 2005;3531:99-102
2. Bamias et al. *J Clin Oncol*. 2006;23:8580-8587.
3. Marx et al. *J Oral Maxillofac Surg*. 2005;63:1567-1575.

Local Risk Factors

- **Dentoalveolar procedures**
  - 7-fold increased risk in patients receiving IV bisphosphonates and oral bisphosphonates
- **Local anatomy**
  - Exostoses, tori
- **Concomitant inflammatory dental disease**

Demographic/Systemic Risk Factors

- **Age**
- **Race**
- **Cancer diagnosis**
  - Multiple myeloma > breast > other
- **Corticosteroids, diabetes, smoking, alcohol use, poor oral hygiene, thalidomide**
  - May be associated with BRONJ

Patient Reassurance and Education

- **At the initial consult:**
  - Bisphosphonates are excellent medications for metastatic bone disease and osteoporosis
  - Bisphosphonate use is a risk factor for BRONJ
  - BRONJ is a new and potentially serious problem
  - BRONJ is manageable

Bisphosphonate Related Osteonecrosis of the Jaws: Definition for Patients

- **What is BRONJ?**
  - Area of jaw bone that has lost its blood supply
- **Why is it a problem?**
  - BRONJ can lead to infection and delayed healing after dental surgery

BRONJ Management Goals

- **Support patient's oncologic or osteoporotic treatment**
- **Prevent development of BRONJ**
- **Preserve quality of life**
  - Pain control
  - Prevent extension of the lesion and development of new lesions
  - Not expected to resolve

Skepticism is the chastity of the intellect.

Don't give it away to the first comer!

CDC

Bisphosphonate Related Osteonecrosis of the Jaws: *The Role of the Dentist in the Care of Patients on Bisphosphonate Medications*

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Faculty Disclosure

- **John E. Fantasia, DDS,** has no financial interset/arrangement with the following companies that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

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Why This Topic is Important to Dentists

Dentists

- **will be required to evaluate and treat patients prior to bisphosphonate therapy**
- **are likely the first to identify patients with signs and symptoms of BRONJ**
- **will be required to customize treatment plans in patients on varied bisphosphonate regimens and those with BRONJ**

Bisphosphonate Agents

Generic

- Pamidronate
- Zoledronic acid
- Alendronate
- Risedronate
- Ibandronate

Commercial

- Aredia®
- Zometa®
- Fosamax®
- Actonel®
- Boniva®

Which Patients Are at Risk for BRONJ?

- **Oncology patients being treated with IV bisphosphonates**
  - Malignancies and related conditions
    - Multiple myeloma
    - Metastatic breast cancer
    - Prostate cancer
- **Patients taking oral bisphosphonates for osteoporosis and some rare bone diseases (eg, Paget's disease)**
  - Postmenopausal women
  - Older men

Clinical Features

- **Asymptomatic**
  - Exposed bone
- **Symptomatic**
  - Swelling
  - Pain
  - Fistula formation
  - Purulence
  - Sequestration
  - Tooth loss
  - Paresthesia
  - Pathologic fracture

Radiographic Features

Early stage

- No change or minimal change

Late stage

- Sclerotic lamina dura
- Poorly defined radiolucency
- Radiopaque sequestrum

Clinical and Radiographic Differential Diagnosis of BRONJ

- **Early Stage**
  - Limited differential
- **Later Stage**
  - Periodontal disease
  - Inflammatory periapical pathology
  - Osteomyelitis
  - Metastatic disease
  - Lymphoma of bone
  - Other pathologies

Bisphosphonates

Resorption
(inhibition)

vs

Remodeling
(inhibition)

Dental Evaluation and Treatment

- **Prior to bisphosphonate use**
  - Extractions and periodontal surgery prn
  - Optimally maintain dentition and periodontium
- **Post or continued bisphosphonate use**
  - Optimally maintain dentition and periodontium
  - Avoid extractions, endodontics preferred
  - Avoid procedures that will require bone remodeling, ***if possible***

Source: AAOMS position paper

What Oral & Maxillofacial Surgeons Need To Know

Salvatore Ruggiero, DMD, MD
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SUNY at Stony Brook
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Department of Oral and Maxillofacial Surgery
Stony Brook, New York

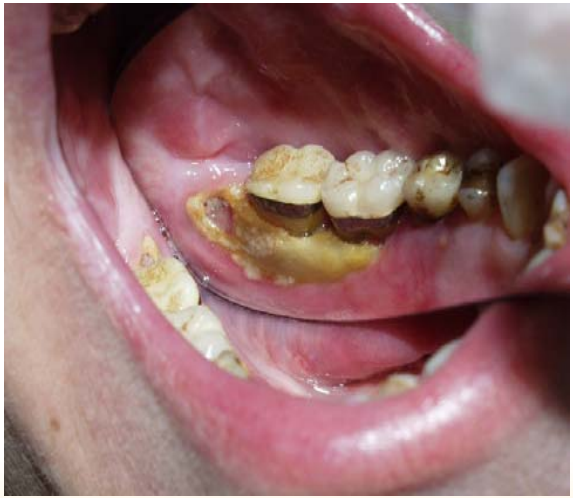
Treatment Objectives in the Management of BRONJ

- **Eliminate pain**
- **Manage or eliminate infection**
- **Prevent additional exposure/necrosis**

Staging

Stage 1

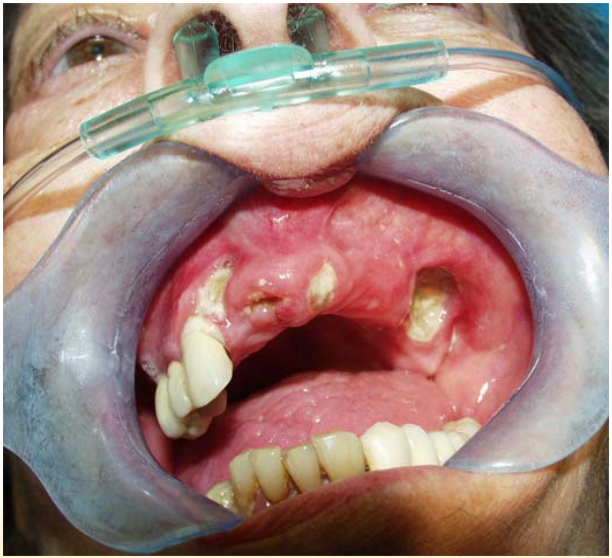
- Characterized by exposed bone that is asymptomatic, with no evidence of significant soft-tissue inflammation



Staging

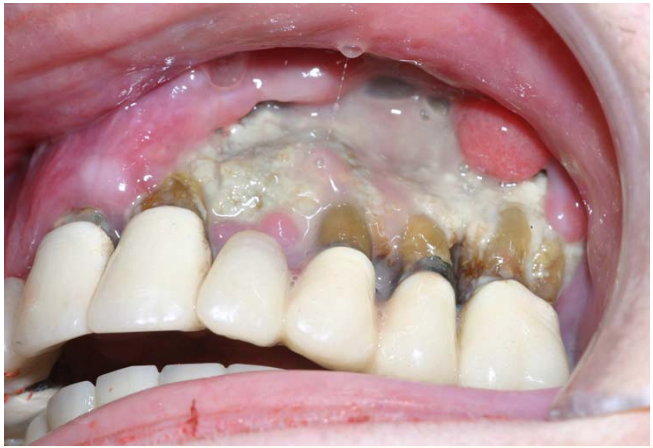
Stage 2

- Exposed bone associated with pain, soft-tissue and/or bone inflammation or infection



Staging

Stage 3



- Pathologic fracture
- Exposed bone associated with soft-tissue inflammation/infection or pain that is not responsive to antibiotics due to the volume of necrotic bone
- Extraoral fistula
- Osteolysis extending to the inferior border

Treatment Recommendations

Clinical Scenarios

- Prior to bisphosphonate therapy (IV)
- During bisphosphonate therapy (IV, PO)
- Patients with established BRONJ

Treatment Recommendations

Prophylactic treatment prior to initiating IV bisphosphonate therapy (ORN model)

ORN: Osteoradionecrosis

- Patients should undergo a routine clinical dental exam that may include a panoramic radiograph to detect potential dental and periodontal infections
- Remove abscessed and non-restorable teeth and teeth with severe periodontal disease
- Remove teeth with poor long-term prognosis
- Functionally rehabilitate salvageable dentition
- *Educate patients* on oral hygiene and signs of disease

Treatment Recommendations

Asymptomatic patients receiving *IV* bisphosphonate therapy

- Avoid invasive dental procedures where possible
- Maintain routine dental cleanings, avoid soft-tissue injury (especially at lingual plate and tori)
- Ensure good fit of dentures
- Aggressively manage dental infections non-surgically (root canal tx if possible)
- Regular dental assessments after initiating bisphosphonate therapy (frequency dependent upon risk)
  - Ibandronate 3 mg/3 months (IV) for treatment of osteoporosis
  - Zoledronic acid in Phase III trials (4 mg/yr) for treatment of osteoporosis

Treatment Recommendations

Asymptomatic patients receiving *oral* bisphosphonate therapy

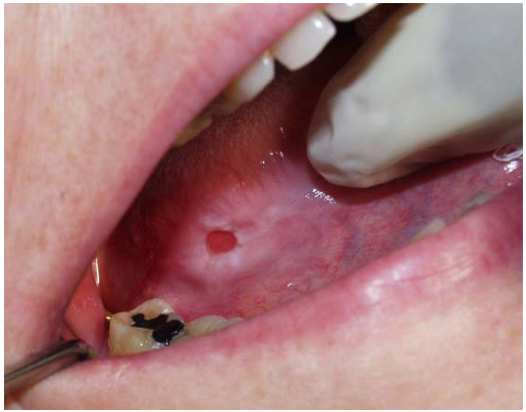
- Much lower risk but not zero (less than 1%)
  - Merck data: 0.7 cases per 100,000 patient yrs[1]
  - Australian data: 0.01%-0.04 [2]
  - Israeli data: 0.01% (unpublished)
- Dentoalveolar surgery not contraindicated
- Consider stopping treatment for 3 months prior to and restarting after bony healing

1. Merck & Co., Inc. data on file
2. JONS, March 2007

Treatment Recommendations

All patients (all stages) with established BRONJ

- *Consultation* between oral and maxillofacial surgeons, general dentists and the treating physician is strongly recommended
- *Superficial* bony debridement to reduce sharp surfaces and prevent further trauma to adjacent soft tissues



- *Protect exposed bone* or adjacent tissues; a removable appliance or protective stent may be used
- *Avoid* invasive dental procedures where possible

Treatment Recommendations

Patients with established BRONJ

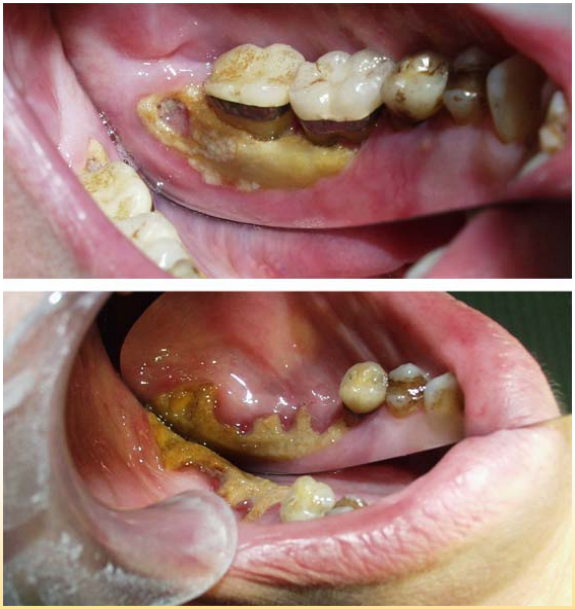
- Biopsy is not recommended unless metastasis to the jaw is *strongly* suspected
- Decisions regarding stopping bisphosphonate therapy should be made in consultation with the treating physician and oral and maxillofacial surgeon, taking into account the potential risk of further osteonecrosis versus the risk of skeletal complications
  - *Benefit of bisphosphonates > risk for most patients*

Treatment Recommendations

Patients with established BRONJ

Stage 1

- A non-surgical approach is recommended to prevent further osseous injury
- Daily irrigation and oral antimicrobial rinses (0.12% chlorhexidine)
- Clinical follow-up every 3 months

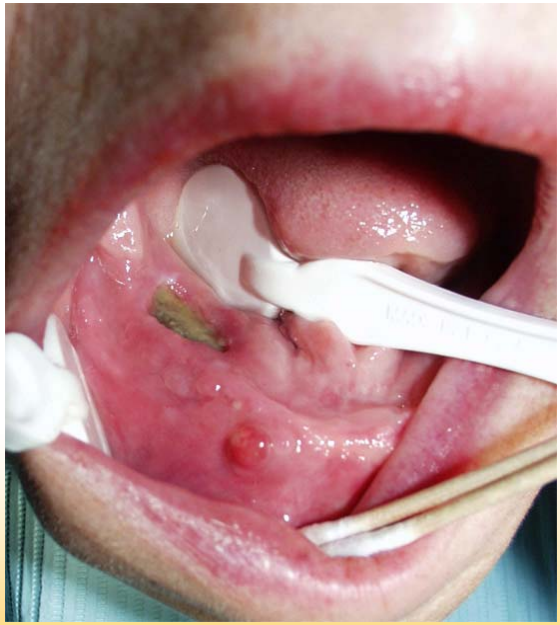


Treatment Recommendations

Patients with established BRONJ

Stage 2

- Culture-directed antibiotic therapy (long-term and maintenance)
- Pain control
- Daily irrigations and oral antimicrobial rinses (0.12% chlorhexidine)
- Clinical follow-up every 3 months

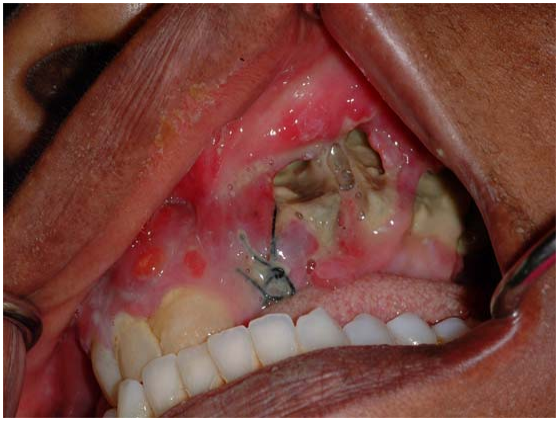


Treatment Recommendations

Patients with established BRONJ

Stage 3

- Culture-directed antibiotic therapy (PO/IV, long- term and maintenance)
- Pain control
- Daily oral antimicrobial rinses (0.12% chlorhexidine)
- Surgical debridement/resection to reduce the volume of necrotic bone



Future Directions: What is Unknown and How Can We Learn More?

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Faculty Disclosure

- **Richard Gliklich, MD** has a financial interest/arrangement with the following companies that could be perceived as a real or apparent interest in the context of the subject of this presentation.
  - Research Contracts/Grants: Harvard University, Outcome

- ***Safeguard*: This presentation has been peer reviewed to ensure an evidence-based presentation free of bias.**

Treating Community Needs Information

- **Clinicians who see patients on treatment for osteoporosis with or at risk for osteonecrosis want to know:**
  - What are the risk factors
  - How to mitigate risk
  - How to counsel patients about bisphosphonate risk/use
  - How to manage patients
  - What are the most likely patient outcomes

Background

- **Several different case definitions are in use and the full spectrum of disease may not yet be known**
- **Bisphosphonate exposure is presumed to be an important risk factor, and has become entangled with case definition**
- **Little is known about prevalence, incidence, and natural history**
  - Risk factors are unclear
  - Antecedent factors prior to disease onset have not been clarified
  - Short-term and long-term outcomes are unknown
- **Prevention and management strategies have not been scientifically studied**

Weak Information on Prevalence and Incidence

- **Current estimates are based on anecdotal reports, single institution case series, standard passive surveillance systems (MEDWATCH) and safety reports to pharmaceutical manufacturers**
- **These estimates have poor validity because of lack of a standardized case definition, incomplete reporting, and the lack of information that could be used to quantify a denominator ("source" population)**

Risk Factors Are Poorly Understood

- **Sociodemographic characteristics (age, gender, race, SES)**
- **Comorbid medical conditions (eg, cancer, osteoporosis, diabetes)**
- **Bisphosphonate exposure (duration, dose, PO versus IV, specific drug, compliance with treatment)**
- **Concomitant medication use (eg, corticosteroids, immunotherapy)**
- **Health behaviors (smoking, alcohol abuse, nutrition)**
- **Other antecedent factors (dental procedures, trauma)**

Role of Population-Based Studies

- **Population-based studies are needed:**
  - To understand the relative public health impact
  - To counsel patients
  - To monitor changes in rates as new drugs are introduced
  - To identify patients for specific clinical studies

How Can We Scientifically Learn More

Active Surveillance Registries

An Active Surveillance Registry

- **Multi-stakeholder initiative**
  - Professional associations
  - Foundations
  - Advocacy groups
  - Manufacturers
  - Government agencies

An Active Surveillance Registry?

- **Registry: to inform cohort and case-control studies**
  - Surveillance network of clinicians to whom most cases present in specified geographic areas (oral & maxillofacial surgeons, some other dentists)
  - Estimate source population via US census data[1]
  - Standardized, structured clinical data collection on potential risk factors, clinical course, and outcomes
  - Case review and adjudication
  - Cohort analysis to estimate prevalence and incidence; case-control sub-study to examine role of bisphosphonates

[1]eg, Johnson LN & Arnold AC. Incidence of nonarteritic and arteritic anterior ischemic optic neuropathy. *J Neuro-Opthalmol*, 1994;14:38-44.

What Can We Learn

- **Rates (eg, point prevalence, period prevalence)**
- **Risk factors/Antecedent factors**
  - Sociodemographic characteristics
  - Comorbid conditions
  - Bisphosphonate or other osteoporosis drug exposures
  - Other medication use
  - Health behaviors
  - Other antecedent factors
- **Prevention, management, outcomes**

Summary

- **With respect to osteonecrosis of the jaws, much is unknown**
- **Properly understanding the individual risks and public health impact are necessary for clinicians to provide sound guidance and treatment to patients. This need demands that we learn more**
- **Population based studies**
  - An Active Surveillance Registry is a scientific approach to learning more

Questions & Answers

- **Enter questions in the text box to the right or email your question to livewebcast@cecity.com**

Questions & Answers

- **Welcome to the Question and Answer section of the presentation.**

Question #1

- **Due to the varied sources of public information, many post-menopausal women are believing that they should discontinue use of oral bisphosphonates or increase the risk of losing their teeth. What is the best response to give these patients, Dr. Ruggiero?**

Question #2

- **How receptive have pharmaceutical companies involved and specialty groups, who would be prescribing bisphosponates, been to the recommendations and treatment strategies outlined in the AAOMS/BRONJ Guidelines?**

Question #3

- **Why suggest a drug holiday when a patient requires oral surgery if the effects of the meds are permanent and irreversible?**

Question #4

- **Has this osteonecrosis process been identified in locations other than the jaws, if not, why?**

Question #5

- **Is there a risk of developing BRONJ in patients receiving IV boniva once every three months or zometa once per year for the treatment of osteoporosis?**

Question #6

- **In his lecture at the last AAOMS meeting on this subject, Dr. Robert Marx talked about a blood test, the CTX, as an indication of the patient's ability to remodel bone. Is there any relevance to this test? Should we be ordering it on our patients who have been on oral bisphosphonates for more than three years, as he suggests? How about the same question in patients having received IV bisphosphonates at doses for severe osteoporosis and cancer?**

Question #7

- **The histology/microbiology reports from patients with bisphosphonate induced necrosis often come back with actinimicites infection identified. Do you think this could be a risk factor for the severity of the osteonecrosis and should patients identified as positive for actinimicites be treated for this, that is with long term penicillin therapy?**

Question #8

- **What are the current recommendations for a patient with a patholgic fracture of the mandible secondary to BRONJ? I began seeing this patient before BRONJ was identified, and she had a patholgic fracture of the mandible that I tried to bone graft. The graft failed, and currently I have the defect bridged with a mandibular reconstruction plate.**

Question #9

- **What is the status with the placement of dental implants? Is it safe to place dental implants in patients who are taking oral bisphosphonates?**

Question #10

- **On a practical basis, what would you do with a patient that must have several teeth extracted but has been on Fosamax for the last few years? What would be your post-op expectations?**

Question #11

- **Is previously bound BP that is released during remodeling effective at a clinical level to decrease OClast activity? i.e. can the BP have a double effect over time.**

Question #12

- **Can you explain patient years exposure?**

Question #13

- **Typically, on a patient on Alendronate, how long after extraction can or has been BRONJ reported to occur? 5 weeks or 6 months, for example.**

Question #14

- **Did I understand that the residual bisphosphonate in bone has no clinical effect?**

Question #15

- **Are there any animal models available to study BRONJ? If yes, what have been found?**

Question #16

- **Dr. Ruggiero, although most oral surgeons have seen this BRONJ in their clinical practice, you perhaps, have one of the larger series of patients. Do you have any outcomes of treated patients?**

Question #17

- **Would you describe how a surveillance network is created?**

Closing Remarks

- **Thank you for participating in this activity.**