Antiresorptives
(Bisphosphonates, Denosumab)

“Concerns to Dentistry”

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No Conflict of Interest
Find Information

Antiresorptives

- **Position Papers**: ADA, Council on Scientific Affairs
  Dental Specialty organizations

- **Dental Specialists** (Local): Experience

- **Pub Med Search**: Research Dental Questions
  - Evaluate abstract
  - Read article: University faculty
  - Private practice - Subscribed journals (JADA)
    - ADA ($7 discounted fee)
    - Medical Library

- **Ebd.ada.org**: Systematic Reviews
WELCOME TO A WEBSITE FOR EVIDENCE-BASED DENTISTRY
A practical resource for scientific evidence
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A practical approach to integrating evidence into your patient care!

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- Comparison of whole body positron emission tomogra...

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- Fluoride Supplements
- Oral Cancer Screening
- Reconstituting Infant Formula
- Sealants
- Topical Fluoride

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Additional support for evidence-based practice. Read more
- ADA Library: Member Access for Cochrane Reviews
- Cochrane Library
- JADA
- PubMed

FOR THE PATIENT
Learn More

Volunteer to become an ADA Evidence Reviewer.

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HIGHLIGHTS
- Promote EBD on your own website - click here!
- Save the Date! Next EBD Champions Conference scheduled for April 25-27, 2013
- Listen here - Podcast for the ADA’s Clinical Recommendations on Nonfluoride Caries Preventive Agents
- ADA Members: Access Cochrane Systematic Reviews Here
- Access the 2012 EBD Champions Conference Presentations
- Access Chairside Guides to ADA Clinical Recommendations
- Subscribe to the EBD website for automatic content updates
Evidence Based Practice

Evidence

Clinical Expertise

Patient Wants & Needs

EBP

Benefit vs. Risk
Osteonecrosis of the Jaw (ONJ)

Suspected Risk: Multiple observations

Pub Med: weak evidence (case report, series)

1860 - 1910 Phossy Jaws


Worker inhalation of white phosphorus
Tooth pain and mobility
Extraction: bone loss, infection

2002 Osteonecrosis of the Jaws (ONJ)


High dose bisphosphonate for Bone Cancer treatment

Tooth pain and mobility (after endo/perio)
Extraction: continued bone loss, infection
Osteonecrosis of the Jaw (ONJ)

Increasing Discovery with Bisphosphonate use

Pub Med: Limited evidence (Japan nationwide study)

1st study: 28 cases ONJ (up to 2006)


Trigger event: Extraction ~ 40% (108 cases)
Curettage - 2 cases
Implant - 1 case
Biopsy - 1 case
Osteonecrosis of the Jaw (ONJ)

“Exposed necrotic bone for 8 weeks, Prior bisphosphonate or denosumab use, No history radiation treatment to jaws”

Stage 1: Asymptomatic

Chlorhexidine rinse 3 x daily, Observe healing

Refer oral surgeon, Inform MD, Report FDA

Courtesy: D. Guyot
Osteonecrosis of the Jaw (ONJ)

Stage 2: Painful, localized infection

Chlorhexidine rinse, Antibiotics, Observe healing

Refer oral surgeon, Inform MD, Report FDA

Courtesy: SB Woo
Osteonecrosis of the Jaw (ONJ)

Stage 3: Severe infection, outside alveolus

Chlorhexidine rinse, Antibiotics, Hospitalization

Refer oral surgeon, Inform MD, Report FDA

Courtesy: SB Woo
Osteonecrosis of the Jaw (ONJ)

Stage 3  Post extraction
Life-threatening infection : Block resection alveolus
Osteonecrosis of the Jaw (ONJ)

**High dose Bisphosphonate : Bone cancer**

**EBD.ADA.ORG** - Limited evidence: systematic review  
2 prospective cohort, 3 retrospective (2,659 patients)


- **Prevalence** : 1 - 12%  (after 12 month BP use)

- **Morbidity** : More extensive  (throughout jaw)

Not easily treated, usually controlled
Osteonecrosis of the Jaw

High dose Bisphosphonate : Bone Cancer

Pub Med: weak evidence (case reports, expert opinion)
Migliorati C et al. JADA 2005; 136: 1658-68

Osteonecrosis prevention

- No elective dental surgeries- keep soft tissue intact
  No extractions, No perio surgery, No implants

Root canals, root scaling, restorative: OK
(non-aggressive to tissue or bone)
Osteonecrosis of the Jaw

Low dose Bisphosphonate : Osteoporosis

ADA, Council on Scientific Affairs : Limited evidence: retrospective

Hellstein JW et al. JADA 2011;142:1243-51

Prevalence : Rare  ~  1: 1000  (1,2)

Extractions  ~  1: 300 – 1: 23  (2, 3)

Morbidity : Localized  (usually stage 1-2 )

Easily treated

Osteonecrosis of the Jaw

Proper term: New Drug

ADA, Council on Scientific Affairs

*Hellstein JW et al. JADA 2011;142:1243-51.*

**ARONJ** — Anti-Resorptive OsteoNecrosis of the Jaws

**Denosumab** : Not Bisphosphonate

- Denosumab
  - Decreases osteoclast formation
  - Does not stay in bone

- Bisphosphonate
  - Decreases osteoclast function
  - Accumulates & stays within bone

Bisphosphonate & Denosumab

- Decrease osteoclast activity (bone resorption) ~ 70 - 80 %
- Decrease osteoblast activity (bone formation) ~ 50 - 60%
Anti Resorptive Osteonecrosis

New Drug : Denosumab

Pub Med: Good evidence (random control trials)

Fizazi K et al. Lancet 2011 Mar 5;377(9768):813-22.

**High Dose Denosumab : High prevalence** (2-5% Osteonecrosis)
Xgeva : Bone cancer treatment - same prevalence as bisphosphonate

**Low Dose Denosumab: Rare** Osteonecrosis
Pharmaceutical Company (Amgen): Weak evidence (case reports)
Prolia : Osteoporosis treatment
Bisphosphonate

Multiple Elimination Rates

Pub Med: Limited evidence (small clinical trials alendronate/pamidronate)


BP Elimination: blood (1 day), bone surface (3 month), bone incorporated (10 year)

<table>
<thead>
<tr>
<th>Blood / Bone Surface</th>
<th>Bone Incorporated</th>
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<tbody>
<tr>
<td>BP elimination:</td>
<td>50% 25%</td>
</tr>
</tbody>
</table>

![Concentration (ng/ml) vs. Time (days)](image)
Bisphosphonate
Inhibits epithelial healing

Progression of evidence

- Decreased epithelial cell growth  (cell culture)

- Decreased epithelial healing post extraction  (rats, dogs)

- Decreased epithelial healing post extraction  (prospective cohort)
Osteonecrosis Prediction

Radiographic Signs

Patients taking low dose bisphosphonate
Radiographic PDL widening prior to extraction

83% Osteonecrosis

(only 11% healed normally)

Widened PDL – Higher risk osteonecrosis for extractions

Early Osteonecrosis Detection

Stage 0

AAOMS / ADA, Council on Scientific Affairs

Patients taking low dose BP (especially after 2 years use)

Stage 0 - No necrotic bone observed

- No dental explanation: symptoms/signs

Symptoms: Pain, tingling (tooth, sinus, mandible radiating TMJ)

Signs: Clinical: Tooth mobility

Fistulas

Radiographic: Sclerotic lamina dura

PDL widening

Osteolysis
Excessive Decreased Bone Function
Stage 0

Sclerosis PDL

Dental: Lower posterior PAs

Progress Ortho: All teeth moved

Changed Radiographic Signs: Bisphosphonate use (Denosumab?)
(unexplained dentally)
Excessive Decreased Bone Function

Stage 0

Widened PDL
(mandibular posterior teeth)

Changed Radiographic Signs: Bisphosphonate use (Denosumab ?)
(unexplained dentally)
Excessive Decreased Bone Function
Stage 0

Non-healed Extraction (6 months)

After extraction:  Bisphosphonate use (Denosumab?)
Evaluate soft tissue healing - clinically
Evaluate bone healing - Radiograph 3-6 months
Medicine Position

**Low dose BP : Osteoporosis**

Pub Med: good evidence (random controlled trials)

**Benefit**

- Prevents 50-75% fractures (hip, vertebra) (1:40-200)


- 40% patients noncompliant BP (1st year) : No benefit
  Explain risks not to affect compliance/benefit


- Benefit may stop after 5 year BP use (hip)
  Vertebral fracture prevention benefits up to 10 yr. BP use

Medicine Position

Low dose BP : Osteoporosis

PubMed: Limited evidence

Risk (5 year bisphosphonate use)

50% Increased atrial fibrillation
Bhuriya R et al. It J Cardiol. 2010 Jul 23;142(3):213-7 (4 RCTs)

2 fold increased esophageal cancer
Green J et al. BMJ 2010 341: 4444. (Large case controlled)

Mild increase atypical fractures
Subtrochanteric or Femoral Fractures
Decreased bone repair, hypermineralization
Park-Wyllie LY et al. JAMA 2011; 305: 783-789. (Large case controlled)
Oral Surgery Position

Low dose Bisphosphonate : Osteoporosis

Extraction: Osteonecrosis Prevention

American Association of Oral Maxillofacial Surgeons
Consider: Drug holiday (with MD approval)
3 mo before & after dental surgery
Weak evidence: expert opinion – osteonecrosis healed better

ADA, Council on Scientific Affairs
Drug holiday: Not recommended
May decrease benefit & compliance, no evidence decreased risk

Consider to limit infections:
Primary closure or semi perm. membrane over extraction site
Chlorhexidine rinse, Amoxicillin 2000mg prophylaxis
Periodontology Position

Low dose Bisphosphonate: Osteoporosis

ADA, Council on Scientific Affairs

Periodontal disease (infection source): osteonecrosis risk
Atraumatic techniques as possible to access roots

American Academy of Periodontists

No position

Periodontist decision: procedural benefit > ARONJ risk
Dental Implant Position

Low dose Bisphosphonate: Osteoporosis

ADA, Council on Scientific Affairs

No effect: short term implant success

Very low risk: osteonecrosis

Hellstein JW et al. JADA 2011;142(11):1243-51

American Association of Oral Maxillofacial Surgeons

Informed consent: possible future implant failure & osteonecrosis

Dental Implant Position

Low dose Bisphosphonate : Osteoporosis

Pub Med: Limited evidence, large retrospective studies

- **Success same, no osteonecrosis**
  Retrospective study: 121 implants BP/ 166 implants control

- **4 year success same, no osteonecrosis**
  Systematic review : 3 controlled, 1 case series (217 pt / 840 implants)

- **3% failure, no osteonecrosis**
  Retrospective large case series: 589 pts BP & implants (Kaiser)

- **Increased ½ % failure , 5 cases osteonecrosis**
  Retrospective survey: 16,000 pts. / 5% oral BP 800 pts (South Australia)
ADA, Council on Scientific Affairs

Dentures are risk factor for osteonecrosis
Recall, adjust removable appliances: minimal tissue pressure
Restorations: minimal trauma to bone
Endodontontology Position

Low dose Bisphosphonate : Osteoporosis

ADA, Council on Scientific Affairs

- Preferable to extraction
- No manipulation beyond root apex

American Association of Endodontists

- Before endo: Consider ARONJ for non dental cause
- Routine endo: no risk
- After endo: symptomatic; evaluate ARONJ before surgical endo
Pediatric Dentistry Position

Low dose Bisphosphonate : Osteoporosis

ADA, Council on Scientific Affairs

No Position

American Academy of Pediatric Dentistry

No osteonecrosis found : BP treatment for osteogenesis imperfecta

Unsure effect on erupting teeth

Concerned with decreased orthodontic tooth movement
Orthodontic Position

Low dose Bisphosphonate: Osteoporosis

ADA, Council on Scientific Affairs
BP compromises tooth movement

American Association of Orthodontists
BP inhibits tooth movement
May lengthen time or stop moving at undesirable position
No orthodontist can predict: BP individual effect
Case #1  **Ortho Initial: 60 yr female**, alendronate 18 months

(small left condyle, periodontitis #14,15)

Mild sclerosis lower posterior teeth - normal?
Case #1

Excessive Decreased Bone Function

Stage 0

(Ortho 2 years, Alendronate 3 ½ years)

Sclerosis, Widened PDL spaces

No tooth movement, Periodontitis #14-15
Orthodontics

Low dose Bisphosphonate : Osteoporosis

Extraction cases (7 BP, 31 control)

- Increased treatment time (38 mo. vs. 27 mo.)
- Greater risk: Non space closure (13x > control)
  Non-parallel roots (26x > control)

Non-Extraction cases - no difference noted
(13 BP, 62 control)

Lotwala, R et al. AJODO 2012: 142:625-634.
Small retrospective controlled cohort (20 BP, 93 control)
Case #1

Extraction (lower left bicuspis): 12 months orthodontics
Alendronate 12 months

Difficult space closure – Non parallel roots
Excessive Decreased Bone Function

Stage 0

Extraction site
Hyper-mineralized

No tooth movement into site
(BP incorporated into site?)

Lower Anteriors
Widen PDL

2+ mobility
No tooth movement
Case #3

Initial: 70 year old female (alendronate 3 years)

#24 crown fractured (unrestorable)

Temporarily bonded # 24, need orthodontic plan
Case #3  

Excessive Decreased Bone Function

Stage 0

Obscured, Sclerotic PDL  (alendronate 3yr.)

BP Risk: Increased osteonecrosis risk with extraction
Little tooth movement or bone healing
Case #3

Call M.D. - BP Benefit Achieved (bone density increased)

- BP Discontinued by MD (recheck bone density 2 yrs)

Extract #24 (3 months after BP stopped)
Orthodontic space closure (normal outcome -14 months)
Case #3

**Final:** No mobility, PDL space OK

Bone healed normally

Mild root resorption #25

(ebd.ada.org : no effect longevity)
Antiresorptive (AR) Therapy

Bisphosphonate/Denosumab

Dental Considerations - Prior AR Therapy

Clinical exam for infections

Radiographs: FMX evaluate for infections
   Very important for High dose AR for bone cancers

Treat any suspected infections hard/soft tissue
   Very important for High dose AR for bone cancers

Emphasize good hygiene & routine visits
   Prevent infection
Antiresorptive (AR) Therapy
Bisphosphonate/Denosumab

Dental Considerations - During AR Therapy

Emphasize: *Good oral hygiene & routine visits: prevent infection*

History/Exam: **Stage 0: Pain or tingling teeth or jaw, tooth mobility, fistula**

Exam: **Oral soft tissue overlying bone for clinical ARONJ**

Especially over tori & posterior lingual of mandible

Radiographs: **Mandibular posterior PAs yearly after 2 yrs. AR therapy**

Stage 0 changes (no dental cause)

Sclerosis, Widened PDL, Osteolysis
Antiresorptive Therapy (AR)

Bisphosphonate/Denosumab

Dental Considerations - ARONJ suspected

Define Stage 0, 1, 2, or 3

Refer & Treat

Contact prescribing physician
   Evaluate Risk vs. Benefit of AR therapy

Report to FDA
   Suspected drug adverse reaction
Anti-Resorptives

Bisphosphonates, Denosumab

WHAT IS YOUR POSITION?
Too Much Information!
Afraid of Risk
(Little Appreciation of Benefit)
Risk Occurred!
Observe & Report

Understand Drug & Dental Procedural Benefits Before Communicating Risks

AUG 17 2004
Thank You!

Report suspected adverse drug effect to FDA (few minutes):
www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm