Quick Reference Guide
Decreasing the Risks of Developing Drug Induced Osteonecrosis of the Jaws (DIONJ)

Adapted from the Division of Oral & Maxillofacial Surgery Position Statement

UNIVERSITY OF MIAMI

ORAL&MAXILLOFACIAL SURGERY

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Drug Induced Osteonecrosis of the Jaws

Exposed non-healing bone in the mandible or maxilla that persists for more than eight weeks in a person who received a systemic drug known to cause ONJ but who has not received local radiation to the jaws.

ICD-10 Code

M87.180 ***Drug Induced Osteonecrosis***

DIONJ Staging

Stage O:

- Radiographic evidence of bisphosphonate toxicity

Stage I:

- Exposed bone limited to one quadrant

Stage II:

- Exposed bone involving two quadrants

Stage III:

- Exposed bone involving three or four quadrants
- Osteolysis/Extension to Inferior Border of Mandible
- Pathologic Fracture
- Extension in to Maxillary Sinus or Nasal Cavity

OFFENDING DRUGS

Decreasing Risks of Drug Induced Osteonecrosis of the Jaws (DIONJ)

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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	1%
Zoledronate (Reclast)	Bisphosphonate	Osteoclast Toxicity	5 mg/yr	IV	6%
Denosumab (Prolia)	Monoclonal Antibody	Osteoclast Impairment	60 mg/6 mos	Subcutaneous	10%

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	Subcutaneous	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.

Bisphosphonates

- Cause osteoclast death at resorption sites
- Cause osteoclast precursor inhibition and death in bone marrow
- Half-Life= 11+ years in bone

Denosumab (Xgeva or Prolia)

- Osteoclast inhibition at resorption sites
- Osteoclast inhibition in blood and tissue spaces
- Osteoclast precursor inhibition in bone marrow
- Half-Life= 26 days in bone

Bevacizumab (Avastin)

- Blocks Action of VEGF in normal cells and cancer cells
- Half-Life= 50 days in bone

Sunitib (Sutent)

- Blocks action of multiple Growth Factors (VEGF, PDGF, TGF-b, etc)
- Half-Life= 4.6 days in bone

Risk Factors

- **Increased Dose (Fosamax vs. Boniva)**
- **Increased Potency (Oral vs. IV)**
- **Increased Frequency (Weekly vs Monthly vs Yearly)**
- **Half-Life (in bone)**
- **Duration of Use/Exposure**

Initiating Factors

- **Extractions**
- **Spontaneous**
- **Traumatic Occlusion**
- **Alveolar Surgery (Implants, Periodontal, Apicoectomy)**

Vulnerable Sites

- **Alveolar Bone**
- **Tori**
- **Mandible >Maxilla 2:1**
- **Lingual Cortex**

Co-Morbidities

Comorbidities Do Not Cause ONJ-

But they do make the ONJ Occur Sooner, More Severe, and More Extensive

- *****Other Drugs (Chemotherapy, Methotrexate, Steroids)*****
- **Diabetes**
- **Smoking**
- **Cancer**
- **Periodontitis,**

Guiding Treatment Decisions with CTX

Indications for the Serum CTX Test

- Patients on Oral or IV Bisphosphonates for *Osteoporosis*.
  - Those with 2+ years of Bisphosphonate Treatment (with additional comorbidities)
  - Those with 3+ years of Bisphosphonate Treatment (without additional comorbidities)
- Guide Treatment Decisions
  - Determination of Need for Drug Holiday Prior to Surgery
  - Monitoring Bone Turn-Over Improvement Drug Holiday
- Results ≥ 151 pg/ml = generally safe to proceed with surgery

The Serum C-Terminal Telopeptide CTX Can Predict Risk Related To Oral Bisphosphonates

CTX	≤ 100 pg/ml	= high risk
CTX	101 to 150 pg/ml	= moderate risk
CTX	≥ 151 pg/ml	= little or no risk

How to Order Serum CTX Test

- CTX (Collagen Type 1 C-Terminal Telopeptide)
  - AM Fasting Serum Draw
  - Report Results in pg/mL
  - Please Fax Results to: xxx-xxx-xxxx
    - ICD-10 Dx Code:
      - M87.180 Drug Induced Osteonecrosis (use this code when there is evidence of exposed bone)
      - Z03.6 Disorder of Bone Unspecified (use this code for screening/pre-op evaluation when there is no evidence of exposed bone)
    - CPT Code: 82523
  - Quest Lab Test Reference Code: 17406
  - LabCorp Test Reference Code: 500089

CTX values improve significantly with discontinuance of the oral bisphosphonates

CTX Limitations

- **Active Cancer Patients-** (Patients with Metastatic Cancer, Multiple Myeloma- being treated with IV Bisphosphonates) show False High CTX results.
- **Methotrexate Patients-** CTX results remain too low
- **Systemic Steroid Patients-** CTX results remain too low
- **8+ years of Bisphosphonates-** CTX results will first rise and then decrease again.

A 9-12 Month Drug Holiday is used instead to guide treatment decision and timing of surgery.

OSTEOPOROSIS PATIENTS (Oral Bisphosphonates / IV Reclast / S.C. Denosumab)
Recommendations BEFORE Initiating Drug Therapy

Dental/OMFS Examination
Prophylaxis/Dental Hygiene/Periodontal Treatment
Caries Control
Endodontic Therapy / Crown & Bridge
Fluoride Carriers / Rx Fluoride Toothpaste
Lighten Excessive/Heavy Occlusal Contacts (Balanced Occlusion)
Extraction of Non-Salvageable/Hopeless Teeth
Selective Removal of Excessively Large/Multi-Lobulated Tori

*****Non Surgical Restorative/General Dental Care Is Safe At All Times******

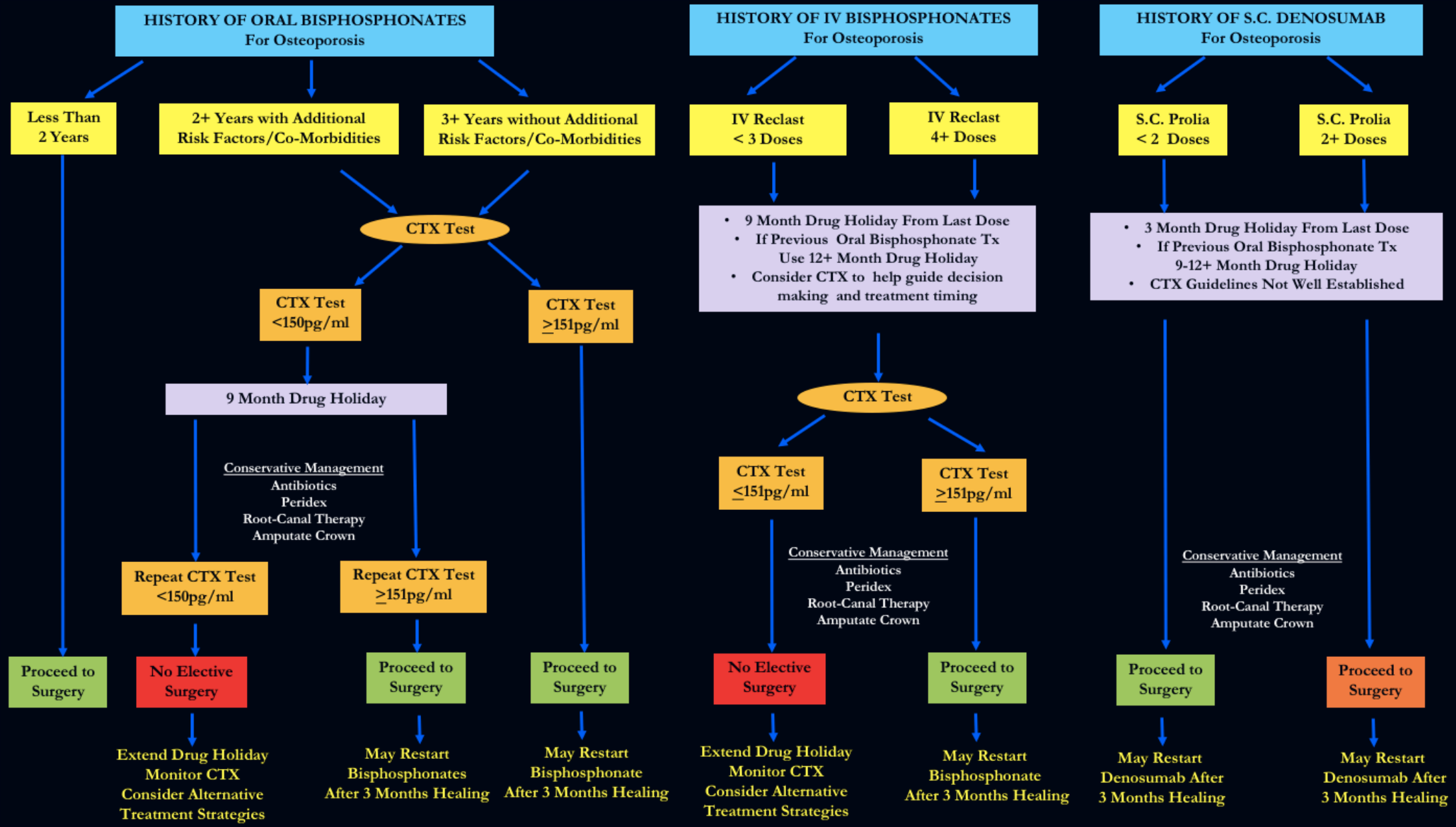
Oral Bisphosphonate
(Fosamax, Actonel, Boniva, etc)
DIONJ Risk Increases Between
2-3 Years of Use

IV Bisphosphonate
(Reclast/Zolendronate)
DIONJ Risk Increases By 4th Dose
Keep In Mind Many Patients May Have Been On Oral Bisphosphonate Before

S.C. RANK-L Inhibitor
(Prolia/Denosumab)
DIONJ Risk Increases After 2 Doses
Keep In Mind Many Patients May Have Been On Oral Bisphosphonate Before

If Elective Dental Treatments (Including Extractions, Periodontal Surgery, Dental Implants) Are Completed
3-6 Months Before Reaching These Risk Thresholds, Routine Wound Healing & Osseointegration Is To Be Expected

OSTEOPOROSIS PATIENTS (Oral Bisphosphonates / IV Reclast / S.C. Denosumab)
Recommendations DURING Drug Therapy



OSTEOPOROSIS PATIENTS (Oral Bisphosphonates /IV Reclast/ S.C. Denosumab)
Management of Exposed Bone / DIONJ

Initial Conservative Management

- Avoid Debridements /Invasive Surgical Procedures
- OK to Smooth Sharp Edges For Patient Comfort
- Pain is Related to Secondary Infection- Treat With Antibiotics & Antimicrobials:
  - Chlorhexidine (0.12%) Rinse
  - Penicillin VK 500mg- 1 tab po q6h x 14 days
  - Doxycycline 100mg - 1 tab po q day x 14 days
- Refractory Cases add :
  - Flagyl 500mg- 1 tab po TID x 10 days
- Consider Antifungal Treatment
  - Mycelex Troches
  - Nystatin Rinse

Drug Holiday
Oral & IV Bisphosphonates- 9 Months
SC Denosumab- 3 Months

50% of Patients

Spontaneous Resolution of DIONJ

☺

40% of Patients

Require Alveolar Debridement or Local Alveolar Resection to Achieve Resolution of DIONJ

☺

10% of Patients

Require Aggressive Surgical Management to Achieve Resolution of DIONJ

Mandible
Continuity Resection
Titanium Reconstruction Plate

Maxilla
Submucosal Resection / Antrostomy/Radical Sinusotomy
2 Layer Closure-
Buccal Fat Pad Reconstruction with Mucosal Advancement Flap

Adjunctive Growth / Healing Factors
PRP- Platelet Rich Plasma
PRF- Platelet Rich Fibrin

**Future bone-graft reconstruction may be considered **

CANCER PATIENTS (IV Bisphosphonates / S.C. Denosumab)
Recommendations BEFORE Initiating Drug Therapy

Dental/OMFS Examination
Prophylaxis/Dental Hygiene/Periodontal Treatment
Caries Control
Endodontic Therapy / Crown & Bridge
Fluoride Carriers / Rx Fluoride Toothpaste
Lighten Excessive/Heavy Occlusal Contacts (Balanced Occlusion)
*****Non Surgical Restorative/General Dental Care May Continue Up To & After Initiation of Drug Therapy******

Extractions of Non-Restorable Teeth, Teeth With Poor Prognosis
Alveoloplasty & Smooth Of Sharp Bone Edges
Primary Closure

Selective Removal of Tori & Exostoses (Excessively Large/Multi-Lobulated)

*****2 Months Healing Before Commencing IV Bisphosphonates/ SC Denosumab Is Preferred If Possible/Agreed Upon By Medical Oncologist. However, Timely Cancer Treatment Remains Greater Priority*****
Risk Factors Increase By 4th Dose of IV Bisphosphonate or 2nd Dose of SC Denosumab-
So Treatment May Still Be Initiated & Completed Within This 2-4 Month Window

CANCER PATIENTS (IV Bisphosphonates / S.C. Denosumab) Recommendations DURING Drug Therapy

Dental/OMFS Examination
Prophylaxis/Dental Hygiene/Supragingival Scaling
Caries Control
Endodontic Therapy / Crown & Bridge
Fluoride Carriers / Rx Fluoride Toothpaste
Splint Mobile Teeth
Exercise Caution When Taking Intraoral Radiographs & Using Rubber-Dam Clamps To Avoid Traumatizing Mucosal Tissues
*****Non Surgical Restorative/General Dental Care Is Safe******

Elective Extractions & Periodontal Surgery Contraindicated

- After 4th Dose of IV Bisphosphonate
- After 2nd Dose S.C. Denosumab

Elective Dental Implant Surgery Contraindicated

- After 4th Dose of IV Bisphosphonate
- After 2nd Dose S.C. Denosumab

Drug Holiday & Conservative Non-Surgical Management Is Preferred

Antibiotics & Chlorhexidine Rinse To Manage Pain and Infection
Non-Restorable Tooth- Consider Root Canal Therapy with Amputation of Crown (Leaving Roots in Place)
Incision & Drainage

Medically Necessary / Emergent Conditions Not Amenable to Drug Holiday and/or Conservative Measures

Informed Consent / Proceed to Surgery (Atraumatic/Minimally-Invasive)
Consider Use of Adjunctive Growth/Healing Factors (PRP or PRF)
Monitor Healing Closely

CANCER PATIENTS IV Bisphosphonates / S.C. Denosumab
Management of Exposed Bone / DIONJ

60 % of Patients
Can Be Managed to Achieve
Pain-Free / Infection-Free State
With Continued Exposed Bone
(No Surgery Required)

Initial / Long-Term Conservative Management

- Avoid Debridements /Invasive Surgical Procedures
- OK to Smooth Sharp Edges
- Pain is Related to Secondary Infection- Treat With Antibiotics & Antimicrobials:
  - Chlorhexidine (0.12%) Rinse
  - Penicillin VK 500mg- 1 tab po q6h x 14 days
  - Doxycycline 100mg - 1 tab po q day x 14 days
- Refractory Cases add :
  - Flagyl 500mg- 1 tab po TID x 10 days
- Consider Antifungal Treatment
  - Mycelex Troches
  - Nystatin Rinse

40% of Patients
Require Surgical Intervention

IF SURGERY IS UNAVOIDABLE
(Severe Chronic/Refractory Infections, Oral-Cutaneous Fistula, Pathologic Fracture, Stage III DIONJ)
Medical Oncologist Consult for Possible Drug Holiday With Close Cancer Monitoring

Pre-Op Drug Holiday
IV Bisphosphonates- 9 Months
SC Denosumab- 3 Months

SURGICAL INTERVENTION

Mandible
Alveolectomy
Continuity Resection
Titanium Reconstruction Plate

Posterior Maxilla
Alveolectomy / Submucosal Resection / Antrostomy/Radical Sinusotomy
2 Layer Closure- Buccal Fat Pad Reconstruction with Mucosal Advancement Flap

Anterior Maxilla
Alveolectomy/Submucosal Resection
Nasal Floor Involvement Requiring Resection (Generally Not Necessary)

Bone-Graft Reconstruction
Generally Not Feasible

Soft-Tissue Reconstruction
Pedicled Myocutaneous or Microvascular Free-Flap may be used if necessary

Adjunctive Growth / Healing Factors
PRP- Platelet Rich Plasma
PRF- Platelet Rich Fibrin

Post-Op
Drug Holiday
3 Months

RESOLUTION of DIONJ ☺

DIONJ Pharmacological Treatment Options

ANTIMICROBIAL RINSE

- Chlorhexidine 0.12%- Swish/Spit 15ml TID

PRIMARY ANTIBIOTIC CHOICES

- Penicillin VK 500mg PO q6h x 14 days
- Doxycylcine 100mg po qday x 14 days (Antibiotic of choice in Penicillin Allergic Patients)
- Add Flagyl 500mg PO q8h x 10 days for refractory cases

SECONDARY ANTIBIOTIC CHOICES

- Levaquin 500mg po q day x 7 days & Flagyl 500mg PO q8h x 10 days, (Extended Courses of Levaquin- Risk of Tendon Rupture)
- Erythromycin 400mg PO q8h x 7 days & Flagyl 500mg PO q8h x 10 days
- Ciproflaxacin 500mg PO q12h x 7 days, & Flagyl 500mg PO q8h x 10 days
- Unasyn 1.5g IV q6h & Flagyl 500mg IV q8h for hospitalization

MOST COMMON MICROBIAL ORGANISMS

- **Actinomyces**
- **Veillonella**
- **Eikenella**
- **Moraxella**

LONG TERM ANTIBIOITICS

- **Penicillin VK and Doxycycline are acceptable long-term options with low side effects**

INEFFECTIVE ANTIOBIOTICS

- **Clindamycin**

INEFFECTIVE THERAPIES FOR DIONJ

- **Ozone Treatment**
- **Hyperbaric Oxygen**
- **Laser Treatment**
- **Pentoxyfiline**

Decreasing Risks of Drug Induced Osteonecrosis of the Jaws (DIONJ)

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Oral Bisphosphonates for Osteoporosis:

- Risk of DIONJ Significantly Increases after 2-3 years of treatment
- Surgical procedures may be safely performed if:
  - CTX ≥ 151pg/ml
  - 9 Month Drug Holiday pre-op
  - 3 Month Drug Holiday post-op
- Dental implants are possible if placed and and permitted to osseointegrate in accordance with Drug Holiday and/or CTX Guidelines
- Beware that patients with 8+ years of bisphosphonate history (as CTX results first rise and then drop again, meaning a longer drug holiday may be necessary).
- Consider use of growth/healing factors (PRP or PRF)

IV Bisphosphonate (Reclast/Zolendronate) for Osteoporosis:

- Risk of DIONJ Significantly Increases by 4th dose
- Invasive surgical procedures are preferably avoided, with strong consideration for alternative procedures such as root canal therapy, or other conservative non-surgical management.
- If surgical intervention is necessary-
  - CTX ≥ 151pg/ml
  - 9 Month Drug Holiday pre-op
  - 3 Month Drug Holiday post-op
- Dental Implants may be considered if placed and osseointegrated in accordance with Drug Holiday and/or CTX Guidelines prior to receiving 4th dose.
- Keep in mind that many patients have previously been on an oral bisphosphonate, and therefore DIONJ RISK IS SIGNIFICANTLY HIGHER. A longer drug holiday is indicated. Consider CTX guidance in decision making/timing.
- Consider use of growth/healing factors (PRP or PRF)

Sub Cutaneous Injection of RANK-L Inhibitor Prolia (Denosumab) for Osteoporosis:

- Risk increases after 2 Doses
  - CTX guidelines not well /fully established at present time.
  - 3 Month Drug Holiday pre-op
  - 3 Month Drug Holiday post-op
- Keep in mind that many patients have previously been on an oral bisphosphonate, and therefore DIONJ RISK IS SIGNIFICANTLY HIGHER. A longer drug holiday is indicated.
- May consider possible CTX guidance in decision making/timing.
- Consider use of growth/healing factors (PRP or PRF)

IV Bisphosphonate (Zometa/Zolendronic Acid, Aredia/Pamidronate) for Metastatic Cancer:

- Risk of DIONJ Significantly Increases by 4th dose
- Invasive surgical procedures are preferably avoided, with strong consideration for alternative procedures such as root canal therapy, or other conservative non-surgical management.
- If surgical intervention is necessary:
  - 9 Month Drug Holiday pre-op
  - 3 Month Drug Holiday post op
  - During Drug Holiday- close monitoring of cancer by Medical Oncologist
- CTX NOT Useful or Indicated in Cancer Patients
- Consider use of growth/healing factors (PRP or PRF)

Sub Cutaneous Injection of RANK-L Inhibitor Xgeva (Denosumab) for Metastatic Cancer:

- Risk of DIONJ increases after 2 Doses
- Invasive surgical procedures are preferably avoided, with strong consideration for alternative procedures such as root canal therapy, or other conservative non-surgical management.
- If surgical intervention is necessary:
  - 3 Month Drug Holiday pre-op
  - 3 Month Drug Holiday post-op
  - During Drug Holiday- close monitoring of cancer by Medical Oncologist
- Keep in mind that many patients previously been on an IV Bisphosphonate and therefore DIONJ RISK IS SIGNIFICANTLY HIGHER. A longer drug holiday (9-12+ months) is indicated
- CTX NOT Useful or Indicated in Cancer Patients
- Consider use of growth/healing factors (PRP or PRF)

IV VEGF Inhibitor (Bevacisumab / Avastin)

- Too few cases exist for guidelines at present time
- Informed consent and proceed with caution
- Consider use of growth/healing factors (PRP or PRF)

IV Tyrosine Kinase Inhibitor (Sutinib / Sutent)

- Too few cases exist for guidelines at present time
- Informed consent and proceed with caution
- Consider use of growth/healing factors (PRP or PRF)

Decreasing Risks of Drug Induced Osteonecrosis of the Jaws (DIONJ)
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Drug Holiday

- **Safe and Effective**
- **Should be initiated by the prescribing physician**
- **Allows for sufficient repopulation of functional osteoclasts to aid in healing**
- **Should extend for 3 months postoperatively to permit sufficient healing**

Alternatives to Anti-Resorptive Medications for Osteoporosis (No Mechanism or Risk of DIONJ)

- **Calcium & Vitamin D3**
- **Raloxifene (Evista)**
- **rhPTH1-34 (Forteo)**

Oral Bisphosphonate With "Lowest Risk" of DIONJ

- **Boniva (Ibandronate)**

Effects Of Continuing Or Stopping Alendronate After 5 Years Of Tx

Black DM, Schwartz AV, Ensrud KE, et. al. JAMA December 27, 2006 Vol. 296 No 24

Conclusions: Women who discontinued alendronate after 5 years showed a moderate decline in BMD and a gradual rise in biochemical markers but no higher fracture risk other than for clinical vertebral fractures compared with those who continued alendronate. These results suggest that for many women, discontinuation of alendronate for up to 5 years does not appear to significantly increase fracture risk. However, women at very high risk of clinical vertebral fractures may benefit by continuing beyond 5 years.

JAMA Editorial- Alendronate: "Five Years of a good thing is enough

Colon-Emeric CS. JAMA. 2006 Dec 27;296(24):2968-9

FDA Statement, September 2011

September 9, 2011: Joint Meeting of the Reproductive Health Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting Announcement

- Every woman on bisphosphonates for osteoporsis must be re-examined after 3 years
- Nobody needs to take bisphosphonates for osteoprososis for more than 5 years