Bisphosphonates
Risks and Rewards
Osteoporosis

- Literally means “porous bones”
- 300,000 people in Ireland have osteoporosis
- 1 in 3 women over 50 (1 in 2 over 65) and 1 in 5 men will develop an osteoporotic fracture
- Due to our changing demographics, by 2031 it is estimated that 500,000 people could have osteoporosis in Ireland
• In the over 60 years of age group:
  – 20% of Irish people who fracture a hip will die within 6-12 months
  – 50% of those that survive will not be able to wash, dress or walk unaided
Osteopenia

- Refers to Bone Mineral Density (BMD) that is lower than normal peak BMD but not low enough to be classified as osteoporosis
- BMD is assessed using a DXA scan
DXA scan

• Dual-energy X ray Absorptiometry
• 2 xray beams at different energy levels are aimed at the patient’s bones. When soft tissue absorption is subtracted out the BMD can be determined from the absorption of each beam by bone.
• The resulting T test score compares the patient’s BMD with that of a healthy 30 year old.
Hip Fractures

• The most common presentation of undiagnosed osteoporosis

• The cost of osteoporotic hip fractures to the Irish Government is estimated to be €402 million annually

• Across the EU the cost of osteoporotic fractures is €36 billion and is greater than that for breast cancer, prostrate cancer and myocardial infarction
Bisphosphonates

- Pyrophosphate analogues
- Share a phosphorous-carbon-phosphorous chemical core, therefore very stable
- Demonstrated an ability to inhibit the precipitation of calcium phosphate
- Principal action is to inhibit resorption of bone thereby increasing the mineral density of bone and reducing serum calcium levels
Mechanism of Action

- There are 2 classes of BPs which have different mechanisms of action:
  - Non nitrogen containing BPs are taken up by the osteoclast and cause cell apoptosis
  - Nitrogen containing BPs have a more complex mechanism of action where they affect the osteoclastogenesis, apoptosis and cytoskeletal dynamics
Bisphosphonate Mechanism of Action

Drug released from bone post-resorption

Inhibits osteoclastic functions

Attaches to bone surface, especially regions of active resorption

No ruffled border
No adherence to bone
No proton production

Lack of bone resorption

Hwang and Wang, 2007
<table>
<thead>
<tr>
<th>Bisphosphonate Name</th>
<th>Indications</th>
<th>Dose/Dosage (for Osteoporosis)</th>
<th>Administration Requirements (for Osteoporosis)</th>
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</thead>
<tbody>
<tr>
<td>Alendronate (Fosamax)(^{16})</td>
<td>Prevention and treatment of osteoporosis in postmenopausal women Treatment to increase bone mass in men with osteoporosis Treatment of glucocorticoid-induced osteoporosis</td>
<td>Prevention</td>
<td>35-mg tablet weekly</td>
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<td></td>
<td>Treatment</td>
<td>5-mg tablet daily</td>
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<td></td>
<td>Administration Requirements (for Osteoporosis)</td>
<td></td>
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<tr>
<td>Ibandronate (Boniva)(^{12,18})</td>
<td>Prevention and treatment of osteoporosis in postmenopausal women</td>
<td>Prevention 2.5-mg tablet daily</td>
<td>Same as prevention dosage</td>
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<tr>
<td></td>
<td></td>
<td>Treatment</td>
<td>150-mg tablet monthly</td>
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<td></td>
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<td>Administration Requirements (for Osteoporosis)</td>
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<tr>
<td>Risedronate (Actonel)(^{19})</td>
<td>Prevention and treatment of osteoporosis in postmenopausal women Treatment to increase bone mass in men with osteoporosis Prevention and treatment of glucocorticoid-induced osteoporosis</td>
<td>Prevention 75 mg 2 consecutive days/month</td>
<td>Same as prevention dosage</td>
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<tr>
<td></td>
<td></td>
<td>Treatment</td>
<td>5 mg/day</td>
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<td></td>
<td></td>
<td>Admission Requirements (for Osteoporosis)</td>
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<tr>
<td>Zoledronic acid (Reclast)(^{20})</td>
<td>Treatment of osteoporosis in postmenopausal women</td>
<td>Administration Requirements (for Osteoporosis)</td>
<td>A single 5-mg infusion once a year given intravenously over no less than 15 minutes in a 100-mL ready-to-infuse solution</td>
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</tbody>
</table>
### Appendix I  Bisphosphonate Preparations Currently Available in the US *

<table>
<thead>
<tr>
<th></th>
<th>Primary Indication</th>
<th>Nitrogen Containing</th>
<th>Dose</th>
<th>Route</th>
<th>Relative Potency**</th>
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<tbody>
<tr>
<td>Etidronate</td>
<td>Paget’s Disease</td>
<td>No</td>
<td>300 - 750 mg daily for 6 months</td>
<td>Oral</td>
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<td>(Didronel)</td>
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<tr>
<td>Tiludronate</td>
<td>Paget’s Disease</td>
<td>No</td>
<td>400 mg daily for 3 months</td>
<td>Oral</td>
<td>50</td>
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<td>(Skelid)</td>
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<tr>
<td>Alendronate</td>
<td>Osteoporosis</td>
<td>Yes</td>
<td>10 mg/day 70 mg/week</td>
<td>Oral</td>
<td>1,000</td>
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<tr>
<td>(Fosamax)</td>
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<tr>
<td>Risedronate</td>
<td>Osteoporosis</td>
<td>Yes</td>
<td>5 mg/day 35 mg/week</td>
<td>Oral</td>
<td>1,000</td>
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<tr>
<td>(Actonel)</td>
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<tr>
<td>Ibandronate</td>
<td>Osteoporosis</td>
<td>Yes</td>
<td>2.5 mg/day 150 mg/month</td>
<td>Oral</td>
<td>1,000</td>
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<td>(Boniva)</td>
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<td>Pamidronate</td>
<td>Bone Metastases</td>
<td>Yes</td>
<td>90 mg/3 weeks</td>
<td>IV</td>
<td>1,000 – 5,000</td>
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<td>(Aredia)</td>
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<tr>
<td>Zoledronate</td>
<td>Bone Metastases</td>
<td>Yes</td>
<td>4 mg/3 weeks</td>
<td>IV</td>
<td>10,000 +</td>
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<td>(Zometa)</td>
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</table>

*A once-yearly infusion of zoledronic acid for the treatment of postmenopausal osteoporosis is under FDA review. **

**Relative to etidronate
Remember, Duration and Potency
Approved Uses

• They were initially licensed for the management of the skeletal complications of malignancy

• Efficacy of controlling skeletal events and apparent low incidence of adverse effects has lead to an increase in applications including Paget’s disease, osteogenesis imperfecta and osteoporosis
BPs, Friend or Foe?

• BP treatment improves the clinical outcome of non surgical periodontal treatment and may be an appropriate adjunctive treatment to preserve periodontal bone mass
  • Lane et al, 2005
BPs, Friend or Foe?

- There is benefit to oral BP therapy in that it protects individuals against periodontal bone loss and osteoporosis. *Jeffcoat, 2006*

- A bisphosphonate coating has been shown to improve the fixation of metal implants in bone using a randomized trial of dental implants. *Abathi, 2012*
History of Bisphosphonate associated osteonecrosis of the Jaw

- The first clinical report of osteonecrosis associated with phosphorous compounds was in 1846
History

• Between 1840 and 1906 white phosphorous was the used in the matchmaking industry
• Affected workers would present with pain, subsequent exposure of the jaw bone and infection associated with sequestration
• Termed “Phossy Jaw”
• In pre-antibiotic era mortality was high
• In 1999 ulceration of the oral mucosa was reported as a complication of oral BP, however this was felt to be due to direct tissue trauma rather than the drug itself

• At this stage none of the clinical trials reported cases of BONJ
• In 2003, three groups of clinicians independently reported on osteonecrosis associated with the use of bisphosphonates.
• 2004, FDA sends letters to clinicians and alters packaging information to highlight the risk of BONJ
• 2006, Stephen Flint publishes an article in the JIDA highlighting the risk of BONJ in oral BP patients receiving certain dental treatments
Diagnosis of BONJ

• Tricky to define the condition when it can’t even be agreed what to call it!

• Definition given by the AAOMS
  – Patients may be considered to have BONJ if they have exposed bone in the maxillofacial region for at least 8 weeks, are currently on or have taken bisphosphonates and have no history of radiotherapy to the jaws
Pathophysiology of BONJ

• Unknown, but there are a number of theories which may solely or in part have merit:
  – Suppression of bone turnover
  – Soft tissue toxicity
  – Compounding effects such as the presence of infection, other medications or pathologies that may suppress bone or soft tissue healing
• BPs are taken up by the skeleton and produce most of their effects on osteoclasts when they resorb bone during remodelling. The BP is then released into the demineralized matrix within the osteoclast border and absorbed by it.

• This metabolic process is increased in response to trauma (including invasive dental treatment) and infection.
• BP are tissue toxic but concentrations in tissue are never high enough to produce the toxic effect
• BP may reduce vascularity of bone due to their anti-angiogenic properties, however histological studies have shown normal vasculature
Why does BONJ only affect the maxillofacial skeleton

• Unknown, however the answer is thought to be related to the relatively high turnover of alveolar bone, and to the exposure of the maxillofacial skeleton to the outside environment through the teeth and the periodontal ligament
• Recently in orthopaedics a new phenomenon termed the “hot spot” fracture has been attributed to oral BP therapy
Clinical Presentation

- Asymptomatic exposed bone without any evidence of erythema or discharge
- Presents in pain with evidence of local infection or widespread infection, a discharging sinus or even a pathological fracture
- There may be a clinical history of invasive dental treatment or trauma from a prosthesis
Radiographic Signs

generalized osseous sclerosis of uniform thickness involving the cortical plates and the lamina dura.
Staging of BONJ

- **Stage 0**: No apparent exposed/necrotic bone (signs/symptoms present)
- **Stage 1**: Exposed/Necrotic bone in asym pt, no evidence of infection
- **Stage 2**: Exposed/Necrotic bone associated with localised infection
- **Stage 3**: Exposed/Necrotic bone associated with pathological fracture, extra-oral fistula or extension into surrounding basal bone
Incidence of BONJ

- Difficult to establish
- Clearer picture of BPs administered IV but incidence rates vary from 0.94% to 10% in the literature
- Oral BPs have less follow up and incidence rates vary a lot but a range of 0.01-0.06% seems reasonable to assume.
- The sheer volume of prescriptions for oral BPs (190 million) mean that many cases will present
Risk Factors

• Drug Related
  – Duration and Potency of treatment

• Local Factors
  – Dentoalveolar surgery – 5-21 fold increase in BONJ with dentoalveolar sx and IV BPs
  – Local anatomy – mandible > maxilla, areas of thin tissue
  – Concomitant oral disease, IV BPs and periodontal disease have a 7 fold ↑ for developing BONJ
Management Strategies

• For patients about to start a course of IV BPs, the goal of treatment is to minimize the risk of developing BONJ

• If systemic conditions permit, initiation of IV BPs is delayed until dental health is optimised, i.e., 14-21 days for extraction site to mucosalised

• Examine prostheses for sharp edges
Implants and Bisphosphonates

- Good reports of implant success in patients on oral BPs
- Important to assess the duration and potency of BP treatment
- Patient specific risks should be considered and the patient appropriately consented
The “Drug Holiday”

• It is suggested that cessation of the BPs allows for regeneration of osteoclasts and so some improvement in bone turnover.
• Generally off BPs for 3 months pre procedure and 3 months after with medical consent.
• Only for patients on oral BPs for less than 3 years.
• Largely empirical evidence although some support from “extrapolated data”
Non Surgical Management

- If there is exposed bone but no signs of infection (AAOMS Stage 1) the treatment is CHX rinses and analgesia.
- Where there is exposed bone and localised infection (AAOMS Stage 2) antibiotics are advised. The choice of antibiotic and duration of the course is not clear from the literature with no broad consensus.
Surgical Treatment

• The goal of surgical treatment is the removal of necrotic bone and to create soft tissue coverage of healthy bone

• Difficult to do as there is no “clean” margin as the whole skeleton is affected

• Most commonly symptomatic bony sequestra are removed with minimal soft tissue disturbance

• If there are large segments of necrotic bone more radical surgical approaches are advocated
Management strategy at DUDH

- Conservative approach
- Peri-operative antibiotic
- CHX rinses
- No adrenaline in local anaesthetics
- Atraumatic extractions
- Pull down splint to protect extraction site
- If BONJ occurs and there is infection, use Augmentin and CHX rinses
Management at Mid West Regional

- Conservative
- 6 week course of doxycycline post treatment
- Atraumatic extractions
- CHX rinses
Take Home Message

• For patients on oral BPs there is a very low risk of developing BONJ (0.01-0.06%)
• There are ways to minimize the risk but not eliminate it
• Good OH and regular dental care is the best way to reduce risk of developing BONJ
• There are no diagnostic techniques to identify those at increased risk of BONJ
Take Home Message

- Explain treatment options and risks to patients and get good informed consent.
- Be conservative
- Keep exposed bone clean with CHX
- Treat local infection with antibiotics
- Reassure the patient and wait for sequestration of exposed bone
- Notify the Irish Medicines Board