Introduction
Bisphosphonates are an important class of drugs that have widespread use in managing osteoporosis and treating certain cancers. A recently recognized adverse effect, bisphosphonate-associated osteonecrosis of the jaws (ONJ), has important medical and dental implications. The American Association of Endodontists offers this Position Statement to help make our members aware of these implications. It is, of course, up to the individual endodontist to determine what course of treatment to undertake with respect to any given patient.

Bisphosphonates
Bisphosphonates are commonly used to treat certain resorptive bone diseases such as osteoporosis, Paget’s disease and hypercalcaemia associated with certain malignancies such as multiple myeloma and bone metastasis from the breast or prostate (Lipton 2003; Licata 2005; Lipton 2005). Bisphosphonates inhibit bone resorption by inhibiting osteoclast activity (Lindsay and Cosman 2001), although other actions such as inhibition of angiogenesis have also been reported (Wood et al. 2002; Santini et al. 2003; Vincenzi et al. 2005).

Bisphosphonate-Associated Osteonecrosis of the Jaws
There is growing recognition that bisphosphonates may be associated with a rare adverse event called osteonecrosis of the jaws (ONJ). Several case reports, letters to the editor, reviews and position statements from the U.S. FDA and interested pharmaceutical companies have been published on bisphosphonate-associated ONJ (Carter and Goss 2003; Marx 2003; Migliorati 2003; Hellstein and Marek 2004; Ruggiero and Mehrotra 2004; Carter et al. 2005; Cheng et al. 2005; Durie et al. 2005; Katz 2005; Markiewicz et al. 2005; Marx et al. 2005; Melo and Obeid 2005; Melo and Obeid 2005; Migliorati 2005; Migliorati et al. 2005; Migliorati et al. 2005; Novartis Pharmaceuticals Corporation 2005; Purcell and Boyd 2005; Sarathy et al. 2005; Wooltorton 2005; Zarychanski et al. 2006). Because there currently are no available randomized controlled trials or higher levels of clinical evidence, the following information is presented based on retrospective analysis of case reports and expert opinions.

Patients presenting with bisphosphonate-associated ONJ typically present with at least some of the following signs and symptoms:
• An irregular mucosal ulceration with exposed bone in the mandible or maxilla
• Pain or swelling in the affected jaw
• Infection, possibly with purulence
• Altered sensation (e.g., numbness or heavy sensation).

Additional important issues related to bisphosphonate-associated ONJ include:
• The site of occurrence of the osteonecrosis is the jaws, and presentation occurs more frequently in the mandible than in the maxilla. The reasons for the presentation of osteonecrosis in the jaws versus other parts of the skeleton are unknown at this time.
• The mechanism for bisphosphonate-associated ONJ is unknown.
• The treatment for bisphosphonate-associated ONJ is problematic. Case reports document no response or a limited response to local surgical wound debridement, marginal or segmental resection, antibiotics and hyperbaric oxygen. Therefore, recognition of risk factors and application of preventive dental treatment procedures are important for patients taking I.V. or oral bisphosphonates.

Common risk factors associated with the development of bisphosphonate-associated ONJ include:
• History of taking bisphosphonates, especially I.V. formulations. The concurrent use of steroids appears to contribute to this risk.
• Previous history of cancer (e.g., multiple myeloma or metastatic disease to bone), osteoporosis, Paget’s disease or other indications for bisphosphonate treatment.
• A history of a traumatic dental procedure. Most case reports occur after a tooth extraction, although other traumatic dental procedures may also be associated with the occurrence of ONJ. One case report describes bisphosphonate-associated ONJ occurring 6 months after placement of five dental implants with the subsequent loss of all implants (Starck and Epker 1995).
• Several reports indicate the spontaneous development of bisphosphonate-associated ONJ without a prior traumatic dental procedure.

A question exists as to whether bisphosphonate-associated ONJ is a drug effect (i.e., observed with only a few bisphosphonates) or a class effect (i.e., may occur with all bisphosphonates with the incidence varying according to potency or other factors). To date, the majority of reports have described ONJ occurring in patients taking I.V. bisphosphonates (e.g., zolendronate [Zometa®], or pamidronate [Aredia®]). However, in several publications, oral bisphosphonates have been associated with the development of ONJ (Starck and Epker 1995; Carter and Goss 2003; Marx 2003; Chang 2004; Ruggiero and Mehrotra 2004; Migliorati et al. 2005; Purcell and Boyd 2005). In addition, a recent FDA ODS Postmarketing Safety Review stated that bisphosphonate-associated ONJ “may be a class effect” (Chang 2004). Recently revised product packages for oral bisphosphonate medications (e.g., alendronate [Fosamax®] and risedronate [Actonel®]) now describe a risk for bisphosphonate-associated ONJ (Merck 2005; P&G 2005).

Therefore, until further information is available, it would appear prudent to consider all patients taking bisphosphonates to be at some risk for ONJ, with the recognition that the magnitude of the risk probably varies depending upon the particular bisphosphonate taken, patient factors (e.g., concurrent drugs, diseases, etc.), and dental treatment history. The information at this time suggest that patients taking I.V. bisphosphonates have a higher risk for developing ONJ, while patients taking oral bisphosphonates have a lower risk.

Examples of commercially available bisphosphonates include:

<table>
<thead>
<tr>
<th>Subclass of Bisphosphonate</th>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminobisphosphonate</td>
<td>Zolendronate</td>
<td>Zometa®</td>
<td>I.V.</td>
</tr>
<tr>
<td>Aminobisphosphonate</td>
<td>Pamidronate</td>
<td>Aredia®</td>
<td>Oral and I.V.</td>
</tr>
<tr>
<td>Aminobisphosphonate</td>
<td>Alendronate</td>
<td>Fosamax®</td>
<td>Oral</td>
</tr>
<tr>
<td>Aminobisphosphonate</td>
<td>Ibandronate</td>
<td>Boniva®</td>
<td>Oral and I.V.</td>
</tr>
<tr>
<td>Aminobisphosphonate</td>
<td>Risedronate</td>
<td>Actonel®</td>
<td>Oral</td>
</tr>
<tr>
<td>Nonaminobisphosphonate</td>
<td>Tiludronate</td>
<td>Skelid®</td>
<td>Oral</td>
</tr>
<tr>
<td>Nonaminobisphosphonate</td>
<td>Clodronate</td>
<td>Bonefos®, Ostac®</td>
<td>Oral</td>
</tr>
<tr>
<td>Nonaminobisphosphonate</td>
<td>Etidronate</td>
<td>Didronel®</td>
<td>Oral</td>
</tr>
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**Recommendations**

The following is recommended when considering the endodontic implications of treating patients taking bisphosphonates:

- Recognize the risk factors of bisphosphonate-associated ONJ.
- Patients at higher risk for bisphosphonate-associated ONJ include those patients taking I.V. bisphosphonates. Preventive procedures for high risk patients are important to reduce the risk of developing ONJ because treatment of ONJ is not predictable at this time. Preventive care might include caries control, conservative periodontal and restorative treatments, and, if necessary, appropriate endodontic treatment. Similar to the management of the patient with osteoradionecrosis, this might include nonsurgical endodontic treatment of teeth that otherwise would be extracted. Teeth with extensive carious lesions might be treated by nonsurgical endodontic therapy possibly followed by crown resection and restoration similar to preparing an overdenture abutment. For patients at higher risk of developing bisphosphonate-associated ONJ, surgical procedures such as tooth extractions, endodontic surgical procedures or placement of dental implants should be avoided if possible.
- Patients at low risk for bisphosphonate-associated ONJ include those patients taking oral bisphosphonates. Appropriate clinical procedures might include intraoral examination, indicated dental procedures (e.g., regular checkups, caries control, appropriate periodontal and restorative treatments), and patient education about the symptoms of bisphosphonate-associated osteonecrosis of the jaws and their low risk for developing ONJ from surgical or soft tissue procedures.
- As usual, informed consent for endodontic procedures should involve a discussion of risks, benefits and alternative treatments with the patient.
- Consider bisphosphonate-associated ONJ when developing a differential diagnosis of nonodontogenic pain.
- Utilize the entire health care team, including the patient’s general dentist, oncologist and oral surgeon, when developing treatment plans for these patients.
- Cases of bisphosphonate-associated osteonecrosis of the jaws should be reported to the U.S. FDA MedWatch Online at: [https://www.accessdata.fda.gov/scripts/medwatch/](https://www.accessdata.fda.gov/scripts/medwatch/). Additional background information on how to report adverse effects of drugs can be found at: [www.fda.gov/opacom/backgrounders/problem.html](http://www.fda.gov/opacom/backgrounders/problem.html).
- Be aware that the knowledge base for bisphosphonate-associated ONJ is rapidly increasing, and it is likely that these recommendations may change over time. Thus, the practitioner is encouraged to monitor developments in this area.

**References**


