

# Factors Associated with Osteonecrosis of the Jaw among Bisphosphonate Users

Lisa M. Hess, PhD,<sup>a</sup> Joanne M. Jeter, MD,<sup>a</sup> Marge Benham-Hutchins, RN, PhD,<sup>a,b</sup> David S. Alberts, MD<sup>a</sup>

<sup>a</sup>College of Medicine, Arizona Cancer Center, and <sup>b</sup>College of Nursing, University of Arizona, Tucson.

## ABSTRACT

**BACKGROUND:** Bisphosphonates are medications that impact bone reformation by inhibiting osteoclast function. Osteonecrosis of the jaw has been reported among patients receiving these medications. It is unclear if the risk factors associated with osteonecrosis of the jaw among cancer patients taking bisphosphonates also are possible risk factors among patients receiving these medications for other indications.

**METHODS:** A systematic review search strategy was used to identify cases of osteonecrosis of the jaw among patients taking bisphosphonates for an indication other than cancer to identify potential contributing factors. Data were analyzed according to previous models to develop a more expanded model that may explain possible mechanisms for the development of osteonecrosis of the jaw among patients without cancer.

**RESULTS:** Ninety-nine cases of osteonecrosis of the jaw were identified among patients who were prescribed a bisphosphonate for an indication other than cancer. These cases included 85 osteoporosis patients, 10 patients with Paget's disease, 2 patients with rheumatoid arthritis, 1 patient with diabetes, and 1 patient with maxillary fibrous dysplasia. The mean age was 69.4 years, 87.3% were female, and 83.3% were receiving oral, but not intravenous, bisphosphonates. Of the 63 patients reporting dental care information, 88.9% had a dental procedure before the onset of osteonecrosis of the jaw. Of all cases providing medical information, 71% were taking at least one medication that affects bone turnover in addition to the bisphosphonate, and 81.3% reported additional underlying health conditions.

**CONCLUSIONS:** The case details suggest a multiplicity of factors associated with this condition and provide the foundation for a model outlining the potential mechanism for the development of osteonecrosis of the jaw among patients taking bisphosphonates for an indication other than cancer.

©2008 Elsevier Inc. All rights reserved. • The American Journal of Medicine (2008) 121, 475-483

**KEYWORDS:** Bisphosphonates; Osteonecrosis of the jaw; Osteoporosis; Paget's disease

Bisphosphonates impact bone reformation by the inhibition of osteoclast function and are currently used to treat hypercalcemia of malignancy, bone metastases, Paget's disease, and osteoporosis. However, widespread use of bisphosphonates has been curbed by reports of osteonecrosis of the jaw among both cancer and osteoporotic patients receiving these medications. Although direct causation has not been established, the associated risk has been deemed sufficient for the US Food and Drug Administration and drug manufacturers

to include risk of osteonecrosis of the jaw in bisphosphonate package insert materials.

Osteonecrosis of the hip, knee, jaw, or other bones affects approximately 20,000 individuals per year.<sup>1,2</sup> Osteonecrosis of the jaw has been reported as a rare complication of bone disorders and phosphorus exposure since the 1830s.<sup>3</sup> However, many incident cases may have been underreported over the years, until it was noticed that osteonecrosis of the jaw was occurring among some patients receiving bisphosphonates.<sup>4</sup>

Hundreds of cases of osteonecrosis of the jaw have been reported to national adverse event reporting systems. Approximately 94% of reported cases among bisphosphonate users have occurred among cancer patients who receive the more potent intravenous bisphosphonate formulations.<sup>5</sup> Incidence estimates of osteonecrosis of the jaw vary consid-

This work was supported in part by NCI grants P30-CA023074 and R25T-CA078447.

Requests for reprints should be addressed to Lisa M. Hess, PhD, Arizona Cancer Center, Cancer Prevention and Control, 1515 N Campbell Avenue, Tucson, AZ 85724-5024.

E-mail address: [hess@u.arizona.edu](mailto:hess@u.arizona.edu)

erably, from 1 in 1260 to <1 in 100,000 osteoporosis patients.<sup>6,7</sup> Among those undergoing dental procedures, incidence may range from 1 in 296 to 1 in 1130.<sup>6,7</sup> Recent prevalence studies show that approximately 10%-50% of cases of osteonecrosis of the jaw occur among bisphosphonate users, while 50%-90% of cases occurred in the absence of these medications.<sup>8,9</sup> Equivalent rates of osteonecrosis of the jaw were shown among the bisphosphonate-treated as compared with the control population in a randomized zoledronate trial of 3889 osteoporosis patients.<sup>10</sup> The potential preventive effects of bisphosphonates are important; therefore, we have the responsibility to fully understand the attribution of side effects such as osteonecrosis of the jaw so that the risk-to-benefit ratio can be accurately represented to patients without cancer as well as to cancer patients. This knowledge will help to identify appropriate candidates for preventive care who stand to receive the most benefit with the least risk based on the presence or absence of risk factors for osteonecrosis of the jaw.

Although osteonecrosis of the jaw is known to occur in patients who have received bisphosphonates and those who have never been exposed to these medications,<sup>10,11</sup> it is unclear which patients may be at greatest risk. Recent oral surgery, tooth extraction, denture use, and poor oral hygiene are factors that have been implicated in osteonecrosis of the jaw among patients taking bisphosphonates.<sup>12-14</sup> Other risk factors for osteonecrosis of the jaw have been proposed and may include diabetes, comorbid conditions, and steroid use.<sup>15,16</sup>

Osteonecrosis in general has been associated with a wide variety of factors, including advanced age, arthritis, chronic inactivity, corticosteroids, estrogen, female sex, hemodialysis, thrombophilic disorders, hyperlipidemia, hypertension, infection, and many other disorders.<sup>2,13,17</sup> Published models of the possible contributing factors for osteonecrosis of the jaw have focused on issues related to bisphosphonate use in cancer populations, but may be useful to guide the exploration of potential contributing factors in patients taking bisphosphonates for indications other than cancer as well.<sup>13,18</sup>

This study was designed to identify cases of osteonecrosis of the jaw in patients taking bisphosphonates for an indication other than cancer to identify potential contributing factors that may be unique to this population. Data were collected using a systematic review strategy to obtain information related to previous models of osteonecrosis of the jaw among cancer patients (Figure 1) and prior suggested

risk factors.<sup>2,13,17</sup> The goal was to develop a model that may explain possible mechanisms for the development of osteonecrosis of the jaw in patients with no history of cancer who receive bisphosphonates.

### CLINICAL SIGNIFICANCE

- Osteonecrosis of the jaw among patients taking bisphosphonates for an indication other than cancer appears to occur:
- In patients over the age of 60 years;
- Following invasive dental procedures, such as tooth extraction;
- Among patients with underlying medical conditions, in addition to their bone disease;
- Among patients receiving multiple drugs affecting bone metabolism.

### METHODS

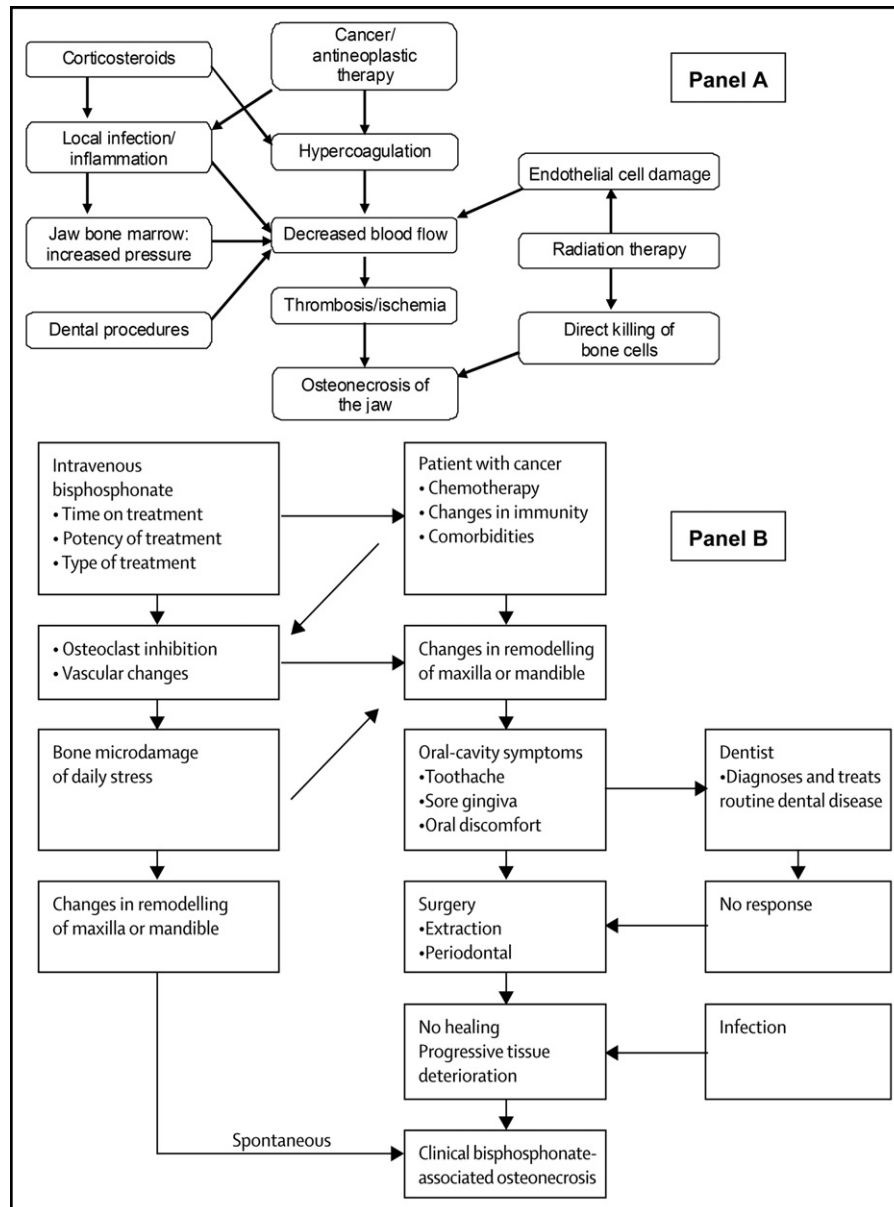
A systemic review was conducted to identify cases of osteonecrosis of the jaw among individuals receiving bisphosphonates for an indication other than cancer. The search included articles published from January 1996 through October 2007. Prior reviews<sup>16,19-21</sup> were used to identify cases that may have been published before 1996. The Medline search strategy included any of the following terms: “bisphosphonate,” “risedronate,” “ibandronate,” “alendronate,” “pamidronate,” “etidronate,” “etidronic acid,” “clodronate,” “clodronic acid,” “tiludronate,” “zoledronate,” or “zoledronic acid.” These terms then were combined with the expanded terms “osteonecrosis” or “jaw.”

A second Medline search was performed in which each bisphosphonate term was utilized with a category term for clinical trials. Each clinical trial was reviewed to assess the reported adverse events for indications of osteonecrosis of the jaw among study participants without cancer.

Articles were excluded if they were letters, case reports, or reviews exclusively related to a cancer population, if the abstract specifically stated there were no cases of osteonecrosis of the jaw, the article focused only on treatment or diagnosis, or if the article did not reference specific cases of osteonecrosis of the jaw. Articles published in languages other than English were translated by MultiLingual Solutions, Inc. (Rockville, Md). Citations from the obtained articles also were reviewed. Data about patient age, sex, diagnoses, concomitant medications, dose and duration of bisphosphonate use, and dental procedures were abstracted. To be eligible, a published case must have explicitly stated the diagnosis of osteonecrosis in the jaw. All citations were reviewed to identify potential case duplication. Authors of published articles were contacted in an attempt to obtain any unpublished clinical information that would make data for this study complete. Potential factors for the development of the proposed model of risk factors were restricted to those characteristics in at least 40% of cases.

### RESULTS

The initial Medline search strategy resulted in 6132 articles that included a bisphosphonate term. This number was reduced to 199 when the expanded terms osteonecrosis



**Figure 1** Models of the development of osteonecrosis of the jaw among cancer patients treated with bisphosphonates. Reprinted with permission from Elsevier Limited and Lancet Oncology, respectively. Panel A<sup>13</sup>; Panel B<sup>18</sup>.

crisis and jaw were required. The article abstracts were reviewed, and 37 articles were obtained for review. An additional 42 articles were identified within the citations of articles reviewed. Several of the full case reports<sup>22-24</sup> were preceded by brief commentaries;<sup>25-27</sup> thus, only the more recent report of those cases was included to avoid duplication. Cases that were reported in more than one publication were limited to the more recent or most detailed publication. The clinical trials search resulted in 72 zoledronate, 286 alendronate, 217 pamidronate, 57 ibandronate, 107 clodronate, 13 tiludronate, 215 etidronate, and 77 risedronate clinical trials. The results of the review process are presented in Figure 2. Of the included

articles, 1 in Hebrew,<sup>28</sup> 1 in French,<sup>29</sup> and 1 article in German<sup>30</sup> were translated to English. The 30 articles identified in this systematic review discussed 99 cases of osteonecrosis of the jaw among patients without cancer who had been treated with bisphosphonates (85 osteoporosis patients, 10 patients with Paget's disease, and 4 patients with other diseases). The mean age was 69.4 years; 87.3% were female, and 83.3% were receiving oral, but not intravenous, bisphosphonates. Of the 63 patients reporting dental care information, 88.9% had a dental procedure before the onset of osteonecrosis of the jaw. Of the cases reporting concomitant medication use, 71% were taking at least 1 medication that affects bone turnover in

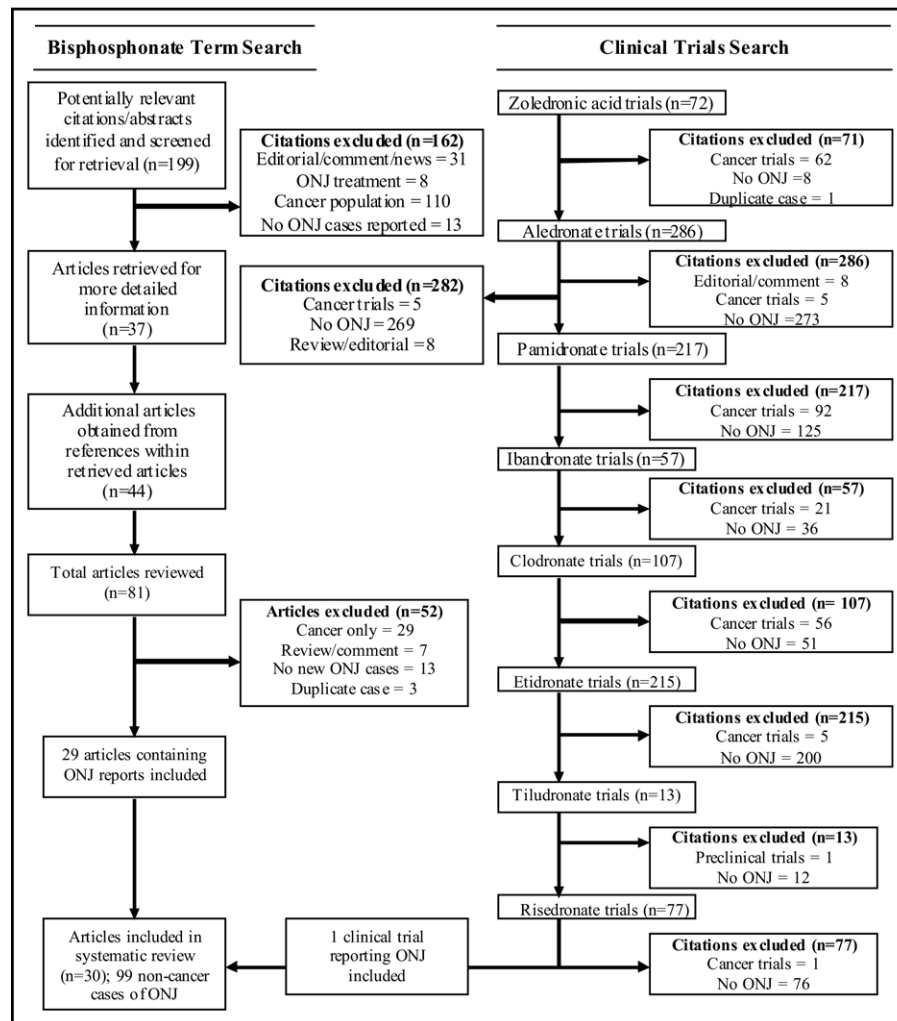


Figure 2 Results of literature search.

addition to the bisphosphonate, and 80.6% had additional underlying medical conditions. A summary of the identified articles is presented in Table 1, and a summary of individual cases in Table 2, available online.

## Osteoporosis

Eighty-five osteoporotic patients using bisphosphonates had been diagnosed with osteonecrosis of the jaw. The mean age was 68.7 years (SD 9.4), and 90.6% were female. The majority of these patients (93.4%) were receiving oral bisphosphonates. Sixty-three (74.1%) were taking oral alendronate, 6 (7.1%) were taking oral risedronate, 2 (2.4%) were receiving intravenous pamidronate, 1 (1.2%) was receiving intravenous zoledronate, and 4 patients were receiving dual bisphosphonate therapy: oral alendronate plus intravenous zoledronate (n = 1, 1.2%); alendronate plus risedronate (n = 2, 2.4%); and pamidronate plus zoledronate (n = 1, 1.2%). An additional 9 patients (10.6%) did not provide individual-level data, but were taking oral alendronate alone or alendronate plus clodronate.

Of the 53 (62.4%) cases with dental information, 49 (92.5%) had a dental procedure before the onset of osteonecrosis of the jaw. Twenty-four cases (28.2%) provided information on concomitant medication use. Of these, 17 (70.8%) were taking between 1 and 5 medications, in addition to a bisphosphonate, that are known to affect bone turnover (Table 3). The most common medications included steroids (n = 10, 41.7%), diuretics (n = 5, 20.8%), statins (n = 4, 16.7%), and calcium channel blockers (n = 3, 12.5%). Three of the osteoporosis cases had associated Therapeutic Goods Association adverse event reports that indicated incorrect dosing, or a drug-prescribing error had occurred with the bisphosphonate prescribed. Among cases providing clinical information, 26.3% reported poor oral health or other underlying oral conditions (eg, periodontitis, gingivitis), 21.1% had rheumatoid arthritis or lupus, and 15.8% had diabetes or impaired glucose function.

## Paget's Disease

Ten patients with Paget's disease who experienced osteonecrosis of the jaw while receiving bisphosphonates were

**Table 1** List of Publications Identified

Publication	Cases Reported	Concomitant Medications Provided	Dental Work Information Provided
Black et al <sup>10</sup>	Osteoporosis = 1	No	Yes
Brooks et al <sup>31</sup>	Osteoporosis = 1 Osteopenia = 1	Yes	Yes
Carter et al <sup>22</sup>	Paget's disease = 3	Yes	Yes
Cheng et al <sup>32</sup>	Osteoporosis = 3 Paget's disease = 2	Yes	Yes
Clarke et al <sup>33</sup>	Osteoporosis = 1	Yes	Yes
Danneman et al <sup>34</sup>	Osteoporosis = 3	No	Yes
Dimitrakopoulos et al <sup>35</sup>	Fibrous dysplasia = 1	No	Yes
Farrugia et al <sup>36</sup>	Osteoporosis = 4 Paget's disease = 1	No	Yes
Friedrich and Blake <sup>37</sup>	Diabetes = 1	Yes	Yes
Heras-Rincón et al <sup>38</sup>	Osteoporosis = 2	No	Yes
Hoefert and Eufinger <sup>30</sup>	Osteoporosis = 1	Yes	Yes
Kademani et al <sup>12</sup>	Osteoporosis = 1	Yes	No
Khamaisi et al <sup>15</sup>	Osteoporosis = 1 Rheumatoid arthritis = 1	No	No
Levin et al <sup>39</sup>	Osteoporosis = 1	Yes	Yes
Malden and Pai <sup>40</sup>	Osteoporosis = 1 Rheumatoid arthritis = 1	Yes	Yes
Marunick et al <sup>41</sup>	Osteoporosis = 1	Yes	Yes
Marx <sup>42</sup>	Osteoporosis = 4*	No	No
Mavrokki et al <sup>6</sup>	Osteoporosis = 24† Paget's disease = 4‡	No	No
Merigo et al <sup>43</sup>	Osteoporosis = 3	No	Yes
Migliorati et al <sup>24</sup>	Osteopenia = 1	Yes	Yes
Milillo et al <sup>44</sup>	Osteoporosis = 9	No	Yes
Najm et al <sup>29</sup>	Osteoporosis = 3	No	Yes
Nase and Suzuki <sup>45</sup>	Osteoporosis = 1	Partial	Yes
Oltolina et al <sup>46</sup>	Microfractures = 1	Yes	Yes
Phal et al <sup>47</sup>	Osteoporosis = 4	No	Yes
Pozzi et al <sup>48</sup>	Osteoporosis = 1	Yes	Yes
Purcell and Boyd <sup>49</sup>	Osteoporosis = 1	No	Yes
Ruggiero et al <sup>50</sup>	Osteoporosis = 7	No	No
Shlomi et al <sup>28</sup>	Osteoporosis = 3	Yes	Yes
Wang et al <sup>51</sup>	Osteoporosis = 1	Yes	Yes
Yeo et al <sup>52</sup>	Osteoporosis = 1	Yes	Yes

\*Three osteoporosis cases were previously reported by Marx et al.<sup>23</sup>

†Three additional cases were previously reported in Cheng et al,<sup>32</sup> and were removed from this analysis to avoid duplication.

‡Two additional cases were previously reported in Cheng et al,<sup>32</sup> and were removed from this analysis to avoid duplication.

identified. The mean age of Paget's disease patients with osteonecrosis of the jaw was 77.5 years (SD 5.6). Of cases reporting sex, 50% were male and 50% were female. Four patients (40.0%) were taking oral alendronate, 4 patients were taking pamidronate (40.0%), and 2 patients were taking combination therapy: alendronate plus risedronate (n = 1, 10.0%); and alendronate plus pamidronate (n = 1, 10.0%). Four of 6 patients (67%) had a dental procedure before the onset of osteonecrosis of the jaw. Five of 10 cases (50%) included concomitant medication use; 4 of these cases (80%) reported use of between 1 and 3 concomitant drugs that affect bone turnover (Table 3). One of the Paget's disease cases<sup>32</sup> had an associated Therapeutic Goods Association report that indicated that incorrect dosing or a drug-prescribing error had occurred with the bisphosphonate pre-

scribed. Of those reporting concomitant medications or medical conditions, 50% (n = 4) had additional health issues. These included 1 patient with diabetes and hypercholesterolemia, 2 patients with hypertension, 1 with hypercholesterolemia, and 1 patient who had problems with thyroid function. Each of these patients also had a dental procedure preceding the onset of osteonecrosis of the jaw. One patient that did not have a prior dental procedure also did not report concomitant medication use; therefore, the relationship of osteonecrosis of the jaw to other factors for this patient could not be explored.

### Other Conditions

Four additional cases of osteonecrosis of the jaw were identified among women taking bisphosphonates for condi-

**Table 3** Summary of Potential Contributing Factors among Patients with ONJ While Taking Bisphosphonates

Potential Contributing Factor	Osteoporosis	Paget's Disease	Other	Total
Age, mean (SD)	68.7 (9.4)	77.5 (5.6)	65.8 (9.6)	69.4 (9.4)
Dental procedures	92.5%	67%	75%	88.9%
Medications affecting bone turnover, in addition to bisphosphonate use	69.6%	80%	67%	71%
Duration of bisphosphonate use				
<6 months	3.2%	0%	0%	2.6%
6 months-<1 year	3.2%	40%	66.7%	12.8%
1-<5 years	54.8%	20%	33.3%	48.7%
≥5 years	38.7%	40%	0%	35.9%
Underlying medical conditions	90.0%	50%	100%	81.3%
Rheumatoid arthritis/lupus	21.1%	0%	50%	19.4%
Diabetes/impaired glucose*	15.8%	10%	50%	19.4%
Periodontal disease/other oral	26.3%	0%	25%	19.4%
Hypertension/hyperlipidemia/hypercholesterolemia*	21.1%	75%	0%	22.6%
Other cardiac	10.5%	0%	0%	6.5%

\*Explicitly stated or implied by medication use.

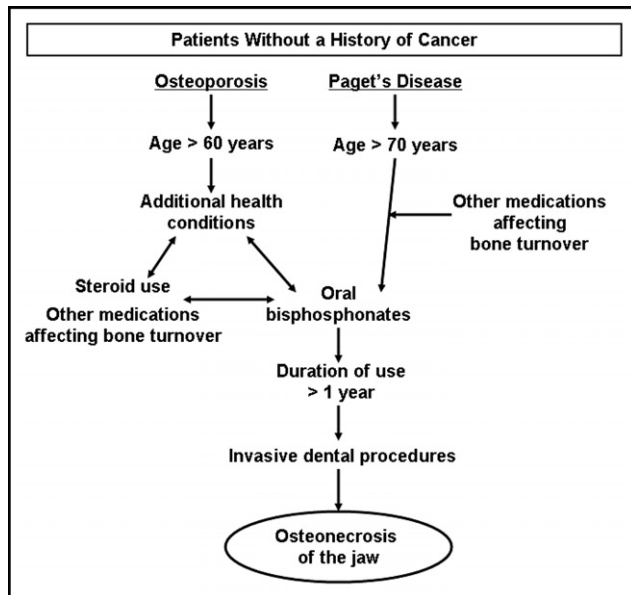
tions other than osteoporosis or Paget's disease. The mean age was 65.8 years (SD 9.6). Two patients were receiving oral alendronate (50%) and 2 were receiving intravenous zoledronate (50%). Three patients (75%) had a dental procedure before the onset of osteonecrosis of the jaw. The patient without a prior dental procedure had a known history of bony disease in her jaw (maxillary fibrous dysplasia). Two cases were identified in patients treated for rheumatoid arthritis, and one case was in a patient with diabetes. All cases (n = 2) reporting medication use were taking medications that affect bone turnover (Table 3).

### Summary of Potential Contributing Factors

Similar to the cancer population, dental procedures were the most common risk factor, which was associated with 88.9% of all noncancer cases of osteonecrosis of the jaw among bisphosphonate users (Table 3). Dental procedures were most common among osteoporosis patients (92.5%) and less common among Paget's disease patients (67%) before onset of osteonecrosis of the jaw. Osteoporosis patients also demonstrated a longer duration of bisphosphonate use (93.5% more than 1 year of use) compared with Paget's disease (60% more than 1 year of use) or other patients (33.3% more than 1 year of use). The majority of patients also had underlying medical conditions (81.3%) and reported concomitant use of medications that affect bone turnover (70.9%). The most common concomitant medical conditions included hypertension, hyperlipidemia, and hypercholesterolemia (22.6%). However, patients with osteoporosis were most likely to have periodontal disease or other oral conditions (26.3%), whereas Paget's disease patients were most likely to have hypertension or hypercholesterolemia (75%), and other patients had a variety of conditions (rheumatoid arthritis, diabetes, or other oral conditions). Among those taking medications that affect bone turnover (Table 4), the most commonly used med-

**Table 4** Summary of Concomitant Use of Medications that Impact Bone Turnover

Osteoporosis	Medications
Case 8	Steroids; immunosuppressant
Case 10	Steroids
Case 12	Diuretic; beta-blocker
Case 13	Calcium channel blocker; diuretic; angiotensin receptor blocker; proton pump inhibitor
Case 14	Steroids; methotrexate
Case 15	Steroids
Case 19	Steroids; immunosuppressant
Case 20	Steroids
Case 22	Steroids
Case 23	Steroids
Case 26	ACE inhibitor; statin; hormone replacement therapy
Case 35	Calcium channel blocker; diuretic; angiotensin receptor blocker; proton pump inhibitor; HMG CoA reductase inhibitor
Case 41	Thyroid hormone
Case 42	Diuretic; steroids
Case 51	Statin, calcium salt, cholecalciferol (Vit D)
Case 52	Steroids, sucralfate, diuretic, ACE inhibitor
Case 53	Statin, calcium channel blocker
Paget's disease	
Case P1	Calcium channel blocker; ACE inhibitor
Case P3	Calcium channel blocker; statin; diuretic
Case P4	Statin; beta blocker; calcitonin
Case P5	Thyroid hormone
Other	
Case OT3	Steroids
Case OT4	Proton pump inhibitor; steroids



**Figure 3** Proposed model of potential risk factors (>40% of the population) associated with osteonecrosis of the jaw among patients with no history of cancer receiving bisphosphonates for osteoporosis or Paget's disease.

ication affecting bone metabolism included steroids (52.2%). All other medications were used by 20% or less of patients. A model of risk factors, representing reported factors present in more than 40% of the osteoporosis and Paget's disease patients in this study population, is presented in Figure 3.

## DISCUSSION

As a result of this search, 99 cases of osteonecrosis of the jaw among patients receiving bisphosphonates for an indication other than cancer were identified in the published medical literature. The increase in published cases of osteonecrosis of the jaw between 2002 and 2007 is likely related to a combination of patient, disease, and concomitant medication factors, as well as awareness in the medical field,<sup>54</sup> as nitrogen-containing bisphosphonates were used for nearly 10 years before the first published case of osteonecrosis of the jaw. In this study, there was a predominance of oral bisphosphonate use, as would be expected for patients treated for osteoporosis or Paget's disease.

There appears to be a consistent association of osteonecrosis of the jaw with invasive dental procedures (eg, tooth extraction, oral surgery) among patients without cancer, similar to the cancer population. In addition to bisphosphonate use, many of these patients reported taking additional medications that impact bone metabolism, which may have resulted in an additive effect on bone turnover. The concomitant medications may be suggestive of the extent of the underlying disease, which may independently increase risk of osteonecrosis of the jaw (eg, multiple medications may

suggest reduced mobility and subsequent loss of bone mass or may suggest advanced bone disease).

A number of identified cases provide no published or unpublished clinical information about patient health or medication use. There were too few data available to include the other diseases in the risk model. Additionally, cases reported from adverse event reports, which are not comprehensive medical reports, lack patient-level clinical details. However, data from the cases with associated clinical information suggest that those individuals experiencing osteonecrosis of the jaw appear to have multiple contributing factors, primarily co-existing conditions (either implied by the multiple medications or explicitly stated), contraindicated medication use or medication error, and invasive dental procedures before the onset of osteonecrosis of the jaw. There were only 2 published spontaneous cases of osteonecrosis of the jaw reported among all osteoporosis patients to date—one in a patient receiving steroid therapy, the other in a patient with controlled hypertension but no steroid use (complete medication information was not reported). Although common among bisphosphonate users diagnosed with osteonecrosis of the jaw, concomitant medication use of additional agents that impact bone turnover appear to be less frequent among osteoporosis patients (69.6%) and other patients (67%) than among those with Paget's disease (80%), and additional underlying medical conditions were more prevalent among osteoporosis (90.0%) and other patients (100%) than among patients with Paget's disease (50%). This suggests that there may be differences among these populations and the risk factors may need to be addressed separately depending on the underlying condition for which the bisphosphonate is prescribed.

This model-based systemic review suggests that in the majority of cases, the risk of this morbid condition may not be solely attributable to the bisphosphonate. Osteonecrosis of the jaw does not appear to occur in an otherwise healthy patient taking bisphosphonates; multiple factors are likely associated with this condition. Of all the cases, only 1 (78-year-old patient with Paget's disease; 90 mg/month intravenous pamidronate for 18 months) reported no underlying medical conditions, concomitant medication use, or dental procedures. These data suggest that osteonecrosis of the jaw may, rather, be due to a combination of factors that impact the bone of the jaw that, when combined with a bisphosphonate, increase the risk of osteonecrosis of the jaw. Although more than half of those reporting these medications used steroids, it is unclear if the underlying morbid condition and concomitant medication use work together or independently to increase the risk of osteonecrosis of the jaw among bisphosphonate users. There were a variety of underlying medical conditions in this population, including those previously believed to put patients at increased risk of osteonecrosis. In this review, the prevalence of diabetes and hypertension in the published cases of osteonecrosis of the jaw in this review was similar to the US prevalence estimates,<sup>55,56</sup> although the extent of disease is unknown.

Therefore, it is unclear if the individual underlying medical conditions in this review truly represent individual risk factors.

In a randomized zoledronate clinical trial,<sup>10</sup> 1 osteoporosis patient receiving placebo and 1 receiving zoledronic acid experienced osteonecrosis of the jaw, suggesting that incidence may be due in part to the underlying medical condition. Others<sup>4,50</sup> have suggested that osteonecrosis of the jaw in the absence of bisphosphonate use has been in existence for some time, but had been underreported, as there is no mechanism of national or international reporting of adverse events in the absence of the concomitant use of an agent monitored by medication safety and regulatory agencies. Of osteonecrosis of the jaw cases identified in 2 medical record reviews, between 50% and 90% had never received bisphosphonates.<sup>8,9</sup> A preliminary Food and Drug Administration review found a total of 100 reports of osteonecrosis/necrosis among users of raloxifene, tamoxifen, estrogen, or calcitonin. This represents a small proportion of the total safety reports (0.18%), but suggests that there may be other cases of osteonecrosis of the jaw unrelated to bisphosphonate use that are not being considered.<sup>57</sup>

Further work should determine the frequency of osteonecrosis of the jaw among osteoporosis and Paget's disease patients not taking bisphosphonates. It is important to investigate osteonecrosis of the jaw independent of any particular medication, as it is evident that this condition occurs among users of a variety of other medications and illnesses, and although less commonly, does occur among those with no contraindicated medication use. Future work must address the challenge of separating the drug effects from the underlying effects of the disease it is designed to treat.

## References

- Guerra JJ, Steinberg ME. Distinguishing transient osteoporosis from avascular necrosis of the hip. *J Bone Joint Surg Am.* 1995;77(4):616-624.
- Roberts A, McMahon R. Causes of ischemic bone damage. The Maxillofacial Center for Diagnostics & Research. Available at: <http://www.maxillofacialcenter.com/NICOcause.html>. Accessed November 28, 2007.
- Donoghue AM. Bisphosphonates and osteonecrosis: analogy to phossy jaw. *Med J Aust.* 2005;183(3):163-164.
- Bouquot JE, McMahon RE. Alveolar osteonecrosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1997;84(3):229-230.
- Shoback D. Update in osteoporosis and metabolic bone disorders. *J Clin Endocrinol Metab.* 2007;92(3):747-753.
- Mavrokokki T, Cheng A, Stein B, Goss A. Nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in Australia. *J Oral Maxillofac Surg.* 2007;65(3):415-423.
- Sambrook P, Oliver I, Goss A. Bisphosphonates and osteonecrosis of the jaw. *Aust Fam Physician.* 2006;35(10):801-803.
- Murad OM, Arora S, Farag AF, Guber HA. Bisphosphonates and osteonecrosis of the jaw: a retrospective study. *Endocr Pract.* 2007;13(3):232-238.
- Walter C, Grotz KA, Kunkel M, Al-Nawas B. Prevalence of bisphosphonate associated osteonecrosis of the jaw within the field of osteonecrosis. *Support Care Cancer.* 2007;15(2):197-202.
- Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med.* 2007;356(18):1809-1822.
- Lenz JH, Steiner-Krammer B, Schmidt W, et al. Does avascular necrosis of the jaws in cancer patients only occur following treatment with bisphosphonates? *J Craniomaxillofac Surg.* 2005;33(6):395-403.
- Kademan D, Koka S, Lacy MQ, Rajkumar SV. Primary surgical therapy for osteonecrosis of the jaw secondary to bisphosphonate therapy. *Mayo Clin Proc.* 2006;81(8):1100-1103.
- Ruggiero SL, Gralow J, Marx RE, et al. Practical guidelines for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in patients with cancer. *J Oncol Pract.* 2006;2(1):7-14.
- Bilezikian JP. Osteonecrosis of the jaw—do bisphosphonates pose a risk? *N Engl J Med.* 2006;355(22):2278-2281.
- Khamaisi M, Regev E, Yarom N, et al. Possible association between diabetes and bisphosphonate-related jaw osteonecrosis. *J Clin Endocrinol Metab.* 2007;92(3):1172-1175.
- Khosla S, Burr D, Cauley J, et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res.* 2007;22(10):1479-1491.
- Glueck CJ, McMahon RE, Bouquot JE, et al. A preliminary pilot study of treatment of thrombophilia and hypofibrinolysis and amelioration of the pain of osteonecrosis of the jaws. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1998;85(1):64-73.
- Migliorati CA, Siegel MA, Elting LS. Bisphosphonate-associated osteonecrosis: a long-term complication of bisphosphonate treatment. *Lancet (Oncol).* 2006;7(6):508-514.
- Gering A, Grange L, Villier C, et al. Bisphosphonates-associated osteonecrosis of the jaw: review on reported cases [French]. *Therapie.* 2007;62(1):49-54.
- Krueger CD, West PM, Sargent M, et al. Bisphosphonate-induced osteonecrosis of the jaw. *Ann Pharmacother.* 2007;41(2):276-284.
- Woo SB, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med.* 2006;144(10):753-761.
- Carter G, Goss AN, Doecke C. Bisphosphonates and avascular necrosis of the jaw: a possible association. *Med J Aust.* 2005;182(8):413-415.
- Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. *J Oral Maxillofac Surg.* 2005;63(11):1567-1575.
- Migliorati CA, Schubert MM, Peterson DE, Seneda LM. Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone: an emerging oral complication of supportive cancer therapy. *Cancer.* 2005;104(1):83-93.
- Carter GD, Goss AN. Bisphosphonates and avascular necrosis of the jaws. *Aust Dent J.* 2003;48(4):268.
- Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg.* 2003;61(9):1115-1117.
- Migliorati CA. Bisphosphonates and oral cavity avascular bone necrosis. *J Clin Oncol.* 2003;21(22):4253-4254.
- Shlomi B, Levy Y, Kleinman S, et al. Avascular necrosis of the jaw bone after bisphosphonate therapy [Hebrew]. *Harefuah.* 2005;144(8):536-9, 600, 599.
- Najm SA, Lysitsa S, Carrel JP, et al. Bisphosphonates-related jaw osteonecrosis [French]. *Presse Med.* 2005;34(15):1073-1077.
- Hoefert S, Eufinger H. Osteonecrosis of the jaws as a possible adverse effect of the use of bisphosphonates [German]. *Mund Kiefer Gesichtschir.* 2005;9(4):233-238.
- Brooks JK, Gilson AJ, Sindler AJ, et al. Osteonecrosis of the jaws associated with use of risedronate: report of 2 new cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2007;103(6):780-786.
- Cheng A, Mavrokokki A, Carter G, et al. The dental implications of bisphosphonates and bone disease. *Aust Dent J.* 2005;50(4 Suppl 2):S4-S13.

33. Clarke BM, Boyette J, Vural E, et al. Bisphosphonates and jaw osteonecrosis: the UAMS experience. *Otolaryngol Head Neck Surg.* 2007;136(3):396-400.
34. Dannemann C, Gratz KW, Riener MO, Zwahlen RA. Jaw osteonecrosis related to bisphosphonate therapy: a severe secondary disorder. *Bone.* 2007;40(4):828-834.
35. Dimitrakopoulos I, Magopoulos C, Karakasis D. Bisphosphonate-induced avascular osteonecrosis of the jaws: a clinical report of 11 cases. *Int J Oral Maxillofac Surg.* 2006;35(7):588-593.
36. Farrugia MC, Summerlin DJ, Krowiak E, et al. Osteonecrosis of the mandible or maxilla associated with the use of new generation bisphosphonates. *Laryngoscope.* 2006;116(1):115-120.
37. Friedrich RE, Blake FA. Avascular mandibular osteonecrosis in association with bisphosphonate therapy: a report on four patients. *Anticancer Res.* 2007;27(4A):1841-1845.
38. Heras-Rincon I, Zubillaga Rodriguez I, Castrillo Tambay M, Montalvo Moreno JJ. Osteonecrosis of the jaws and bisphosphonates. Report of fifteen cases. Therapeutic recommendations. *Med Oral Patol Oral Cir Bucal.* 2007;12(4):E267-E271.
39. Levin L, Laviv A, Schwartz-Arad D. Denture-related osteonecrosis of the maxilla associated with oral bisphosphonate treatment. *J Am Dent Assoc.* 2007;138(9):1218-1220.
40. Malden NJ, Pai AY. Oral bisphosphonate associated osteonecrosis of the jaws: three case reports. *Br Dent J.* 2007;203(2):93-97.
41. Marunick M, Miller R, Gordon S. Adverse oral sequelae to bisphosphonate administration. *J Mich Dent Assoc.* 2005;87(11):44-49.
42. Marx RE. *Oral and Intravenous Bisphosphonate-Induced Osteonecrosis of the Jaws.* Chicago, IL: Quintessence Publishing Co.; 2007.
43. Merigo E, Manfredi M, Meleti M, et al. Bone necrosis of the jaws associated with bisphosphonate treatment: a report of twenty-nine cases. *Acta Biomed.* 2006;77(2):109-117.
44. Milillo P, Garribba AP, Favia G, Ettorre GC. Jaw osteonecrosis in patients treated with bisphosphonates: MDCT evaluation [Italian]. *Radiol Med (Torino).* 2007;112(4):603-611.
45. Nase JB, Suzuki JB. Osteonecrosis of the jaw and oral bisphosphonate treatment. *J Am Dent Assoc.* 2006;137(8):1115-1119.
46. Oltolina A, Achilli A, Lodi G, et al. Osteonecrosis of the jaws in patients treated with bisphosphonates. Review of the literature and the Milan experience. *Minerva Stomatol.* 2005;54(7-8):441-448.
47. Phal PM, Myall RW, Assael LA, Weissman JL. Imaging findings of bisphosphonate-associated osteonecrosis of the jaws. *AJNR Am J Neuroradiol.* 2007;28(6):1139-1145.
48. Pozzi S, Marcheselli R, Sacchi S, et al. Analysis of frequency and risk factors for developing bisphosphonate associated osteonecrosis of the jaw. *Blood* (ASH Annual Meeting Abstracts). 2005;106:Abst 5157.
49. Purcell PM, Boyd IW. Bisphosphonates and osteonecrosis of the jaw. *Med J Aust.* 2005;182(8):417-418.
50. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg.* 2004;62(5):527-534.
51. Wang H-L, Weber D, McCauley LK. Effect of long-term oral bisphosphonates on implant wound healing: literature review and a case report. *J Periodontol.* 2007;78(3):584-594.
52. Yeo AC, Lye KW, Poon CY. Bisphosphonate-related osteonecrosis of the jaws. *Singapore Dent J.* 2005;27(1):36-40.
53. Boyd IW. *Therapeutic Goods Administration, Public Case Detail.* Symonston, ACT, Australia: Therapeutic Goods Administration; 2006.
54. Damato K, Gralow J, Hoff A, et al. Expert panel recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaws. June 2004. American Dental Association. Available at: [http://www.ada.org/prof/resources/topics/topics\\_osteonecrosis\\_whitepaper.pdf](http://www.ada.org/prof/resources/topics/topics_osteonecrosis_whitepaper.pdf). Accessed November 28, 2007.
55. National Institutes of Health (NIH). *National Diabetes Statistics* (NIH Publication No. 06-3892). Bethesda, MD: National Institutes of Health; 2005.
56. Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991. *Hypertension.* 1995;25(3):305-313.
57. Hess LM. Freedom of Information Act report, request 2007-5566. 2007.

**Table 2** Cases Identified

Case	Year Reported	Age (Years)	Sex	Other Conditions	Dental Procedure	Other Medications	Bisphosphonate Used	Dose	Duration
1	2004 <sup>50</sup>	77	F	NS	NS	NS	Oral alendronate	NS	NS
2	2004 <sup>50</sup>	82	F	NS	NS	NS	Oral alendronate	NS	NS
3	2004 <sup>50</sup>	80	F	NS	NS	NS	Oral risedronate	NS	NS
4	2004 <sup>50</sup>	72	M	NS	NS	NS	Oral alendronate + IV zoledronate	NS	NS
5	2004 <sup>50</sup>	59	F	NS	NS	NS	Oral alendronate	NS	NS
6	2004 <sup>50</sup>	60	F	NS	NS	NS	Oral alendronate	NS	NS
7	2004 <sup>50</sup>	68	F	NS	NS	NS	Oral alendronate	NS	NS
8	2005 <sup>49</sup>	67	F	NS	NS	Prednisolone, leflunomide,* celecoxib	Oral alendronate	NS	NS
9	2007 <sup>42</sup>	70	F	Controlled hypertension	None	NS†	Oral alendronate	70 mg/wk	5 years
10	2007 <sup>42</sup>	58	F	Osteopenia	Six dental implants (occluding against a fixed prosthesis)	NS, steroid for 5 days during infection	Oral alendronate	70 mg/wk	5 years
11	2007 <sup>42</sup>	58	F	None	Dental implant	NS†	Oral alendronate	10 mg/day, followed by 70 mg/week	1 year followed by 3 years
12	2007 <sup>42</sup>	60	F	NS	Root canal, extraction	Atenolol, hydrochlorothiazide	Oral alendronate	10 mg/day followed by 70 mg/week	3 years followed by 7 years
13	2005 <sup>24</sup>	61	F	NS	Oral surgery†	Losartan, amlodipine, furosemide, esomeprazole, aspirin, potassium	Oral alendronate	NS	3 years
14	2005 <sup>41</sup>	59	F	Rheumatoid arthritis	Tooth extraction	Prednisone, methotrexate†	Oral alendronate	70 mg/wk†	~3 years†
15	2005 <sup>32</sup>	58	F	Lupus erythematosus	Tooth extraction	Prednisolone, glucosamine sulfate	Oral alendronate	70 mg/wk	NS
16§	2005 <sup>32</sup>	72	M	NS	Tooth extraction	None	Oral alendronate	40 mg/wk	3 years
17§	2005 <sup>32</sup>	60	M	NS	Tooth extraction	None	Oral alendronate	40 mg/wk	1 year
18§	2005 <sup>32</sup>	58	F	NS	Deep bony impacted wisdom tooth removal	Bactrim, neurontin, amitriptyline	Oral alendronate	40 mg/wk	Started alendronate after tooth removal
19	2005 <sup>46</sup>	64	M	Cardiac graft, microfractures of the spinal column	Tooth extraction	Cyclosporine, high-dose steroids	IV pamidronate	90 mg/4 wk†	18 months†
20	2005 <sup>29</sup>	45	M	NS	None	Cortisone	IV pamidronate + IV zoledronate	P: 30 mg/3 mo + Z: 4 mg/mo	79 months
21	2005 <sup>29</sup>	83	F	NS	Removal of dental implant		Oral alendronate	70 mg/wk	44 months
22	2005 <sup>29</sup>	84	F	NS	Tooth extraction	Cortisone	Oral alendronate	70 mg/wk	25 months
23	2005 <sup>28</sup>	73	F	Rheumatoid arthritis†	Tooth extraction†	Prednisone†	Oral alendronate	NS	5 years
24	2005 <sup>28</sup>	48	F	Diabetes†	Tooth extraction†	Oral hypoglycemic agent†	Oral alendronate	NS	2 years
25	2005 <sup>28</sup>	72	F	Diabetes†	Tooth extraction†	Insulin, daily†	Oral alendronate	NS	5 years
26	2005 <sup>30</sup>	65	F	Hypertonic disease†	Oral surgery†	Premarin, aspirin, enalapril, fluvastatin†	Oral alendronate	70 mg/wk	2 years
27	2006 <sup>12</sup>	64	F	NS	Tooth extraction	Antibiotics	IV pamidronate	NS	NS
28	2006 <sup>43</sup>	70	F	NS	Tooth extraction	NS†	Oral alendronate	70 mg/wk	3 years
29	2006 <sup>43</sup>	61	F	NS	Tooth extraction	NS†	Oral alendronate	70 mg/wk	2.5 years
30	2006 <sup>43</sup>	78	F	NS	Tooth extraction	NS†	Oral alendronate	70 mg/wk	~5 years
31	2007 <sup>34</sup>	NS	F	NS	Tooth extraction	NS	Oral alendronate	NS	>5 years
32	2007 <sup>34</sup>	NS	F	NS	Tooth extraction	NS	Oral alendronate	NS	>5 years

Table 2 Continued

Case	Year Reported	Age (Years)	Sex	Other Conditions	Dental Procedure	Other Medications	Bisphosphonate Used	Dose	Duration
33	2007 <sup>34</sup>	NS	F	NS	Tooth extraction	NS	Oral alendronate	NS	>5 years
34	2007 <sup>15</sup>	71	F	Impaired fasting glucose	Dental surgery†	NS	Oral alendronate	70 mg/wk	>6 months‡
35	2007 <sup>33</sup>	75	F	Hypertension; hyperlipidemia; history of fibromuscular dysplasia, cerebral aneurysm†	Recent dental work	Hydro-chlorothiazide + losartan, simvastatin, nifedipine, omeprazole†	Oral alendronate	NS	1 year
36	2006 <sup>36</sup>	83	F	NS‡	Tooth extraction	NS‡	Oral alendronate	NS	NS
37	2006 <sup>36</sup>	77	F	NS‡	Tooth extraction	NS‡	Oral alendronate	NS	NS
38	2006 <sup>36</sup>	63	F	NS‡	Tooth extraction	NS‡	Oral alendronate	NS	NS
39	2006 <sup>36</sup>	78	F	NS‡	Tooth extractions	NS‡	Oral alendronate	NS	NS
40	2007 <sup>10</sup>	NS	F	NS	Oral surgery	NS	IV zoledronic acid	5 mg/year	NS
41	2007 <sup>51</sup>	65	F	Arthritis, periodontitis, endentulism with functional deficit	Tooth extraction, dental implant	Calcium; teniparide (at discontinuation of alendronate following dental implant); postsurgical azithromycin, hydrocodone, acetaminophen, ibuprofen, cephalixin	Oral alendronate	Daily	10 years
42	2007 <sup>31</sup>	70	F	Advanced periodontitis; chronic obstructive pulmonary disease	Extraction	Prednisone; sertaline; clonidine; hydrochlorothiazide; fexofenadine; ipratropium and albuterol inhaler; tiotropium inhaler; fluticasone and salmeterol inhaler; potassium; supplemental oxygen	Oral risedronate	35 mg/week	~2 years
43	2007 <sup>31</sup>	62	F	Advanced periodontitis	Dental implant	NS	Oral risedronate	35 mg/week	1 year
44	2007 <sup>38</sup>	75	F	NS	Tooth extraction†	NS	Oral alendronate	NS	NS
45	2007 <sup>38</sup>	73	F	NS	Tooth extraction†	NS	Oral alendronate	NS	NS
46	2007 <sup>40</sup>	64	F	Periodontal disease with regular tooth extractions	Tooth extraction	NS	Risedronate	NS	NS
47	2007 <sup>47</sup>	82	F	NS	Tooth extraction	NS	Oral alendronate	NS	NS
48	2007 <sup>47</sup>	70	F	NS	Tooth extraction	NS	Oral alendronate	NS	NS
49	2007 <sup>47</sup>	85	F	NS	Tooth extraction	NS	Oral alendronate	NS	NS
50	2007 <sup>47</sup>	74	F	NS	None	NS	Oral alendronate	NS	NS
51	2006 <sup>45</sup>	78	F	Renal insufficiency, diverticulosis, clinical depression, poor oral self-care, gingivitis, xerostomia	Tooth extraction	Tolterodine, sertraline, atorvastatin, aspirin, calcium salt, cholecalciferol, ginkgo bilboa	Oral alendronate	10 mg/day	5 years
52	2005 <sup>48</sup>	NS	F	Myelo-dysplasia‡	Patient edentulous, with prosthesis†	Prednisone, sucralate, furosemide, delapril, potassium canrenoate‡	IV zoledronic acid†	Every 2 months‡	1.5 years‡
53	2007 <sup>39</sup>	66	F	Hypertension, hypercholesterolemia‡	No (removable partial denture)	Statin, calcium channel blocker†	Oral alendronate	10 mg/day followed by 70 mg/week	6 years followed by 2 years
54-62**	2007 <sup>44</sup>	NS	NS	NS	Tooth extraction (all pts)	NS	Oral alendronate or Oral alendronate + clodronate	NS	NS

**Table 2** Continued

Case	Year Reported	Age (Years)	Sex	Other Conditions	Dental Procedure	Other Medications	Bisphosphonate Used	Dose	Duration
63-85**	2007 <sup>6</sup>	NS	NS	NS	NS	NS	Oral alendronate (n = 19) Risedronate (n = 2) Alendronate + risedronate (n = 2)	NS	NS
Page's disease									
P1	2005 <sup>22</sup>	73	M	NS	Tooth extraction	Anlodipine, tramadol, perindopril	Oral alendronate	40 mg/day	5 years
P2	2005 <sup>22</sup>	78	F	NS	None	None	IV pamidronate	90 mg/mo	18 months
P3	2005 <sup>22</sup>	84	F	NS	Tooth extraction	Diltiazem, simvastatin, ferrous sulfate, aspirin, bendrofluzazine	IV pamidronate	60 mg/mo	6 months
P4§	2005 <sup>32</sup>	69	M	NS	Tooth extraction	Metformin, atenolol, simvastatin, morphine, calcitonin, amitriptyline	Oral alendronate	40 mg/wk	6 months
P5	2005 <sup>32</sup>	82	F	NS	Tooth extraction	Thyroxine, NSAIDs	IV pamidronate + oral alendronate	P: 90 mg (1 dose) + A: 20 mg/day	P: 5 years A: 1 year
P6	2006 <sup>36</sup>	79	M	NS¶	None	NS¶	Oral alendronate	NS	NS
P7-10**	2007 <sup>6</sup>	NS	NS	NS	NS	NS	Oral alendronate (n = 2) Pamidronate (n = 2)	NS	NS
Other									
OT1	2006 <sup>35</sup>	59	F	Maxillary fibrous dysplasia†	None	None‡	IV zoledronic acid	NS	6 months
OT2	2007 <sup>15</sup>	73	F	Rheumatoid arthritis, impaired fasting glucose	Dental surgery‡	NS	Oral alendronate	70 mg/wk	>6 months‡
OT3	2007 <sup>37</sup>	75	F	Diabetes, sarcoidosis	Tooth extraction	Prednisone, insulin	IV zoledronic acid	NS	3 years
OT4	2007 <sup>40</sup>	56	F	Rheumatoid arthritis	Tooth extraction	Leflunomide, prednisone, diclofenac, iron, omeprazole	Oral alendronate	NS	NS

NS = not stated.

\*Contraindicated in patients over age 65 years due to increased risk of infection.

†Patient was not taking corticosteroids.

‡Personal communication with author.

§Incorrect dose/drug prescribing error noted in TGA report associated with this case.<sup>53</sup>

¶Per author, the original publication incorrectly noted this patient's age as 39 years. The correct age of this patient was 60 years.

‡Although details of medications/illnesses were not provided, publication states there were none that could have contributed to the ONJ.

\*\* Summary data only, no individual case details provided.