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J Am Dent Assoc 2008;139;23-30

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Bisphosphonate use and the risk of adverse jaw outcomes

A medical claims study of 714,217 people

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Bisphosphonates (BPs) commonly are used to manage osteoporosis and Paget disease, or to treat hypercalcemia of malignancy or metastatic bone lesions in oncology. They also have limited use in pediatric patients for the management of certain inherited conditions such as osteogenesis imperfecta. BPs localize in areas of the bone that are undergoing inflammation or resorption. They subsequently are phagocytosed and internalized by osteoclasts. These internalized BPs, in turn, trigger apoptosis (cell death) of the osteoclasts, thus inhibiting osteoclast-mediated bone resorption.¹ BPs seem to affect osteoclasts in terms of both numbers and function; the effects on the osteoblast and the osteocyte are not well-understood, and a number of studies are under way to better describe BPs' mode of action. In animal studies, BPs also have demonstrated some antiangiogenic properties; this may partially explain the development of osteonecrosis, in the sense that the bone has limited healing ability because of reduced vasculature.²

While most etiologic hypotheses have focused on the biological pathway that affects bone turnover, Reid and colleagues³ recently proposed a model in which the toxic effect is targeted toward the soft tissue. According to the authors, BPs are accumulated in bone in

ABSTRACT

Background. While osteonecrosis of the jaw (ONJ) has been associated with the prolonged use of bisphosphonates (BPs), there is limited information about the risk of ONJ among users of oral BPs or about the magnitude of the risk among users of intravenous (IV) BPs.

Methods. The authors studied medical claims data from 714,217 people with osteoporosis or cancer to identify diagnostic codes or procedure codes for three outcomes: inflammatory conditions of the jaws, including osteonecrosis; major jaw surgery necessitated by necrotic or inflammatory indications; and jaw surgeries necessitated by a malignant process. The authors calculated stratified odds ratios and 95 percent confidence intervals.

Results. The results indicate that oral administration of BPs decreases the risk of adverse bone outcomes. In contrast, IV administration strongly and significantly increases the risk ($P < .05$) of adverse jaw outcomes or surgery. Across both osteoporosis and cancer, patients receiving IV BPs had a fourfold increased risk of having inflammatory jaw conditions and a greater than sixfold increased risk of having undergone major surgical resection in the jaw.

Conclusions. Mode of bisphosphonate use results in different risk profiles for adverse jaw outcomes. While the authors documented an increased risk of inflammatory conditions and surgical procedures of the jaw for users of IV BPs, they did not find these observed increases for users of oral BPs.

Clinical Implications. Physicians and dentists must be aware of the higher frequency of adverse jaw effects in patients receiving IV BPs, especially osteonecrosis of the jaw. While the authors' results have internal consistency, more clinical studies are needed to replicate and clarify the observed associations over long follow-up periods.

Key Words. Adverse effect; alendronate; bisphosphonates; cancer; drug safety; medical claims; osteonecrosis of the jaw; osteoporosis; pamidronate; surveillance; zoledronic acid.

JADA 2008;139(1):23-30.

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high concentrations that are sufficient to be directly toxic to the oral epithelium.

BPs are administered either intravenously (IV) (pamidronate and zoledronic acid) or orally (alendronate, etidronate, ibandronate, risedronate, tiludronate). The most potent BP is zoledronic acid (Zometa, Novartis, Annandale, N.J.). It is used mainly in oncology, as approved by the U.S. Food and Drug Administration (FDA) in 2001, to treat hypercalcemia of malignancy or bone metastases. It is given in 4-milligram infusions over 15 minutes every three or four weeks for long periods.⁴ Its indication recently was expanded to include the management of osteoporosis in postmenopausal women. In August 2007, a single 5-mg infusion of zoledronic acid (marketed by Novartis under the trade name Reclast) was approved to be given once per year for the management of osteoporosis.⁵

Since 2003, several articles have described a serious adverse effect, osteonecrosis of the jaw (ONJ), affecting primarily users of zoledronic acid or pamidronate.⁶⁻¹⁵ Oral BPs have been used in the United States to treat osteoporosis since 1977,^{16,17} and some cases of ONJ also have been described among users of oral BPs.¹⁸

BP-related ONJ is defined as exposed necrotic bone in patients receiving BPs that persists for at least eight weeks. Risk factors include dental extractions, inflammation and poor oral hygiene, and a number of medications prescribed in oncologic treatment such as steroids, antiangiogenics and various other chemotherapeutics. ONJ is difficult to treat and affects the patient's quality of life. While the incidence of ONJ among patients with cancer varies, most retrospective studies estimate that a minimum of 5 percent of IV BP users develop ONJ. For example, a hospital retrospective chart review of 479 oncologic patients at the University of Arkansas Medical Center identified 25 patients who had received BPs for an average of 4.4 years (range, one to eight years), mostly pamidronate, and had developed ONJ. Most patients had been treated for multiple myeloma, and had a mean age of 63.4 years. Ten of the 25 patients had received steroids within the month before diagnosis, and 11 of them had undergone dental treatment

before their development of ONJ.⁶

Because BPs constitute a well-accepted and popular class of medications, especially in the management of osteoporosis, providing details on causation of ONJ becomes a matter of public health.

Several unanswered questions exist regarding, among other things, the etiology of ONJ, the background rate of osteonecrosis among the general public, its predilection for users of BPs, the role of concomitant chemotherapies and the frequency of spontaneous occurrence of ONJ among users of orally administered BPs. The aim of the study we describe here was to analyze medical claims data from a large national sample to describe the prevalence and to quantify the risk of inflammatory or necrotic adverse bone effects in the mandible or the maxilla in two groups of patients: those with osteoporosis and those with cancer. We also aimed to examine whether BP use is a potential risk factor for ONJ, and to compare the risk of ONJ among patients with cancer receiving high IV doses with the risk of ONJ in patients with osteoporosis receiving oral BP doses to assess if BPs' mode of administration and dose used—given that cancer doses are often 10-12 times higher than osteoporosis doses—is a significant predictor of adverse outcomes.

MATERIALS, SUBJECTS AND METHODS

The basis of this study is a medical claims database from a large national health insurance plan that provides health coverage to approximately 15 million members. The first step was to extract all medical claims data from April 2000 through April 2006 across the United States for people who had claims for International Classification of Diseases, ninth revision (ICD-9), codes for osteoporosis or cancer. For osteoporosis, the specific codes we included were ICD-9 codes 7330 (oste-

Several unanswered questions exist regarding the frequency of spontaneous occurrence of osteonecrosis of the jaw among users of orally administered bisphosphonates.

ABBREVIATION KEY. **BPs:** Bisphosphonates.

CPT: Current Procedural Terminology. **FDA:** Food and Drug Administration. **ICD-9:** International Classification of Diseases, ninth revision. **IV:** Intravenous.

NADP: National Association of Dental Plans.

ONJ: Osteonecrosis of the jaw.

porosis), 73300 (generalized osteoporosis), 73301 (postmenopausal osteoporosis), 73302 (idiopathic osteoporosis) and 73309 (other osteoporosis). The specific malignancies we studied were as follows: female breast cancer (ICD-9 174), lung cancer (ICD-9 162), prostate cancer (ICD-9 185), and multiple myeloma (ICD-9 203.0). We chose to enroll people with osteoporosis and people with cancer because both of these diseases are relatively common and because both often are treated with oral or IV BPs. By selecting these two separate groups of patients, we aimed for adequate sample sizes of exposed and unexposed people (defined later) for all stratified statistical analyses. We decided that research subjects should have had a minimum of two consecutive months of continuous enrollment in the health plan before their selection by the research algorithm to qualify for inclusion in the study base. In addition, we decided that those with positive bone outcomes should have received BPs before having made their first-ever claim for that outcome. In this way, we identified 714,217 people as having either osteoporosis or cancer.

For all patients with osteoporosis and all patients with cancer, we recorded demographics, pharmacy claims for drug dispensings, claims for medical procedure codes indicating drug infusions, claims for ICD-9 diagnostic codes for the adverse bone outcomes and claims for American Medical Association Current Procedural Terminology (CPT) codes for major surgery in the oral cavity.

We stratified BP use according to mode of administration and created three strata: “none,” for those who had no claims for dispensing of any type of BP; “intravenous,” for those receiving pamidronate and/or zoledronic acid infusions; and “oral,” for those receiving alendronate, etidronate, ibandronate, risedronate or tiludronate. We compared patients who never received any form of BP with the ones who were identified by pharmacy claims as taking oral BPs and the ones who were identified by procedure records as using “intravenous” BPs (pamidronate and/or zoledronic acid). We did a separate analysis of patients with claims for both oral and IV BPs but found them to have results similar to those of the “intravenous” group. Owing to the high potency

TABLE 1

Descriptive statistics.			
POPULATION GROUP	MODE OF BISPSPHONATE ADMINISTRATION		
	None	Intravenous*	Oral†
Osteoporosis Frequency (percentage)	263,352 (59.2)	1,858 (0.42)	179,870 (40.4)
Female/male (no.)	236,850/26,502	1,451/407	168,241/11,629
Mean age (years)	59.9	62.4	61.5
Cancer Frequency (percentage)	235,553 (87.5)	8,545 (3.2)	25,039 (9.3)
Female/male (no.)	119,034/116,519	5,361/3,184	22,377/2,662
Mean age (years)	61.0	59.9	62.4

* Centers for Medicaid and Medicare Services Healthcare Common Procedure Coding System (HCPCS) J codes specific for zoledronic acid and pamidronate were used.
 † U.S. Food and Drug Administration Center for Drug Evaluation and Research National Drug Codes specific for alendronate, etidronate, ibandronate, risedronate and tiludronate were used.

and dose of IV BPs as compared with oral BPs, we subsequently included them with the IV group.

The main ICD-9-coded outcomes of the study were three:

- inflammatory conditions of the jaws, including osteonecrosis (referred to here as “ONJ”);
- major jaw surgery necessitated by necrotic or inflammatory indications;
- jaw surgeries necessitated by a malignant process.

While there is no specific ICD-9 code for BP-related osteonecrosis of the jaws, the ICD-9 code 526.4 is a specific code that describes inflammatory or necrotic processes in the mandible or the maxilla, including osteitis of jaw (acute, chronic or suppurative), osteomyelitis, periostitis and sequestrum of jaw bone. In addition to the ICD-9 diagnostic code, this analysis includes evaluations of the frequencies of major jaw resections, coded by CPT. As mentioned in previous work, there is an advantage in using CPT codes for surgery owing to the reliability of CPT codes as compared with the ICD-9 codes in claims databases.⁷

We calculated descriptive statistics for each group, including frequencies of each sex and mean age (Table 1). Because we had no data on exposed and unexposed person-time, our statistical analysis used a case-control approach. Within the populations of subjects with osteoporosis or cancer, cases were subjects with one of the three coded bone outcomes and controls were subjects with no outcomes. We calculated crude and stratified odds ratios (ORs), along with their 95 percent confidence intervals (CIs), by com-

TABLE 2

Counts and crude odds ratio (95% confidence interval) for study outcomes, stratified by mode of bisphosphonate administration in patients with osteoporosis.*

OUTCOMES	MODE OF ADMINISTRATION		
	None	Intravenous†	Oral‡
Inflammatory Necrosis of Jaw (No. of Patients) Present Absent	339 263,013	9 1,742 OR _{crude} = 4.01§ 95% CI: 2.06–7.78	150 176,739 OR _{crude} = 0.65§ 95% CI: 0.54–0.79
Surgery: Necrotic Process (No. of Patients) Yes No	73 263,279	4 1,849 OR _{crude} = 7.80§ 95% CI: 2.84–21.36	43 179,784 OR _{crude} = 0.86 95% CI: 0.59–1.26
Surgery: Cancer Process (No. of Patients) Yes No	105 263,247	0¶ 1,853 OR _{crude} = 1.35 ^{corr.} 95% CI: 0.19–9.7 ^{corr.}	58 179,769 OR _{crude} = 0.80 95% CI: 0.59–1.11

* International Classification of Diseases, ninth revision, codes for osteoporosis were used.
 † Centers for Medicaid and Medicare Services Healthcare Common Procedure Coding System J codes specific for zoledronic acid and pamidronate were used.
 ‡ U.S. Food and Drug Administration Center for Drug Evaluation and Research National Drug Codes specific for alendronate, etidronate, ibandronate, risedronate and tiludronate were used.
 § $P < .05$.
 ¶ As this cell contained no observations, we calculated a corrected odds ratio by substituting the number zero (0) for the number one (1).

paring naïve patients (no use of BPs) with patients who had received BPs (exposed). Results are presented in stratified fashion, according to status of osteoporosis or cancer and mode of BP administration (IV or oral).

RESULTS

We analyzed medical claims from a large national health insurance plan to detect signals of risk associated with the use of a widely used class of medications, BPs. The two populations we chose to study were patients with osteoporosis, for whom orally administered BPs were indicated, and patients with certain cancers, for whom high-dose IV BPs were indicated. While low-dose IV zoledronic acid recently was approved for the management of osteoporosis, patients with cancer tend to receive doses four to 12 times higher than those administered to patients with osteoporosis.¹⁹

As expected, significantly more women (236,850 with no exposure to BPs and 168,241 who had taken oral BPs) than men (26,502 with no exposure to BPs and 11,629 who had taken

oral BPs) were in the osteoporosis group. In the cancer group, this difference in sex was significantly reduced, although women were again over-represented (Table 1). The mean age of all strata was close to 60 years. This homogeneity in age and the lack of older age groups must be due to the epidemiology of the osteoporosis or cancers and the fact that

private medical insurance is carried usually by workers and their immediate families and rarely by retirees. Among the patients with osteoporosis, we found that 40.4 percent (179,870 people) had pharmacy claims for oral BPs and 0.42 percent (1,858 people) had claims for IV BPs. Among the patients with cancer, 9.3 percent (25,039 people) had claims for oral BPs and 3.2 percent (8,545 people) had claims for IV BPs. With regard to the analytic statistics of risk, Table 2 presents the results for the osteoporosis group and Table 3 for the cancer group.

Among the naïve patients (those who had not used BPs) who had osteoporosis, the claims frequency of inflammatory conditions was 1.3/1,000. Among the naïve patients who had cancer, the claims frequency of inflammatory conditions was 1.1/1,000.

In general, people with osteoporosis taking oral BPs versus those receiving IV BPs had a significantly reduced risk of developing adverse bone outcomes. Similarly, they had a reduced risk of having undergone a major oral surgical procedure. The OR of osteonecrosis of the jaw was

0.65 ($P < .05$), implying a protective association with the use of oral BPs. However, the risk profile for patients with osteoporosis who had received IV BPs was very different, with a significant fourfold increase in the risk of having had a claim for ONJ. Similarly, we observed a significant almost eightfold increase in the risk of having undergone a major oral surgical procedure owing to a necrotic or inflammatory process.

The same pattern emerged in the analyses of people with cancers of the breast, lung or prostate or with multiple myeloma. Those who had received oral BPs experienced protective associations or slightly increased risks that were not statistically significant. Those who received IV BPs, however, experienced significantly increased risks, with a significant 4.4-fold increase in the risk of developing ONJ and a significant 6.8-fold increase in their risk of having undergone surgery because of a necrotic or inflammatory process.

Our results suggest that orally administered BPs do not increase the risk of osteonecrosis, whereas IV BPs are significantly and strongly associated with adverse bone outcomes in the mandible or the maxilla.

DISCUSSION

The limitations of claims-based analyses are many and often preclude any firm conclusions. Some of the limitations of claims-based analyses are related to the fact that the primary role of the claims database is administrative (billing and operations) and that, thus, it has not been designed for medical research. In comparison

with the medical record, medical claims do not contain as many details and, at times, are prone to error. As with all observational studies, medical claims studies often are subject to selection bias; thus, the results may not be representative of the total population. One common form of selection bias in medical insurance databases is the fact that medical insurance often is carried by employed people and their families, excluding senior citizens and the unemployed. Often, medical claims analyses are based on ICD-9 coding that is not specific for the disease under investigation but rather is used to describe a group of clinical conditions that have similarities. It also has been found that certain diseases (such as long QT syndrome²⁰) are not good candidates for medical claims analyses.

One of the limitations of our study is the fact that at the time of the analysis, there was no ONJ-specific ICD-9 code available. The ICD-9 code 526.4 codes not only for ONJ, but also for other inflammatory or necrotic conditions of the jaws. To overcome a potential misclassification bias (misclassifying the disease of interest as

TABLE 3

OUTCOMES	MODE OF ADMINISTRATION		
	None	Intravenous†	Oral‡
Inflammatory Necrosis of Jaw (No. of Patients)			
Present	251	39	31
Absent	235,302	8,168	24,548
		OR _{crude} = 4.47§ 95% CI: 3.19–6.27	OR _{crude} = 1.18 95% CI: 0.81–1.72
Surgery: Necrotic Process (No. of Patients)			
Yes	81	20	7
No	235,472	8,513	25,018
		OR _{crude} = 6.8§ 95% CI: 4.18–11.14	OR _{crude} = 0.81 95% CI: 0.37–1.76
Surgery: Cancer Process (No. of Patients)			
Yes	161	6	11
No	235,392	8,527	25,014
		OR _{crude} = 1.03 95% CI: 0.45–2.32	OR _{crude} = 0.64 95% CI: 0.35–1.18

* International Classification of Diseases, ninth revision, codes for cancers of the breast, lung and prostate and multiple myeloma were used.
 † Centers for Medicaid and Medicare Services Healthcare Common Procedure Coding System J codes specific for zoledronic acid and pamidronate were used.
 ‡ U.S. Food and Drug Administration Center for Drug Evaluation and Research National Drug Codes specific for alendronate, etidronate, ibandronate, risedronate and tiludronate were used.
 § $P < .05$.

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another disease), we chose to include dental “procedure outcomes” (major oral surgeries) in the analysis and to ascertain whether there was internal consistency between the diagnostic outcome and the surgical outcomes. Thus, we included CPT codes for major oral surgeries, which are captured accurately in medical claims, as a proxy for ONJ or other serious inflammatory conditions such as osteomyelitis. Furthermore, we evaluated major jaw surgeries according to their indication (necroses versus malignancies) and we report the results separately.

An additional potential limitation is the fact that we studied CPT codes (used by medical insurance plans) and not CDT codes (used by dental insurance plans). The corresponding CDT codes in dentistry are D7490 (radical resection of maxilla or mandible) and D7550

(partial osteotomy/sequestrectomy for removal of nonvital bone). If we missed a significant number of surgeries because they were submitted to dental insurance rather than medical insurance, the result would be potential misclassification that could lead to errors. To address this question, we communicated with the National Association of Dental Plans (NADP) in 2005. The NADP represents member dental plans that provide dental benefits to approximately 133 million of the 163 million Americans who have dental benefits (82 percent of the total dental health maintenance organization market). In 2005, NADP conducted an informal inquiry of its largest dental insurance members, and the results were presented in a workshop entitled “Medical Dental Insurance Databases and Drug Safety Surveillance” at the 35th Annual Meeting of the American Association for Dental Research.²¹ While this informal survey was based on personal communications and was not designed as a formal research project, it indicated that it is rather unusual for dental insurance plans to receive the specific CPT or corresponding CDT surgical codes, with fewer than 1,000 claims for codes D7490 and D7550 for the 133 million enrollees.²¹

Despite the above limitations, medical claims studies have a unique role to play in pharmaco-epidemiology and outcomes research. They are efficient and are used increasingly by the FDA

and other regulatory authorities for safety surveillance. Medical claims studies provide the unique benefit of having longitudinal health care utilization data from very large reference populations. Our analysis, to our knowledge, is the largest analysis of inflammatory and necrotic jaw bone outcomes for users of BPs. Here we report on the health care experience of 10,403 people receiving IV BPs and 204,909 people receiving oral BPs as compared with that of 498,905 people who had not received BPs. Many of the limitations can be addressed with careful construction of computer algorithms that track longitudinal data of health care utilization and cross-validate the outcomes.

This study significantly expands our previous work⁷ by comparing the frequency of various adverse bone outcomes between users and nonusers of BPs. Our basic null hypothesis was that the two frequencies would not differ significantly, that both users and nonusers of BPs would have comparable rates of adverse outcomes. For those who received oral BPs, indeed, BPs did not seem to increase the risk for any of the three outcomes. A different risk profile emerges, however, for IV BPs containing nitrogen. Consistently, in all analyses across the two reference diseases, osteoporosis and cancer, people who had received IV BPs had significantly higher risks of experiencing adverse outcomes.

Limitations inherent in this study design would be expected to affect the results equally for both modes of BP administration. The emerging differential risk profile seems to validate our conclusions that IV BPs are associated with elevated risk of experiencing adverse bone outcomes.

Other researchers have confirmed the finding that IV BPs, mostly zoledronate, increase the risk of ONJ among patients with cancer. Ortega and colleagues²² studied the association between ONJ and zoledronate in 52 consecutively seen patients with prostate cancer followed up for three years and found that ONJ occurred in 12 percent of patients, starting seven months after initiation of zoledronate therapy or after the ninth administration. It is important to note that this finding of a seven-month lag between initiation of zoledronate therapy and the occurrence of ONJ is

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In all analyses across the two reference diseases, osteoporosis and cancer, people who had received intravenous bisphosphonates had significantly higher risks of experiencing adverse outcomes.

consistent with the timing of the first reports to the FDA's MedWatch Adverse Event Reporting Program after the approval and subsequent marketing of zoledronate for the treatment of cancer in 2002.²³ Ortega and colleagues²², however, raised the possibility that an interaction may occur with docetaxel, as this chemotherapy was associated with an increased, but not statistically significant, risk.

In a retrospective study of 106 patients with multiple myeloma, Corso and colleagues²⁴ found that a reduced dose of zoledronate seemed to decrease the risk of ONJ. Interestingly, this study addresses three of Hill's²⁵ criteria for causation: magnitude of the effect, dose-response and temporal sequence. ONJ occurred in six patients receiving the higher-dose zoledronate regimen and in one patient receiving the reduced dose. With regard to the comparison between pamidronate and zoledronate, zoledronate alone was associated with an incidence of 9.1 per 100 person-years, whereas no ONJ was observed in patients treated only with pamidronate. On the basis of the findings, the authors²⁴ recommended that a reduced schedule of zoledronate dosing should be considered while maintaining anti-resorptive efficacy.

There is insufficient evidence with regard to the incidence of ONJ among patients with osteoporosis receiving long-term oral BP therapy. According to Bilezikian,¹⁹ among several million patients who have received oral treatment for osteoporosis, fewer than 50 cases of ONJ have been reported to date. Moreover, with more than 60,000 patient-years of exposure to nitrogen-containing BPs in clinical trials of treatment for osteoporosis (involving follow-up for as long as 10 years in some patients), ONJ was not reported among the adverse events. In an Australian study that used a postal survey of oral and maxillofacial surgeons plus members of the Commonwealth of Australia Adverse Drug Reaction Committee, the frequency of ONJ in patients receiving weekly oral doses of alendronate was one per 2,260 to 8,470 patients (0.01 to 0.04 percent).¹⁸ The frequency increased significantly if the patients had received tooth extractions (one per 296-1,130 cases, or 0.09-0.34 percent). According to the authors, the total dose of oral alendronate at the onset of ONJ was 9,060 mg (\pm standard deviation of 7,269 mg). For patients receiving IV BPs who had extractions, the frequency of ONJ was one per 11 to 15, or 6.67 to 9.1 percent of the total

estimated sample size. The median time to onset of ONJ was 12 months for zoledronate, 24 months for pamidronate and 24 months for alendronate. While this study provides useful data, there are inherent limitations with the methods used that preclude firm conclusions.¹⁸

Another consistent finding between the osteoporosis and cancer groups in our study was the elevated risk of having had a major surgical procedure involving the mandible or the maxilla for a necrotic or inflammatory indication for those receiving IV BPs. The OR of oral surgery among the patients with osteoporosis was 7.8 (95 percent CI, 2.84-21.36) and 6.8 among patients with cancer (95 percent CI, 4.18-11.14). The result is statistically significant, with the lowest confidence bound equal to 2.84. We noted that this pattern did not apply to CPT claims that characterized major surgeries for tumor resection. Again, this distinction seems to be compatible with expected health care practices of treating necrotic conditions in the mandible or the maxilla, and not with cancer metastasis to the jaws.

CONCLUSION

IV, but not oral, BPs seem to be strongly associated with adverse outcomes in the jaws. The increased risks reported here may reflect an increased risk of experiencing ONJ among users of IV BPs. The fact that we were able to replicate a previous study, and the fact that there is internal consistency in both referent conditions (osteoporosis and cancer), raise our confidence about the results and the conclusions of our study. However, carefully controlled clinical studies are required to establish the incidence and risk of ONJ, as well as to look for additional serious adverse bone outcomes in patients who receive IV BPs. While our results strongly indicate that patients taking oral BPs seem to benefit from this class of drugs, more studies are needed to assess any long-term effects. Similarly, as physicians who care for patients with osteoporosis start substituting oral agents for once-per-year IV zoledronate, more data are required with regard to possible synergies between different types of BPs. ■

This research was partially supported by National Institute of Dental and Craniofacial Research grant 1 R21 DE018143-01.

The authors thank i3 Drug Safety, Basking Ridge, N.J., for providing the data for this study at no charge. They also acknowledge the support of Hubert Park, BS, who assisted with the literature review.

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