An Observational Study of Musculoskeletal Pain Among Patients Receiving Bisphosphonate Therapy

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OBJECTIVE: To seek evidence for the association of bisphosphonate use with diffuse musculoskeletal pain (MSKP) in a large national cohort, controlling for conditions associated with MSKP.

PATIENTS AND METHODS: This retrospective cohort study enrolled all US veterans aged 65 years or older with a vertebral or hip fracture who were treated for at least 1 year between October 1, 1998, and September 30, 2006 (N=26,545). All *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* diagnostic codes, demographics, and pharmaceutical data were obtained from national databases. A composite end point, based on *ICD-9-CM* codes compatible with diffuse MSKP, was constructed. The primary outcome was time until MSKP. We performed regression analysis using the Cox proportional hazards model, controlling for age, sex, race, alcoholism, depression, anxiety, smoking, recent 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) use, rheumatic disease, and comorbidity score.

RESULTS: The univariate regression identified an association of bisphosphonate exposure and MSKP (hazard ratio, 1.22; 95% confidence interval, 1.04-1.44). In the multivariate regression, however, patients prescribed a bisphosphonate were not more likely to be assigned an *ICD-9-CM* code compatible with diffuse MSKP (hazard ratio, 1.10; 95% confidence interval, 0.93-1.30). Consistent with prior studies, we found that female sex, depression, anxiety, comorbidity score, and the presence of a rheumatic disease were all associated with a greater risk of a diagnosis of diffuse MSKP. There was no demonstrable association with statin exposure.

CONCLUSION: Bisphosphonate use was not associated with a statistically higher rate of MSKP in this cohort. Individual patients may rarely report MSKP while taking bisphosphonates; however, for our studied cohort, incident MSKP does not appear to explain bisphosphonate discontinuation rates.

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HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; HR = hazard ratio; ICD-9-CM = *International Classification of Diseases, Ninth Revision, Clinical Modification*; MSKP = musculoskeletal pain; OR = odds ratio; VA = US Department of Veterans Affairs

Osteoporosis has been defined as a disease of reduced bone mass and microarchitectural deterioration that increases the susceptibility to fracture.¹ The lifetime risk of an osteoporotic fracture at age 50 years is 40% to 53% among women and 13% to 22% among men.² For 1995, osteoporotic fractures in the United States accounted for expenditures of \$13.7 billion.³ Bisphosphonates have a seminal role in preventing these adverse outcomes of osteoporosis.

Unfortunately, inadequate adherence to bisphosphonate therapy (as measured by the medication possession ratio, the percentage of time during a course of therapy for which a patient obtained the medication) may result in a relative decline in bone mineral density⁴ and increased fracture risk.⁵ Despite the proven ability of bisphosphonates to decrease fracture rates, premature discontinuation (non-persistence) rates for bisphosphonate therapy may exceed 50% at 1 year.^{6,7} Previously identified risk factors for premature bisphosphonate discontinuation include age, dosing regimen, polypharmacy, type of health plan,⁸ mental disorders,⁷ and the occurrence of an adverse drug reaction, particularly one that is gastrointestinal.⁸

An association between bisphosphonate therapy and the onset of severe, diffuse musculoskeletal pain (MSKP) has been suggested by a case series derived from US Food and Drug Administration postmarketing surveillance data⁹ and an uncontrolled observational study of oral bisphosphonates.¹⁰ This observational study reported that, among patients taking oral bisphosphonates once weekly, 25.0% of those taking risedronate and 20.1% of those taking alendronate reported musculoskeletal adverse effects; however, the difference in these percentages was not statistically significant. More recently, 2 randomized controlled trials of a parenterally administered bisphosphonate described a

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greater incidence of MSKP in the active treatment arm,^{11,12} leading to the release of a Food and Drug Administration alert.¹³ These trials, however, did not control for risk factors associated with MSKP that may confound this relationship, nor did they address the question of whether those taking oral bisphosphonates are at increased risk of diffuse MSKP.

We sought evidence for the association of bisphosphonates and nonspecific MSKP in a large national cohort, controlling for conditions associated with MSKP.

We hypothesize that, among an elderly cohort of patients with prior hip or vertebral fractures, the risk of incident MSKP is greater for patients exposed to bisphosphonates than for those who are unexposed. We further hypothesize that the risk of MSKP varies depending on the specific bisphosphonate and the dosing regimen. Finally, we anticipate that patients experiencing MSKP are more likely to discontinue bisphosphonate use than those without MSKP.

PATIENTS AND METHODS

Data for this study were collected from national administrative databases operated by the US Department of Veterans Affairs (VA). Clinical and administrative data were derived from clinical encounters occurring between October 1, 1998, and September 30, 2006, at VA facilities (about 160 hospitals and 800 community-based outpatient clinics). This study was approved by the Human Studies Committees of the Hines (IL), St Louis, and Denver VA Medical Centers.

To be included, patients were required to have at least 2 separate outpatient or inpatient clinical encounters, one to serve as a baseline and at least one to serve as a follow-up visit. To enrich the study cohort for the presence of osteoporosis and more closely approximate the populations studied in randomized controlled trials of bisphosphonates, we restricted the study to patients 65 years or older with a femoral or vertebral fracture (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes 805.2-805.5, 806.2-806.5, 820.X, and 821.X). A list of ICD-9-CM codes used to develop outcome and potential confounder variables is provided in eTable 1 (online linked to this article).

We also required that patients have their sex recorded because of its recognized importance in the risk of osteoporosis. To diminish the likelihood of preexisting MSKP at the first visit, we required that patients have no diagnostic code compatible with nonspecific MSKP for 12 months after their initial affiliation with the VA. To participate in the study, patients had to have taken a nonbisphosphonate medication for at least 12 months before the first receipt of a bisphosphonate to ensure that they relied on the VA for

their medications and to capture patients more likely to be first-time bisphosphonate users. Thus, the bisphosphonate start time was equivalent to the date of a participant's first bisphosphonate prescription that occurred after a minimum of 1 year's observation without a bisphosphonate.

OUTCOME

The first occurrence during the period of observation of an ICD-9-CM code compatible with diffuse MSKP represents the primary outcome. This end point includes codes for pain without a specific anatomic site (*chronic pain*), pain syndromes (*generalized pain*), or pain occurring at multiple sites that are not specified (*joint pain, multiple sites*). Patient records were censored at the time of first occurrence of MSKP or at 12 months after the end of the last prescribed medication course or the last clinical encounter, whichever came last. Censoring signifies that data subsequent to an event were not included in the analysis. Thus, recurrent MSKP was excluded from our analyses, and we did not investigate pain persistence. Uncensored patients were followed up through September 30, 2006.

POTENTIAL CONFOUNDERS

The list of potential confounders includes age, sex, race, prior fracture, and smoking. We included specific psychiatric disorders, such as depression and anxiety, because they may be associated with pain tolerance or somatic complaints. Prior exposure to 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (ie, statins) was also included because these medications have been associated with the development of myalgias.¹⁴ To account for comorbid medical conditions, we used the Romano implementation of the Charlson index, modeled as a continuous single score. The Romano score represents the best comorbidity adjustment in administrative data,¹⁵ has been reweighted to better estimate current prognoses of medical conditions, and has been validated in data derived from both ambulatory and hospital encounters.¹⁶

BISPHOSPHONATES

The bisphosphonates appearing in the VA's national pharmacy database include alendronate (94.41% of all bisphosphonate prescriptions), risedronate (4.32%), etidronate (1.11%), pamidronate (0.13%), and zoledronic acid (0.03%). Dosing regimens suggestive of treatment for Paget disease of bone (eg, 40 mg/d of alendronate or 30 mg/d of risedronate) were excluded. The dose of the most common bisphosphonate—alendronate—was treated as an effect modifier and was classified as either low (average weekly dose, 33-37 mg) or high (65-82 mg). Slight variations in the dose were attributable to the conversion of

daily-dose regimens and monthly prescriptions into weekly-dose equivalents.

VALIDATION OF OUTCOME

The MSKP outcome was validated by (1) calculating diagnostic metrics and (2) comparing nurse-recorded pain scores on the 11-point Numerical Rating Scale (range of scores, 0-10) from a sample of cases with the pain scores from a sample of controls. For the first procedure, a convenience sample of 62 records was selected for medical record review. We examined 31 cases that included an *ICD-9-CM* code compatible with MSKP (according to the administrative data), matched with 31 controls without an MSKP code. Using health care professional–provided descriptions in the medical record, we classified participants according to the presence or absence of MSKP simultaneously occurring at multiple sites (≥ 2 areas of the body). We then calculated sensitivity, specificity, and positive and negative predictive values.

For the second procedure, a second convenience sample of 60 records was selected, 30 with and 30 without an *ICD-9-CM* code compatible with MSKP. We abstracted pain scores recorded by nurses as part of routine vital sign measurement at the time of every clinical encounter. The Veterans Health Administration National Pain Management Strategy, which mandated consistent pain assessments at all outpatient, inpatient, home, and nursing home encounters, was initiated on November 12, 1998, preceding the current study.¹⁷ For cases, we used the pain score recorded on the date that the MSKP *ICD-9-CM* code was documented. For controls, we chose a random date on which a non-MSKP *ICD-9-CM* code was assigned. Pain scores were compared for these 2 sample cohorts using the *t* test.

DATA SOURCES AND MEASUREMENT

We obtained all *ICD-9-CM* codes, inpatient and outpatient encounter data, and demographic data from the VA Corporate Franchise Data Center, a national centralized computer-processing center. This restricted-access archive houses inpatient and outpatient diagnosis codes and demographic characteristics assigned to all patients enrolled in the VA health care system. (Detailed information regarding VA data may be accessed at the VA Information Resource Center Web site.¹⁸) For our study, we relied on the patient treatment file, which contains a statistical record for each inpatient care episode, including data on admission, diagnosis (primary admitting diagnosis; primary discharge diagnosis; and up to 13 additional treated, observed, or known diagnoses that influenced the patient's length of stay), procedures, surgical episodes, and disposition (discharge) information. Outpatient data were drawn from the visit and event data sets, which contain up to 10 diagnostic

and 20 procedure codes per encounter. We obtained inpatient and outpatient pharmacy data on our patients from the Pharmacy Benefits Management Database,¹⁸ a national repository of pharmacy data for all patients in the VA health care system. Each month, all local medication-related data (including product, dosage, quantity dispensed, prescription signature, refills, dispensing location) for both inpatient and outpatient veterans are extracted to the national level. Clinical and pharmacy data may be linked through use of a unique patient identifier.

STATISTICAL ANALYSES

Time-to-event analysis was performed using Cox proportional hazards regression. In the regression modeling, membership in the bisphosphonate or nonbisphosphonate group was modeled as a *nonreversible* time-dependent dummy variable to account for the change in groups over time. Each bisphosphonate (and, in the case of alendronate, each dosage class) was modeled separately and adjusted for age, sex, race, and potential confounders in addition to the comorbidity score. Modeling of confounders such as fractures and comorbid conditions in a time-dependent fashion allowed us to account for the timing of these risk factors relative to bisphosphonate exposures. Logistic regression was used to compare the odds of bisphosphonate persistence among patients who experienced MSKP vs those who did not. Bisphosphonate persistence was defined as the appearance of a prescription for bisphosphonates within the most recent 90-day interval of prescription data for each patient. A 2-sided $P \leq .05$ was considered statistically significant. Risk of outcomes was described using hazard ratios (HRs) and 95% confidence intervals (CIs). All analyses were performed using SAS software version 6.12 (SAS Institute, Cary, NC). A time-to-event graph was created using R software version 2.5.1 (R Foundation, Vienna, Austria).

RESULTS

A flow diagram (Figure 1) illustrates the process for assembly of the study cohort. Very few veterans were excluded on the basis of an MSKP-compatible *ICD-9-CM* code occurring in the 12 months after their initial affiliation with the VA. The final cohort of 26,545 patients contributed more than 37.5 million patient-days of observation. During the course of the study, 3818 patients initiated bisphosphonate therapy. The mean $\pm$ SD and median times from entry into the cohort until initiation of bisphosphonate therapy were 2.87 ± 1.75 years and 2.74 years, respectively.

DESCRIPTIVE DATA

Patient demographics and comorbid medical conditions appear in Table 1. The cohort was predominantly male and

FIGURE 1. Study flow diagram. “Censored” refers to those patients who did not have a code for incident musculoskeletal pain (MSKP) at the time of last clinical encounter or termination of the observation period for the data set.

TABLE 1. **Demographics and Clinical Characteristics of Cohort During Exposure to Bisphosphonates or While Naive to Bisphosphonates^a**

	Exposure to bisphosphonates (n=3818)	Naive to bisphosphonates (n=26,498)	Total (N=26,545) ^b
Age (y), mean $\pm$ SD	77.4 $\pm$ 6.3	75.3 $\pm$ 6.6	75.3 $\pm$ 6.6
Male sex	3473 (91.0)	25,563 (96.5)	25,601 (96.4)
Race			
White	3341 (87.5)	22,326 (84.3)	22,364 (84.2)
Black	178 (4.7)	2451 (9.3)	2454 (9.2)
Other	41 (1.1)	215 (0.8)	216 (0.8)
Unknown	258 (6.8)	1506 (5.7)	1511 (5.7)
Qualifying fracture			
Vertebral	1810 (47.4)	6057 (22.9)	6655 (25.1)
Femoral	2163 (56.7)	19,722 (74.4)	20,369 (76.7)
Multiple	1083 (28.4)	5673 (21.4)	5687 (21.4)
Smoking	888 (23.3)	5175 (19.5)	5337 (20.1)
Romano comorbidity score, mean $\pm$ SD	5.5 $\pm$ 3.8	5.6 $\pm$ 3.9	5.8 $\pm$ 3.9
Depression	1317 (34.5)	8230 (31.1)	8532 (32.1)
Anxiety	821 (21.5)	4868 (18.4)	5045 (19.0)
Alcoholism	461 (12.1)	3339 (12.6)	3402 (12.8)
Receiving 3-hydroxy-3- methylglutaryl reductase inhibitor	1908 (50.0)	10,589 (40.0)	10,988 (41.4)
History of rheumatic disease	2595 (68.0)	15,484 (58.4)	15,859 (59.7)
Rheumatoid arthritis	329 (8.6)	1233 (4.7)	1279 (4.8)
Osteoarthritis	2412 (63.2)	14,367 (54.2)	14,773 (55.7)
Crystal-associated arthropathy ^c	353 (9.2)	2297 (8.7)	2346 (8.8)
Other ^d	105 (2.8)	427 (1.6)	459 (1.7)

^a Data represent number (percentage) of patients, unless otherwise indicated.

^b Because an individual patient may contribute patient time to both the nonbisphosphonate group and the bisphosphonate group, the total number of patients does not equal the sum of the bisphosphonate and nonbisphosphonate groups.

^c Gout and pseudogout.

^d Systemic lupus erythematosus, scleroderma, and spondyloarthritis.

TABLE 2. Bisphosphonate Use

	No. of patients	Total patient-years of medication use	MSKP ^a	Incident MSKP (per 100 patient-years)
Alendronate	3691	7363	155	2.1
Alendronate, low dose ^b	373	264	9	3.4
Alendronate, high dose ^c	3427	6777	145	2.1
Risedronate	233	362	5	1.4
Other ^d	88	128	5	3.9
Any bisphosphonate	3818	7706	164	2.1
No bisphosphonate	26,498	94,455	2041	2.2

^a Expressed as number of incident cases of musculoskeletal pain (MSKP).

^b Includes 5 mg/d or approximately 35 mg/wk.

^c Includes 10 mg/d or approximately 70 mg/wk.

^d Includes etidronate, pamidronate, and zoledronic acid.

white. A substantial proportion of this elderly population (n=15,859 [59.7%]) was classified as having a rheumatic disease, the most frequent of which was osteoarthritis (n=14773 [55.7%]). Comorbid conditions were common (mean $\pm$ SD number of conditions, 5.8 $\pm$ 3.9). Almost a third of patients (n=8532 [32.1%]) were assigned diagnostic codes compatible with depression. Of the study patients, 10,988 (41.0%) were prescribed HMG-CoA reductase inhibitors (ie, statins). Bisphosphonate use in the cohort is described in Table 2. In unadjusted analysis, patients prescribed one of the bisphosphonates were subsequently assigned a diagnostic code of MSKP at a rate of 1.4 to 3.9 events per 100 patient-years of observation, whereas for patients not taking bisphosphonates, this value was 2.2 events per 100 patient-years.

OUTCOME DATA

Results of the univariate Cox proportional hazards regressions are available in eTable 2 (online linked to this article). In this unadjusted analysis, bisphosphonate use was

weakly associated with incident MSKP (HR, 1.22; 95% CI, 1.04-1.44; $P=.02$). In the multivariate time-to-event analysis, a number of predictors were associated with a greater risk of MSKP, as is demonstrated in Table 3. Notably, when we controlled for all potential confounders, bisphosphonate use was associated with no increase in the risk of MSKP (HR, 1.10; 95% CI, 0.93-1.30; $P=.29$). Male sex (HR, 0.71; 95% CI, 0.58-0.86) and age (HR, 0.98; 95% CI, 0.98-0.99) were associated with reduced risk of MSKP. Statin prescriptions were not associated with increased risk of MSKP (HR, 1.03; 95% CI, 0.94-1.12).

A survival plot of incident MSKP (Figure 2), constructed according to the methods of Schultz et al,¹⁹ suggests no differences in rates of diagnosis of diffuse MSKP between those receiving bisphosphonate therapy vs those who were not. Rates remain parallel among those naive to bisphosphonates and those exposed to bisphosphonates for the entire period of observation.

We performed a series of subgroup analyses controlling for all significant covariates (Table 4). Compared with

TABLE 3. Risk Factors for Musculoskeletal Pain, Multivariate Regression

	MSKP	No MSKP	P value	HR (95% CI)
Age (y), mean $\pm$ SD	74.0 $\pm$ 4.4	75.5 $\pm$ 6.6	<.001	0.98 (0.98-0.99)
Male sex	2097 (95.1)	23,504 (96.6)	.001	0.71 (0.58-0.86)
Vertebral fracture	694 (31.5)	5961 (24.5)	<.001	1.29 (1.14-1.47)
Femoral fracture	1575 (71.4)	18,794 (78.7)	.03	0.90 (0.81-0.99)
Multiple fractures	614 (27.9)	5073 (20.8)	<.001	1.22 (1.11-1.34)
Smoking	347 (15.7)	4990 (20.5)	.24	0.93 (0.83-1.05)
Romano comorbidity score, mean $\pm$ SD	4.4 $\pm$ 3.5	5.9 $\pm$ 3.9	<.001	1.04 (1.02-1.05)
Depression	690 (31.3)	7842 (32.2)	<.001	1.25 (1.13-1.38)
Anxiety	508 (23.0)	4537 (18.6)	<.001	1.42 (1.27-1.58)
Alcoholism	220 (10.0)	3182 (13.1)	.43	0.94 (0.82-1.09)
Receiving a statin	1108 (50.3)	9 880 (40.6)	.56	1.03 (0.94-1.12)
History of rheumatic disease	1487 (67.4)	14,372 (59.0)	<.001	1.93 (1.76-2.11)
Bisphosphonate use	164 (7.4)	3654 (15.0)	.29	1.10 (0.93-1.30)

Data represent number (percentage) of patients, unless otherwise indicated. CI = confidence interval; HR = hazard ratio; MSKP = musculoskeletal pain.

FIGURE 2. Time-dependent survival plot: time to musculoskeletal pain (MSKP) in patients taking bisphosphonates.

bisphosphonate-naïve patients, those prescribed alendronate (HR, 1.12; 95% CI, 0.94-1.34), even at higher doses (HR, 1.14; 95% CI, 0.95-1.36), and those prescribed risedronate (HR, 0.50; 95% CI, 0.07-3.58) were at no greater risk of MSKP.

Of patients assigned a diagnostic code of MSKP, 54.0% continued to receive their bisphosphonate therapy (ie, were taking bisphosphonates during the most recent 90-day in-

terval for which any prescription data were available). Of patients without an MSKP code, 53.9% continued to receive bisphosphonate therapy. The odds of bisphosphonate continuation among patients with a diagnosis of MSKP was 1.01 (95% CI, 0.74-1.38; $P=.95$).

Compared with medical record review, the occurrence of an MSKP *ICD-9-CM* code was found to exhibit the following diagnostic metrics: sensitivity, 67.7%; specificity,

TABLE 4. Risk Factors for MSKP, Subgroup Analyses^a

	MSKP	No MSKP	<i>P</i> value	HR (95% CI) ^b
Bisphosphonate use				
Alendronate	155 (7.0)	3536 (14.5)	.19	1.12 (0.94-1.34)
Alendronate, low dose ^c	9 (0.4)	364 (1.5)	.89	1.05 (0.54-2.02)
Alendronate, high dose ^d	145 (6.5)	3282 (13.5)	.17	1.14 (0.95-1.36)
Risedronate	5 (0.2)	228 (0.9)	.49	0.50 (0.07-3.58)
Other	5 (0.2)	83 (0.3)	.32	1.64 (0.61-4.38)
History of rheumatic disease				
Rheumatoid arthritis	182 (8.3)	1097 (4.5)	<.001	1.68 (1.44-1.97)
Osteoarthritis	1385 (62.8)	13,388 (55.0)	<.001	1.80 (1.64-1.97)
Crystal-associated arthropathy ^e	221 (10.0)	2125 (8.7)	<.001	1.30 (1.13-1.50)
Other ^f	68 (3.1)	391 (1.6)	<.001	1.85 (1.45-2.36)
Sensitivity analysis				
Diffuse and localized pain	7044 (26.5)	19,501 (73.5)	.93	1.00 (0.90-1.11)

^a Data represent number (percentage) of patients, unless otherwise indicated. CI = confidence interval; MSKP = musculoskeletal pain.

^b Proportional hazard ratio (HR) compared with bisphosphonate-naïve patients, controlling for age, sex, race, fracture site, multiple prior fractures, smoking status, comorbid conditions, depression, anxiety, alcoholism, statin use, and (in the models examining bisphosphonate use) rheumatic disease or (in the models examining rheumatic disease) bisphosphonate use.

^c Includes 5 mg/d or approximately 35 mg/wk.

^d Includes 10 mg/d or approximately 70 mg/wk.

^e Gout and pseudogout.

^f Systemic lupus erythematosus, scleroderma, and spondyloarthropathy.

61.3%; positive predictive value, 63.6%; and negative predictive value, 65.5%. The mean pain score for patients assigned an *ICD-9-CM* code compatible with MSKP exceeded the mean pain score for those not assigned such a code (4.33 vs 2.23; $P=.01$).

DISCUSSION

Oral bisphosphonate prescription in elderly patients at high risk of osteoporosis does not appear to be associated with a statistically significant risk of subsequent MSKP diagnoses. Visual inspection of the survival plot reveals that the rate of MSKP in patients receiving bisphosphonate therapy paralleled that of bisphosphonate-naïve patients throughout the period of observation. Similarly, in our study, MSKP did not result in a statistically significant increase in the rate of bisphosphonate discontinuation. From these data, we may infer that, even if oral bisphosphonates are responsible for MSKP in a statistically undetectable minority of patients, this MSKP is likely not sufficiently severe in a sufficient number of patients to affect overall adherence rates for the cohort as a whole. As an alternative explanation, clinicians may simply be unaware of the putative association of bisphosphonates and MSKP and therefore may not consider discontinuing bisphosphonate therapy.

The findings of this study contrast with prior reports, which suggest an association of bisphosphonates with MSKP. However, the prior reports of oral bisphosphonates consist of postmarketing surveillance data⁹ and an uncontrolled observational study.¹⁰ The analysis in our study, by comparison, incorporated conditions that may confound assessments of pain. Our cohort also differed from previously studied populations in that it consisted preponderantly of older white men. The most convincing prior evidence linking bisphosphonates with incident MSKP occurred in the setting of randomized controlled trials with parenteral bisphosphonate formulations.^{11,12} However, oral formulations accounted for the vast majority of the bisphosphonates in our study. Together, these differences may explain the disparate findings.

Bisphosphonates were initiated in only 14% of patients at risk of osteoporosis. This low rate of bisphosphonate use corroborates the findings of prior studies of diverse populations.²⁰⁻²² The failure to adequately treat osteoporosis and optimize fracture prevention strategies warrants further inquiry. Novel methods of addressing this pervasive problem should be studied.

Our cohort was deliberately composed of patients with prior vertebral or femoral fracture. Because MSKP has been described after bisphosphonate use in patients without prior fractures, further studies should be conducted to elucidate whether our findings extend to patients without

prior fractures. Because our population was primarily male, additional investigations should be performed in cohorts that reflect the female predominance of osteoporosis. It is possible that male veterans may not admit feeling pain for fear of being stigmatized. For this reason, a similar study should be replicated in a primarily female population.

A number of expected associations demonstrate face validity for our results. Specifically, the risk of a diagnosis of MSKP increased with preexisting vertebral fractures, multiple fractures, comorbid conditions, depression, anxiety, and rheumatic diseases. Furthermore, the risk declined with male sex. Although statin-associated myalgias appear to be a fairly common adverse drug reaction and to occur with greater frequency in observational trials than in randomized controlled trials, we found no association between statin use and MSKP diagnoses.²⁰

A plausible biological mechanism explaining the association between parenteral bisphosphonates and MSKP has yet to be elucidated. Any pathophysiologic explanation would be complicated by the observation that bisphosphonates may alleviate the bone pain associated with a variety of disorders, including malignancies metastatic to bone,²³ Paget disease of bone,^{24,25} and osteoporosis.²⁶ Possible mechanisms of bone pain may include osteitis, including direct cytokine-mediated acute phase reactions,²⁷ bone marrow pressure changes, localized bone hypoxemia,²⁸ and direct stimulation of mechanical nociceptors.²⁸ Furthermore, extraosseous effects may occur in surrounding soft tissues, as may be the case with statins. Of note, both statins (which inhibit HMG-CoA reductase) and bisphosphonates (which inhibit farnesyl diphosphate synthase) disrupt the HMG-CoA/mevalonate pathway; however, the effect of bisphosphonates occurs more distally.

Our study has several limitations. Perhaps most importantly, patients did not provide systematic assessments of pain. A more rigorous approach would have used prospective measurements of pain obtained with a validated pain scale for the entire cohort. Instead, we relied on administrative codes assigned by providers (ie, physicians, nurse practitioners, physician assistants). Because our method depends on a dichotomous outcome (presence of a provider-assigned diagnostic code vs the absence of a code), it would likely be insensitive to detecting changes in pain (compared with a validated continuous pain scale). Thus, our mechanism of data capture could underestimate the true rate of diffuse MSKP. Of note, our validation procedures for the MSKP codes suggested that patients classified as having MSKP according to the administrative data exhibited a mean pain score roughly double that of patients without an MSKP *ICD-9-CM* code.

Patients with malignancies metastatic to bone were not excluded from our study population because *ICD-9-CM* codes cannot identify metastatic disease. In addition, the

race variable derived from the VA Corporate Franchise Data Center has been shown to exhibit poor correlation with patient self-report.²⁹ However, because race may play a role in susceptibility to osteoporosis, we included race in our analyses, recognizing that this variable may not have fully controlled for the confounding associated with race. Administrative data may also be relatively insensitive for detection of mood disorders and alcoholism. Furthermore, because this is a nonrandomized observational study, its results are susceptible to confounding by indication. Confounding by indication means that the characteristics that providers used to select bisphosphonates may also affect the likelihood of developing pain. Unfortunately, minimal use of parenteral bisphosphonates precluded comparisons of route of administration.

The current study accounts for the time sequence between exposure and hypothesized outcome. Although our results are not definitive, patients may be reassured that, for large populations, MSKP associated with oral bisphosphonate use does not appear to interfere with likelihood of continuing the therapy.

Only a very limited number of studies have investigated the issue of MSKP among patients receiving oral bisphosphonate therapy, and no controlled observational studies were performed before this report. Thus, before being accepted, our findings should be evaluated in additional administrative data sets and through reanalysis of existing controlled trial data. Similarly, this study should be replicated in demographically distinct populations to assess the consistency of the results.

CONCLUSION

Bisphosphonate use was not associated with a statistically higher rate of MSKP in this cohort of patients receiving (predominantly oral) bisphosphonate therapy. Although individual patients may rarely report MSKP while taking bisphosphonates, for our studied cohort, incident MSKP does not appear to explain bisphosphonate discontinuation rates.

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