Association Between Gastrointestinal Events and Persistence with Osteoporosis Therapy: Analysis of Administrative Claims of a U.S. Managed Care Population

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ABSTRACT

BACKGROUND: A large proportion of patients do not persist with osteoporosis (OP) therapy. Gastrointestinal (GI) events (e.g., gastroesophageal reflux disease and nausea/vomiting) are common among OP patients receiving OP therapy and may impact persistence with treatment.

OBJECTIVE: To examine the association of GI events and persistence with OP therapy.

METHODS: Using a large U.S. administrative claims database, we studied women aged ≥ 55 years who received oral bisphosphonate (BIS) as their first OP therapy from 2002-2009. The index date was the first pharmacy claim date recorded for oral BIS therapy; the baseline period was 12 months pre-index, and follow-up was 12 months post-index. Patients were considered persistent with therapy if they had continuous refills of the index drug class without additional drug therapy from a different drug class from the index date until the end of the follow-up period with no gaps in supply greater than 45 days. Discontinuation was defined as the first gap greater than 45 days during which there was no evidence of refills of OP medication. The association between post-treatment GI events and the risk of discontinuation or switching was modeled with Cox regression stratified by presence of baseline GI events and adjusted for baseline clinical and demographic characteristics.

RESULTS: Of the 75,593 women who met eligibility criteria, 59.9% discontinued BIS; 39.3% were persistent; and 0.5% switched to non-BIS. GI events were diagnosed in 20,073 patients (26.6%) during baseline and in 21,142 (28.0%) in the post-treatment period (12-month follow-up post-index). Patients with post-treatment GI diagnosis were 35.6% more likely to discontinue or switch treatment (HR = 1.356, 95% CI = 1.318-1.396) during the 12-month follow-up compared with those without post-treatment GI diagnosis. GI events that occurred closer to treatment discontinuation or switching were associated with a greater risk of discontinuation or switching: 37.9% (HR = 1.379, 95% CI = 1.338-1.421) for GI events within 6 months of discontinuation or switching and 45.6% (HR = 1.456, 95% CI = 1.408-1.505) for GI events within 3 months of discontinuation or switching.

CONCLUSIONS: Among women aged 55 years or older in a U.S. managed care population, post-treatment GI events were associated with a higher risk of discontinuation of oral BIS or switching to non-BIS.

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What this study adds

- This study evaluated the association between post-treatment gastrointestinal events and treatment discontinuation and switching patterns among women during the first year of oral bisphosphonate treatment.
- Following initiation of oral bisphosphonate therapy, women who experienced gastrointestinal events were 36% more likely to discontinue therapy or switch to nonbisphosphonates than women who did not experience gastrointestinal events while on therapy.

Osteoporosis is a disease characterized by reduced bone mineral density and deterioration of bone microarchitecture. In the United States, there are an estimated 10 million people who have osteoporosis, and an additional 43 million have low bone density.¹ By 2020, it is expected that half of all Americans over 50 will be diagnosed with osteoporosis or develop clinically significant low bone density.²

Pharmacotherapy is recommended for patients diagnosed with osteoporosis and those at high risk for fragility fractures.³ The U.S. Food and Drug Administration had approved several agents for the treatment of osteoporosis, including bisphosphonates (e.g., alendronate, risedronate, ibandronate, and zoledronic acid); calcitonin; selective estrogen receptor modulators (e.g., raloxifene); parathyroid hormone (e.g., teriparatide); and the receptor activator of nuclear factor-kappa B ligand (RANKL) inhibitor (denosumab) during the 2002-2010 time frame. Among osteoporosis treatments, oral bisphosphonates are currently considered the first-line treatment option, with more than 150 million bisphosphonate prescriptions dispensed from 2005-2009 in the United States alone.⁴

However, suboptimal compliance and low persistence to osteoporosis medication pose significant challenges for reducing the risk of fragility fracture.^{5,6} Even though medication compliance is strongly linked to reduction in fracture risk,⁷⁻¹¹ several studies have indicated that compliance with osteoporosis medication is suboptimal as evidenced by a medication possession ratio less than 0.8.¹²⁻¹⁴ Additionally, many patients started on osteoporosis medication do not persist with treatment.^{9,10,15-17} Approximately 50% or more of patients newly started on bisphosphonates discontinue treatment within 12

What is already known about this subject

- Osteoporosis treatment significantly decreases the risk of fragility fracture. However, many patients do not persist with osteoporosis therapy long enough to gain the protective benefits of therapy.
- Gastrointestinal symptoms have been linked with osteoporosis therapy discontinuation in clinical practice.

months of initiation and, as a consequence, experience significantly higher risk of fracture compared with persistent patients.^{15,18-23}

Multiple studies indicate that medication side effects may be one of the key factors influencing patients' suboptimal treatment persistence and adherence behavior.²⁴⁻²⁶ Gastrointestinal (GI) events are common among patients receiving bisphosphonate therapy for the treatment of osteoporosis. GI events may significantly affect medication tolerability. Woo et al. (2010) recently conducted a prospective analysis that concluded that having any GI events at study entry was associated with increased therapy discontinuation.²⁷ However, there is limited evidence examining the association between GI events and treatment persistence within a managed care setting in the United States.

The purpose of this study was to estimate the proportion of patients with GI events post-treatment initiation and examine the association between GI events and osteoporosis treatment persistence in a U.S. managed care population.

Methods

Design and Data Source

The retrospective cohort study was conducted using the i3 InVision Data Mart (now the Optum Clinformatics Data Mart). This large, national U.S. claims database contains de-identified patient information, including demographic characteristics and medical and pharmacy claims data. Medical claims include *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis and procedures codes. The outpatient pharmacy claims data contain National Drug Code numbers for dispensed medications. Over 3 million patients with a diagnosis of osteoporosis, osteoporosis-related fracture, and/or a prescription for a medication used to treat or prevent osteoporosis were included in the database during the study period from January 2001 through December 2010.

Sample Selection

Women aged 55 years and older were eligible for the study if they initiated oral bisphosphonate (alendronate, ibandronate, or risedronate) therapy from January 1, 2001, through December 31, 2009 (index date is date of first oral bisphosphonate claim) and were continuously enrolled with medical and pharmacy benefits for 1 year before (baseline period) and 1 year after (follow-up period) the index date.

Patients were excluded if they had Paget's disease or a malignant neoplasm during the baseline or follow-up period or had claims for 2 oral osteoporosis therapies on the index date.

Measures

Patient characteristics assessed on the index date or during the baseline period included age (as of index date); comorbid conditions (celiac disease, chronic kidney disease, depres-

sion, diabetes, fatigue, GI mucositis and urination problems, hyperparathyroidism, hypertension, inflammatory bowel disease, inflammatory joint disease, or vitamin D deficiency); Deyo-Charlson Comorbidity Index (CCI);²⁸ and medication use (estrogen, gastroprotective agents, glucocorticoid, and non-steroidal anti-inflammatory drugs [NSAIDs]). Osteoporosis-related fractures (i.e., fragility fractures) were defined based on ICD-9-CM codes in the primary or secondary position from all medical and inpatient claims. Fractures of the hip (femur neck), vertebra, as well as nonvertebral fractures (pelvis, humerus, forearm, other femoral sites, tibia, fibula, rib, clavicle, scapula, and trunk) were included. The ICD-9-CM codes used to identify osteoporotic fractures are described in the Appendix. Fractures of hand, skull, digits, feet and ankle, and any open fractures were not considered as osteoporosis-related fractures.²⁹ Fractures of the same site were defined as distinct fractures if the occurrences were at least 30 days apart.

The occurrence of GI events was assessed during the baseline period and at 3, 6, and 12 months of follow-up (i.e., post-treatment). GI events and their severity classification were defined by the presence of relevant ICD-9-CM codes in the primary and/or secondary position from all medical or inpatient claims. The list of GI events, encompassing minor symptoms such as heartburn and nausea through major acute conditions such as GI hemorrhage and ulcers, is shown in the Appendix. Certain ICD-9-CM codes, typically those involving hemorrhage or perforation, were classified as serious GI events. The proportion of patients with GI events was defined as the percentage of individuals having at least 1 GI event and was calculated at baseline and at 3, 6, and 12 months in the follow-up period.

Treatment patterns assessed during follow-up were persistence, discontinuation, switching, and augmentation. Persistence was defined as continuous refills of the index drug class, without additional drug therapy from a different drug class, from the index date until the end of the follow-up period with no gaps in days supply greater than 45 days. The use of 45 days as the allowable gap was determined based on the fact that a typical prescription of oral bisphosphonate is usually 30 days, and we allowed a "leeway" of up to 1.5 times the typical duration of a prescription refill. Discontinuation was defined as the first gap in supply greater than 45 days at any time from the index date to the end of the follow-up period.

Switching was defined as a change in the index drug class, that is, from a bisphosphonate to a nonbisphosphonate, with discontinuation of the index drug class. For example, a medication change from ibandronate to raloxifene was considered a switch because these drugs represent different classes, while a medication change from alendronate to ibandronate was not considered a switch because both are within the bisphosphonate class.

Augmentation was defined as a new drug prescription for a nonindex drug class being observed while the index drug class

FIGURE 1 Patient Selection

^aOral osteoporosis therapy is alendronate, ibandronate, raloxifene, or risedronate.

was still being refilled. If a patient exhibited multiple treatment patterns (e.g., first switching, then augmenting), the first exhibited pattern was used to define their treatment pattern status for the study. All forms of osteoporosis therapy (oral, injectable, intranasal, and intravenous) were considered in the definition of switching and augmentation, including bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid), calcitonin, denosumab, raloxifene, and teriparatide.

Statistical Analysis

Baseline characteristics were assessed and compared between patients with and without post-treatment GI events. Differences in baseline characteristics were evaluated using t-tests for continuous variables and chi-square tests for binary and categorical variables.

The association between post-treatment GI events and treatment discontinuation or switching during 12-month follow-up was examined and quantified using Cox regression. In the regression model, the study outcome was time to discontinu-

ation or switch, right censored at end of the 12-month follow-up. The independent variable of interest was a time-varying variable indicating the occurrence of a post-treatment GI event, censored at discontinuation or switching. Because the patients with baseline GI events could be more prone to post-treatment GI diagnoses than those without baseline GI events, the regression model was developed by stratifying the presence of baseline GI events. Furthermore, the model also included age (grouped as 55-59, 60-69, 70-79, and 80-89), CCI, and the following baseline clinical characteristics expressed as binary variables (presence or absence): comorbid conditions, medication use, and osteoporosis-related fracture, as control variables. In addition, sensitivity analyses were conducted to assess the association for the occurrence of post-treatment GI events within 3 and 6 months before the discontinuation and/or switching. Augmenters were excluded from the regression analysis as only 189 (0.3%) patients in the study were taking 2 osteoporosis medications simultaneously.

Results

Patient Selection and Baseline Characteristics

A total of 617,989 women with at least 1 claim for an oral osteoporosis therapy during the index window January 1, 2002-December 31, 2009, were identified, and the final sample included 75,593 eligible patients (Figure 1). The predominant reasons for exclusion were aged less than 55 years as of the index date (n=239,756, 38.8%) and lack of continuous eligibility with medical and pharmacy benefits during baseline and follow-up (n=223,412, 36.2%). Mean age at index was 64.4 years (Table 1). GI events were diagnosed in 26.6% of the patients in the baseline period, and 3.6% of patients had a serious baseline GI event. There were 4,531 (6.0%) patients with an osteoporotic fracture, and 17.9% of patients used gastro-protective agents. There were several differences in the baseline characteristics among patients who did versus those who did not experience a post-treatment GI event, most notably a higher rate of baseline GI events in patients who subsequently had a post-treatment GI event (48.6% vs. 18.0%). A higher proportion of patients who experienced a post-treatment GI event also had an osteoporotic fracture (7.4% vs. 5.4%), used gastro-protective agents (34.3% vs. 11.5%), and had osteoporosis-related comorbidities during baseline.

Rate of GI Events

For all patients, the rate of GI events at 3, 6, and 12 months post-treatment was 10.7%, 17.5%, and 28.0%, respectively (Table 2). Compared with patients who did not experience a baseline GI event (73.4% of patients), patients with a baseline GI event (26.6% of patients) had a higher rate of GI events during the post-treatment period: 23.0% vs. 6.3% during the first 3 months post-treatment, 35.3% vs. 11.1% at 6 months, and 51.2% vs. 19.6% at 12 months.

Association Between Gastrointestinal Events and Persistence with Osteoporosis Therapy: Analysis of Administrative Claims of a U.S. Managed Care Population

TABLE 1 Baseline Patient Characteristics

Characteristics	All Patients (N = 75,593)	With Post-Treatment GI Event (n = 21,142)	Without Post-Treatment GI Event (n = 54,451)	P Value ^a
Index age in years, mean (SD)	64.4 (8.4)	64.9 (8.5)	64.3 (8.4)	<0.001
Age group, n (%)				<0.001
55-59	27,820 (36.8)	7,267 (34.4)	20,553 (37.8)	-
60-69	28,770 (38.1)	8,223 (38.9)	20,547 (37.7)	-
70-79	12,038 (15.9)	3,558 (16.8)	8,480 (15.6)	-
≥80	6,965 (9.2)	2,094 (9.9)	4,871 (9.0)	-
GI event, n (%)	20,073 (26.6)	10,276 (48.6)	9,797 (18.0)	<0.001
Serious GI event, n (%)	2,707 (3.6)	1,380 (6.5)	1,327 (2.4)	<0.001
Osteoporosis-related fracture, n (%)	4,531 (6.0)	1,568 (7.4)	2,963 (5.4)	<0.001
Hip	978 (1.3)	331 (1.6)	647 (1.2)	<0.001
Vertebral	1,677 (2.2)	652 (3.1)	1,025 (1.9)	<0.001
Nonvertebral	2,574 (3.4)	855 (4.0)	1,719 (3.2)	<0.001
Number of distinct fracture sites, n (%)				<0.001
1	3,876 (5.1)	1,319 (6.2)	2,557 (4.7)	-
2	612 (0.8)	228 (1.1)	384 (0.7)	-
3	43 (0.1)	21 (0.1)	22 (0.0)	-
Medication use, n (%)				
Gastroprotective agents	13,523 (17.9)	7,254 (34.3)	6,269 (11.5)	<0.001
Proton pump inhibitor	11,222 (14.9)	6,279 (29.7)	4,943 (9.1)	<0.001
H2 receptor antagonist	2,596 (3.4)	1,243 (5.9)	1,353 (2.5)	<0.001
Cytoprotective agent	790 (1.1)	399 (1.9)	391 (0.7)	<0.001
NSAIDs	18,985 (25.1)	6,539 (30.9)	12,446 (22.9)	<0.001
Glucocorticoids	13,094 (17.3)	4,679 (22.1)	8,415 (15.5)	<0.001
Estrogen	16,116 (21.3)	4,700 (22.2)	11,416 (21.0)	<0.001
Charlson Comorbidity Index, mean (SD)	0.56 (1.0)	0.8 (1.2)	0.5 (0.9)	<0.001
Common osteoporosis-related comorbidities, n (%)				
Chronic inflammatory bowel disease	679 (0.9)	318 (1.5)	361 (0.7)	<0.001
Chronic inflammatory joint disease	15,586 (20.6)	5,751 (27.2)	9,835 (18.1)	<0.001
Celiac disease	246 (0.3)	113 (0.5)	133 (0.2)	<0.001
Diabetes	8,093 (10.7)	2,673 (12.6)	5,420 (10.0)	<0.001
Depression	4,584 (6.1)	1,818 (8.6)	2,766 (5.1)	<0.001
Renal failure	778 (1.0)	335 (1.6)	443 (0.8)	<0.001
Hypertension	32,751 (43.3)	10,575 (50.0)	22,176 (40.7)	<0.001
GI mucositis and/or urination problems	5,649 (7.5)	2,205 (10.4)	3,444 (6.3)	<0.001
Vitamin D deficiency	662 (0.9)	225 (1.1)	437 (0.8)	0.001
Fatigue	12,203 (16.1)	4,471 (21.2)	7,732 (14.2)	<0.001

^aP values are for the comparison between patients with and without post-treatment GI events by t-test (continuous variables) and chi-square test (categorical variables). GI=gastrointestinal; NSAID=nonsteroidal anti-inflammatory drug; SD=standard deviation.

Osteoporosis Treatment Patterns

Discontinuation rate was high in this patient population, observed in 45,310 (59.9%) patients (Table 3). Only 39.3% of patients were persistent with osteoporosis therapy. Switching and augmentation of therapy occurred in 400 (0.5%) and 189 (0.3%) patients, respectively. Among patients with a baseline GI event, 65.0% discontinued treatment; 34.2% were persistent with treatment; 0.6% switched to a new osteoporosis drug class treatment; and 0.3% augmented treatment. Among patients with a post-treatment GI event, 67.1% discontinued; 31.9% were persistent; 0.8% switched; and 0.3% augmented treatment. The mean time from treatment initiation to treatment

TABLE 2 Rate of GI Events Post-Treatment

	Occurrence of GI Events Post-Treatment		
	3 Months	6 Months	12 Months
	n (%)	n (%)	n (%)
All patients (N = 75,593)	8,087 (10.7)	13,217 (17.5)	21,142 (28.0)
Patients without baseline GI event (n = 55,520)	3,478 (6.3)	6,141 (11.1)	10,866 (19.6)
Patients with baseline GI event (n = 20,073)	4,609 (23.0)	7,076 (35.3)	10,276 (51.2)

GI=gastrointestinal.

Association Between Gastrointestinal Events and Persistence with Osteoporosis Therapy: Analysis of Administrative Claims of a U.S. Managed Care Population

TABLE 3 Distribution of GI Events and Mean Time to Discontinuation, Switching, or Augmentation of Therapy

	All Patients	Persistence	Discontinue	Switch	Augment
	n (%)	n (%)	n (%)	n (%)	n (%)
All patients (N = 75,593) ^a	75,593 (100.0)	29,694 (39.3)	45,310 (59.9)	400 (0.5)	189 (0.3)
Patients with baseline GI event ^b (% of all patients, n = 20,073)	20,073 (100.0)	6,863 (34.2)	13,043 (65.0)	117 (0.6)	50 (0.3)
Patients with post-treatment GI event during 0-12 months follow-up ^c	21,142 (100.0)	6,739 (31.9)	14,186 (67.1)	160 (0.8)	57 (0.3)
Patients with post-treatment GI event during 0-6 months follow-up ^c	13,217 (100.0)	4,067 (30.8)	9,004 (68.1)	108 (0.8)	38 (0.3)
Patients with post-treatment GI event during 0-3 months follow-up ^c	8,087 (100.0)	2,448 (30.3)	5,545 (68.6)	70 (0.9)	24 (0.3)
			Mean (SD)	Mean (SD)	Mean (SD)
Days from treatment initiation until discontinuation, switching, or augmentation	-	-	115.6 (98.4)	103.3 (94.4)	102.7 (107.3)

^aDistribution of patients by treatment pattern cohort as a percentage of all patients (N = 75,593).

^bDistribution of patients by treatment pattern cohort expressed as a percentage of all patients with a baseline GI event (n = 20,073).

^cDistribution of patients by treatment pattern cohort expressed as a percentage of all patients with a post-treatment GI event (0-12 months, n = 21,142; 0-6 months, n = 13,217; 0-3 months, n = 8,087).

GI = gastrointestinal; SD = standard deviation.

discontinuation was 115.6 days, 103.3 days from treatment initiation to switching treatment, and 102.7 days from treatment initiation to augmenting treatment.

Association Between GI Events and Osteoporosis Treatment Persistence

The results of the Cox regression model for the association between post-treatment GI events and the likelihood of discontinuation or switching are shown in Table 4. Patients with a post-treatment GI event during the 12-month follow-up were 35.6% more likely to discontinue bisphosphonates or switch to nonbisphosphonates than patients without any post-treatment GI event (hazard ratio [HR] = 1.356; 95% confidence interval [CI] = 1.318-1.396). Advanced age (age categories 70-79 and 80-89) increased the risk of discontinuing or switching therapy by 4.2%-6.4%, and higher baseline CCI scores increased the risk by 3.1%. A baseline osteoporosis-related fracture decreased the risk of discontinuation or switching by 5.1%. Baseline use of NSAIDs or glucocorticoids was associated with a 4.8%-7.6% higher risk of discontinuation or switching.

The association of a post-treatment GI event with discontinuation or switching was stronger when it occurred within 3 or 6 months before treatment discontinuation or switching. In the sensitivity analysis, a post-treatment GI event within 6 months before treatment discontinuation or switching was associated with 37.9% greater likelihood of discontinuation or switching (HR = 1.379, 95% CI = 1.338-1.421). A post-treatment GI event within 3 months of treatment discontinuation or switching was associated with 45.6% greater risk of discontinuation or switching (HR = 1.456, 95% CI = 1.408-1.505). Estimated effects for other patient characteristics were similar in the 3-month, 6-month, and 12-month analyses.

Discussion

A majority of patients (59.9%) initiating bisphosphonate treatment discontinued therapy in the first year. Most patients who discontinued therapy did so within the first 3 months after treatment initiation. GI events that occurred after treatment initiation were associated with a 36% greater risk of discontinuing bisphosphonate or switching to nonbisphosphonate therapy. The sooner the GI event occurred after initiating treatment, the greater was the risk of discontinuation or switching.

The observed association between GI events and decreased osteoporosis treatment persistence is supported by previous work. In a prospective study of postmenopausal women in the United States, new and continuing users of osteoporosis medication (primarily oral bisphosphonates) who reported any GI side effects at study entry had 39% greater odds of discontinuing therapy by month 6 of the study.²⁷ A retrospective analysis of patients in California reported that a GI diagnosis in the year prior to initiating alendronate was associated with a 21% lower odds of being persistent in the following year.¹⁹ Similarly, a history of upper GI problems in the year prior to starting bisphosphonate therapy was associated with 7% lower likelihood of being persistent with therapy in United Kingdom patients.¹⁷ Our study adds to the literature on the association between GI events and bisphosphonate discontinuation or switching; we accounted not only for a history of GI events through stratification in the Cox regression model, but we also examined GI events that occurred after bisphosphonate treatment initiation. No causal relationship between use of oral bisphosphonates and occurrence of GI events after initiation of oral bisphosphonates was established in this study. The occurrence of GI events after initiation of oral bisphosphonates

Association Between Gastrointestinal Events and Persistence with Osteoporosis Therapy: Analysis of Administrative Claims of a U.S. Managed Care Population

TABLE 4 Cox Regression Analysis of Likelihood of Discontinuation and Switching by Post-Treatment GI Event Status

	Main Analysis ^a			Sensitivity Analysis ^a					
	12 Months ^b			6 Months ^c			3 Months ^d		
	HR	95% CI	P Value	HR	95% CI	P Value	HR	95% CI	P Value
Post-treatment GI event before discontinuation or switching	1.356	(1.318, 1.396)	<0.0001	1.379	(1.338, 1.421)	<0.0001	1.456	(1.408, 1.505)	<0.0001
Age group (reference: 55-59)			<0.0001			<0.0001			<0.0001
60-69	0.972	(0.951, 0.993)		0.972	(0.951, 0.993)		0.973	(0.952, 0.994)	
70-79	1.064	(1.035, 1.095)		1.064	(1.035, 1.094)		1.064	(1.035, 1.095)	
80-89	1.042	(1.006, 1.078)		1.042	(1.006, 1.078)		1.042	(1.007, 1.079)	
Baseline osteoporosis-related fractures	0.949	(0.932, 0.967)	<0.0001	0.950	(0.932, 0.967)	<0.0001	0.950	(0.932, 0.968)	<0.0001
Baseline medication use									
Gastroprotective agents	0.991	(0.965, 1.017)	0.4878	0.994	(0.969, 1.021)	0.6775	0.998	(0.972, 1.024)	0.8696
NSAIDs	1.048	(1.025, 1.071)	<0.0001	1.048	(1.025, 1.071)	<0.0001	1.048	(1.025, 1.072)	<0.0001
Glucocorticoids	1.076	(1.050, 1.103)	<0.0001	1.076	(1.050, 1.103)	<0.0001	1.077	(1.050, 1.104)	<0.0001
Estrogen	0.840	(0.821, 0.860)	<0.0001	0.840	(0.821, 0.860)	<0.0001	0.840	(0.821, 0.860)	<0.0001
Charlson Comorbidity Index score	1.031	(1.019, 1.043)	<0.0001	1.031	(1.019, 1.043)	<0.0001	1.032	(1.020, 1.044)	<0.0001
Inflammatory bowel disease	0.948	(0.861, 1.044)	0.2809	0.948	(0.861, 1.044)	0.2791	0.949	(0.861, 1.044)	0.2824
Inflammatory joint disease	1.048	(1.023, 1.073)	0.0001	1.048	(1.024, 1.074)	<0.0001	1.049	(1.025, 1.074)	<0.0001
Celiac disease	0.938	(0.799, 1.100)	0.4304	0.939	(0.800, 1.103)	0.4442	0.941	(0.801, 1.104)	0.4534
Diabetes	1.097	(1.059, 1.135)	<0.0001	1.096	(1.059, 1.135)	<0.0001	1.096	(1.058, 1.135)	<0.0001
Depression	1.110	(1.070, 1.152)	<0.0001	1.111	(1.071, 1.153)	<0.0001	1.112	(1.071, 1.154)	<0.0001
Chronic kidney disease	0.982	(0.895, 1.077)	0.6990	0.980	(0.894, 1.075)	0.6672	0.979	(0.893, 1.073)	0.6473
Hypertension	1.075	(1.054, 1.096)	<0.0001	1.075	(1.054, 1.096)	<0.0001	1.075	(1.054, 1.097)	<0.0001
GI mucositis and urination problems	1.036	(1.001, 1.072)	0.0432	1.036	(1.001, 1.072)	0.0417	1.037	(1.002, 1.073)	0.0396
Hyperparathyroidism	1.011	(0.908, 1.126)	0.8404	1.011	(0.908, 1.125)	0.848	1.012	(0.909, 1.126)	0.8335
Vitamin D deficiency	1.082	(0.985, 1.190)	0.1018	1.082	(0.984, 1.189)	0.104	1.082	(0.984, 1.189)	0.1027
Fatigue	1.101	(1.075, 1.129)	<0.0001	1.102	(1.075, 1.130)	<0.0001	1.103	(1.076, 1.131)	<0.0001

^aAll models included stratification by the presence/absence of baseline GI events and the baseline GI event severity classification.

^bPost-treatment GI event occurred within 12 months of discontinuation or switch; 75,593 observations; pseudo R² = 0.0179.

^cPost-treatment GI event occurred within 6 months of discontinuation or switch; 75,593 observations; pseudo R² = 0.0179.

^dPost-treatment GI event occurred within 3 months of discontinuation or switch; 75,593 observations; pseudo R² = 0.0184.

CI = confidence interval; GI = gastrointestinal; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug.

may be associated with use of oral bisphosphonates, a common underlying condition, or concomitant treatment, such as NSAIDs or corticosteroids, that would either independently cause or predispose patients to GI problems. The sensitivity analyses for GI events that occurred within 3 and 6 months of treatment discontinuation or switching supported not only the main findings at 12 months but also established a link between the proximity of the post-treatment GI event and likelihood of treatment discontinuation or switching.

These results have important clinical implications for osteoporosis treatment in patients with a history of GI events and those who experience GI events post-treatment. Among patients with a GI event within 1 year prior to treatment initiation, 51.2% experienced a GI event during the first 12 months post-treatment, compared with only 19.6% of patients without a pretreatment GI event. Thus, patients with a history of GI events are at an increased risk for experiencing GI events during osteoporosis treatment. We also observed in the sensitivity

analysis that the more recent a GI diagnosis, the stronger its effect on treatment discontinuation or switching. Even though GI events with relatively less severity, such as abdominal pains, may not lead to discontinuation or switching, patients who experienced any GI events after bisphosphonate treatment initiation had significantly greater likelihood of discontinuation or switching. In the main analysis, a post-treatment GI diagnosis increased the likelihood of discontinuation or switching by 35.6%. The association was strengthened when considering only those post-treatment GI diagnoses that occurred within 6 months before discontinuation/switching (HR = 1.379) and the post-treatment GI events that occurred within 3 months (HR = 1.456). This finding further reinforces the clinical implication that the decision to discontinue or switch treatment can be significantly influenced by the presence of GI events after initiation of osteoporosis treatment, especially for patients with a history of GI problems. No causal relationship between occurrence of GI events and discontinuation or switching of

treatment was established in this study. There are unobserved external factors that can impact this association and were not accounted for in our regression model.

The predominant treatment pattern in this study was discontinuation of therapy: 59.9% of patients discontinued bisphosphonate in the first 12 months of treatment, and the mean time to discontinuation occurred soon (115.6 days) after treatment initiation. In previous database studies in the United States and Europe, 17%-58% of patients were persistent with bisphosphonate therapy during the first year of treatment, and our mean persistence rate (39.3%) is within this range.^{17-19,21,30} The wide range in previously reported studies is likely a function of differences in study methodology, oral bisphosphonate dosing schedule (e.g., daily vs. weekly), and patient characteristics (e.g., men vs. women). For example, we used a medication supply gap of 45 days or less to define persistence, and the supply gap in earlier studies ranged from 30-183 days, with larger gaps typically resulting in greater persistence rates.¹⁸⁻²⁰

Nonpersistence with osteoporosis therapy is associated with greater fracture risk,^{10,17,20} and efforts to improve persistence are essential to avoid adverse clinical outcomes and their attendant health care costs. Our results suggest a strong link between post-treatment GI events and decreased bisphosphonate treatment persistence in the first year of therapy. The management of osteoporosis patients should include screening of patients with comorbid GI conditions prior to bisphosphonate initiation and proactive follow-up monitoring of GI complaints to improve medication persistence.

Limitations

This study had several limitations, and the results should be considered in this context. The treatment patterns we observed are based on the allowed refill gap of 45 days and may vary depending on the length of the gap considered. The total number of patients with GI events may have been underestimated because only GI events that resulted in a medical service claim were included in this analysis. GI events that did not result in a medical claim may have also influenced the risk for discontinuation and switching, but these events were not accounted for. We only examined the first change in treatment pattern (i.e., augmentation, discontinuation, or switching); it is possible that some patients re-initiated the same or a different osteoporosis therapy during the study interval. The regression model for risk of discontinuation or switching accounted for several patient demographic and clinical characteristics, but there may have been other unidentified or unmeasured factors that influenced the risk of discontinuation or switching. For example, we did not measure the presence of bone mineral density testing at baseline, which has been associated with higher rates of compliance with bisphosphonate therapy.^{31,32} Augmenters are excluded in the regression analysis, since augmenters are not as clinically meaningful as patients with the

other treatment patterns. It is not common for a patient to take 2 different bisphosphonates or 2 different nonbisphosphonates at the same time. The regression analysis for post-treatment GI events and treatment discontinuation or switching represents an association only and cannot be interpreted to establish causality. Different bisphosphonate dosing frequencies and formulations were not differentiated in the study and may also have influenced treatment patterns. Finally, inclusion required 24 months of continuous health care coverage with medical and pharmacy benefits; thus, the results are primarily applicable to a stable managed care population.

Conclusions

A large proportion (59.9%) of patients receiving bisphosphonate treatment did not persist with treatment during the 12-month follow-up period. Among patients on bisphosphonate therapy, 28% experienced a GI event within a year. Patients who experienced GI events after receiving osteoporosis treatment had increased likelihood of discontinuation or switching by 35.6%. Treatment discontinuation may lead to diminished treatment outcomes and higher health care utilization, causing a burden associated with post-treatment GI events. These findings suggest that post-treatment GI events negatively impact persistence to osteoporosis medication. Clinical management of patients taking bisphosphonate medication should recognize the potential for post-treatment GI events to increase the risk of bisphosphonate treatment discontinuation or switching. Future studies should evaluate the association of nonpersistence as a result of GI events with health care resource use. For osteoporotic patients with GI events, physicians should be cautious to initiate their osteoporosis treatment with oral bisphosphonates, since patients with a history of GI events could have a higher risk of developing subsequent GI events, and occurrence of GI events are associated with treatment discontinuation or switching. Osteoporosis management programs may be considered to improve persistence among patients with osteoporosis.

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Association Between Gastrointestinal Events and Persistence with Osteoporosis Therapy: Analysis of Administrative Claims of a U.S. Managed Care Population

DISCLOSURES

This study was sponsored by Merck & Co., Inc. Modi and Sajjan are employees of Merck & Co., Inc. Yang is a Fellow in the Merck Center for Observational and Real-World Evidence fellowship program in partnership with Temple University. Siris has done consulting for Amgen, Eli Lilly, Merck, Novartis, AgNovos, and Radius. Fan served as a paid consultant by Merck & Co., Inc., in connection with this study and development of the manuscript.

Study concept was designed primarily by Modi, with assistance from Siris, Sajjan, Fan, and Yang. Data collection was conducted by Sajjan, Fan, and Modi, with assistance from Yang, and analysis was performed by Modi and Sajjan, with assistance from the other authors. The manuscript was written by Yang, Siris, Modi, Sajjan, and Fan, and revised by Modi, Yang, and Fan, with help from Siris and Sajjan.

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**Association Between Gastrointestinal Events and Persistence with Osteoporosis Therapy:
Analysis of Administrative Claims of a U.S. Managed Care Population**

APPENDIX Codes for Gastrointestinal Events and Osteoporotic Fractures

Codes Used to Identify Gastrointestinal Events		
ICD-9-CM Code	Description	Severity Indicator
456.0	Esophageal varices with hemorrhage	
456.1	Esophageal varices without hemorrhage	
530.0x	Achalasia & cardiospasm	
530.1x	Esophagitis	
530.2	Ulcer of esophagus	
530.20	Ulcer of esophagus without bleeding	
530.21	Ulcer of esophagus with bleeding	X
530.3	Stricture of esophagus	
530.4	Perforation of esophagus	X
530.5	Dyskinesia of esophagus	
530.7	Mallory-Weiss syndrome	
530.81	Esophageal reflux (GERD)	
530.82	Esophageal hemorrhage	X
530.84	Tracheoesophageal fistula	
530.89	Other disorders of the esophagus	
531.xx	Gastric ulcer	
531	Gastric ulcer, acute with hemorrhage	X
531.1	Gastric ulcer, acute with perforation	X
531.2	Gastric ulcer, acute with hemorrhage and perforation	X
531.3	Gastric ulcer, acute without hemorrhage or perforation	
531.4	Gastric ulcer, chronic or unspecified with hemorrhage	X
531.5	Gastric ulcer, chronic or unspecified with perforation	X
531.6	Gastric ulcer, chronic or unspecified with hemorrhage and perforation	X
531.7	Gastric ulcer, chronic without hemorrhage or perforation	
531.9	Gastric ulcer, unspecified as acute or chronic, without hemorrhage or perforation	
532.xx	Duodenal ulcer	
532	Duodenal ulcer, acute with perforation	X
532.1	Duodenal ulcer, acute with hemorrhage	X
532.2	Duodenal ulcer, acute with hemorrhage and perforation	X
532.3	Duodenal ulcer, acute without hemorrhage or perforation	
532.4	Duodenal ulcer, chronic or unspecified with hemorrhage	X
532.5	Duodenal ulcer, chronic or unspecified with perforation	X
532.6	Duodenal ulcer, chronic or unspecified with hemorrhage and perforation	X
532.7	Duodenal ulcer, chronic without hemorrhage or perforation	
532.9	Duodenal ulcer, unspecified as acute or chronic, w/o hemorrhage or perforation	
533.xx	Peptic ulcer, site NOS	
533	Peptic ulcer, acute with hemorrhage	X
533.1	Peptic ulcer, acute with perforation	X
533.2	Peptic ulcer, acute with perforation and hemorrhage	X
533.3	Peptic ulcer, acute without hemorrhage or perforation	
533.4	Peptic ulcer, chronic or unspecified with hemorrhage	X
533.5	Peptic ulcer, chronic or unspecified with perforation	X
533.6	Peptic ulcer, chronic or unspecified with hemorrhage and perforation	X
533.7	Peptic ulcer, chronic without hemorrhage or perforation	
533.9	Peptic ulcer, unspecified as acute or chronic, w/o hemorrhage or perforation	
534.0	Gastrojejunal ulcer	
534.1	Gastrojejunal ulcer	
534.2	Gastrojejunal ulcer	

**Association Between Gastrointestinal Events and Persistence with Osteoporosis Therapy:
Analysis of Administrative Claims of a U.S. Managed Care Population**

APPENDIX Codes for Gastrointestinal Events and Osteoporotic Fractures *(continued)*

Codes Used to Identify Gastrointestinal Events		
ICD-9-CM Code	Description	Severity Indicator
534.3	Gastrojejunal ulcer	
535.0x	Acute gastritis	X
535.11	Atrophic gastritis with hemorrhage	
535.21	Gastric mucosal hypertrophy with hemorrhage	
535.4x	Gastritis NEC	
535.5x	Gastritis/duodenitis, NOS	
535.6x	Duodenitis	
536.2	Persistent vomiting	
536.8	Dyspepsia and other specified disorders of function of stomach	
536.9	Stomach function disorders NOS	
537.4	Gastric/duodenal fistula	
537.8x	Gastroduodenal disorders NEC	
537.9	Gastroduodenal disorders NOS	
569.83	Perforation of intestine	
578.xx	GI hemorrhage	X
787.0x	Nausea and vomiting	
787.1	Heartburn	
787.2	Dysphagia	
789.0x	Abdominal pain	
792.1	Abnormal stool/occult blood	
793.4	Abnormal exam GI tract	
CPT Code	Description	
43200	Endoscopy, rigid or flexible; diagnostic, with or without collection of specimen(s) by brushing or washing (separate procedure)	
43202	Esophagoscopy, rigid or flexible; diagnostic, with or without collection of specimen(s) by brushing or washing (separate procedure) with biopsy, single or multiple	
43227	Esophagoscopy, rigid or flexible; diagnostic, with or without collection of specimen(s) by brushing or washing (separate procedure) with control of bleeding, any method	
43235	Endoscopy, rigid or flexible; diagnostic, with or without collection of specimen(s) by brushing or washing (separate procedure)	
43239	Upper GI endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; diagnostic with or without collection of specimen(s) by brushing	
43255	Upper GI endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; diagnostic with or without collection of specimen(s) by brushing or washing (separate procedure), with control of bleeding, any method	
44602	Suture of small intestine (enterorrhaphy) for perforated ulcer	
44603	Suture of small intestine (enterorrhaphy) for perforated ulcer	
44605	Suture of large intestine (colorrhaphy) for perforated ulcer	
74240	Radiologic examination, GI tract, upper; with or without delayed film, without KUB	
74241	Radiologic examination, GI tract, upper; with or without delayed films, with KUB	
74245	Radiologic examination, GI tract, upper; with small bowel, includes multiple serial films	
74246	Radiologic examination, GI tract, upper, air contrast, with specific high density barium, effervescent agent, with or without glycagon; with or without delayed films, with KUB	
74247	Radiologic examination, GI tract, upper, air contrast, with specific high density barium, effervescent agent, with or without glycagon; with or without delayed films, without KUB	
74249	Radiologic examination, GI tract, upper, air contrast, with specific high density barium, effervescent agent, with or without glycagon; with small bowel follow-through	

**Association Between Gastrointestinal Events and Persistence with Osteoporosis Therapy:
Analysis of Administrative Claims of a U.S. Managed Care Population**

APPENDIX Codes for Gastrointestinal Events and Osteoporotic Fractures *(continued)*

Codes Used to Identify Osteoporotic Fractures

Skeletal Site	ICD-9-CM Code
Vertebral: dorsal and lumbar	733.13, 805.2, 805.4
Vertebral: other	805.0, 805.1, 805.3, 805.6, 805.7, 805.8, 805.9, 806.x
Hip (femur neck)	733.14, 820.x
Nonvertebral	
Rib	807.x
Pelvis	808.x
Trunk	809.x
Clavicle	810.x
Scapula	811.x
Humerus	733.11, 812.x
Forearm (radius and ulna)	733.12, 813.x
Lower forearm (carpal)	814.x
Femur (other)	733.15, 821.x
Tibia, fibula	733.16, 823.x

National Drug Code Numbers Used to Identify Osteoporosis Medications

Medication	NDC Number
Alendronate, risedronate, ibandronate, zoledronic acid, calcitonin, raloxifene, teriparatide, denosumab	00006003121, 00006003144, 00006007721, 00006007744, 00006021231, 00006027044, 00006071021, 00006071044, 00006092531, 00006092558, 00006093628, 00006093631, 00006093658, 00006093672, 00006093682, 00006383334, 00093514001, 00093514056, 00093514101, 00093514156, 00093514256, 00093517120, 00093517144, 00093517219, 00093517220, 00093517244, 00378356601, 00378356701, 00378356822, 00378356893, 00378356899, 00378356922, 00378356993, 00378356999, 00555071951, 00555071954, 00555072051, 00555072054, 00591003104, 00591007704, 00591317104, 00591317304, 16252059902, 16252059944, 16252060102, 16252060144, 16590049104, 16590071804, 16590071820, 16590071830, 16590099930, 16714063101, 16714063102, 16714063201, 16714063202, 16714063301, 16714063302, 21695090104, 21695090204, 23490917401, 33261055401, 35356059404, 41616063583, 41616063588, 41616063683, 41616063688, 41616063768, 41616063868, 49999050104, 51079094105, 51079094205, 54569486600, 54569521800, 54569539900, 54569604700, 54569605000, 54868385700, 54868438400, 54868446200, 54868446201, 54868446300, 54868548000, 54868586000, 54868586100, 54868586200, 55045390801, 55045391501, 55111058801, 55111058830, 55111058901, 55111058930, 55111059048, 55111059248, 55887051620, 55887051630, 55887051660, 55887051682, 55887051690, 58016061300, 58016061304, 58016061320, 58016061330, 58016061360, 58016061390, 58016078800, 58016078830, 58016078860, 58016078890, 60429077304, 60429077312, 60505259201, 60505259203, 60505259301, 60505259303, 60505259404, 60505259602, 60505259604, 60505259608, 63874008901, 65862032730, 65862032804, 65862032904, 67801032003, 68071079030, 68071079130, 68084032264, 68115075504, 68115079300, 68258301401, 68258598801, 68258598902, 00070449201, 00075130601, 00078014923, 00078031154, 00078031190, 00083648505, 00083649005, 00186160813, 00245000835, 00406807403, 00781632079, 35356058301, 49884016111, 54569199400, 54569523400, 54868382700, 54868382701, 54868549900, 60505082306, 55513071001, 55513073001, 00004018523, 00004018682, 00004018809, 00004019109, 12280041203, 16590040003, 35356042303, 54868532200, 54868532201, 54868582300, 55887064103, 00002416502, 00002416507, 00002416530, 00002416534, 00002416579, 12280040230, 12280041830, 49999045830, 54569462800, 54868417000, 54868417001, 55289026630, 66105053803, 00149047001, 00149047101, 00149047103, 00149047201, 00149047204, 00149047501, 00149047701, 00149047801, 00149047803, 00430047015, 00430047802, 00430097903, 16590072104, 23490924500, 49999044804, 54569546200, 54868438600, 54868467100, 54868551800, 54868606900, 55887068504, 66105015703, 66105015803, 68115068104, 00002840001, 00002897101, 00075205053, 54868540600, 00078035084, 00078038725, 00078043561, 00078059061, 35356035101

CPT= Current Procedural Terminology; GI= gastrointestinal; ICD-9-CM= International Classification of Diseases, Ninth Revision, Clinical Modification; NDC= National Drug Code; NEC= not elsewhere classified; NOS= not otherwise specified.