Bone Reports 4 (2016) 5–10

Contents lists available at ScienceDirect

Bone Reports

journal homepage: www.elsevier.com/locate/bonr

Association between gastrointestinal events and compliance with osteoporosis therapy

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ARTICLE INFO

Article history:
Received 5 June 2015
Received in revised form 6 October 2015
Accepted 29 October 2015
Available online 30 October 2015

Keywords:
Compliance
Bisphosphonate
Gastrointestinal event
Medication possession ratio
Osteoporosis

ABSTRACT

Purpose: The aim of this study was to estimate the rate of gastrointestinal (GI) events, and association between GI events and compliance with osteoporosis therapy among osteoporotic women.
Methods: A retrospective cohort study using a large administrative claims database in the United States from 2001 through 2010 was conducted. We studied women ≥55 years old who were continuously enrolled in a health plan for at least 2 years, a baseline year before and a follow-up year after the date of the first prescription of oral bisphosphonate as the first oral osteoporosis treatment. Compliance with osteoporosis therapy was measured using the medication possession ratio (MPR), with compliance defined as MPR ≥0.8. Multivariate logistic regression was used to assess the association between occurrence of GI events and compliance with osteoporosis therapy after controlling for demographic and clinical characteristics.
Results: A sample consisting of 75,593 women taking at least one oral bisphosphonate with mean (SD) age of 64 (8) years was identified. A total of 21,142 (28%) patients experienced at least one GI event during the follow-up period. Only 31,306 (41%) patients were compliant with osteoporosis therapy. Patients who experienced GI events after initiation of oral bisphosphonates were 29% less likely to adhere to osteoporosis therapy as compared to patients who did not experience GI events (odds ratio [95% CI], 0.71 [0.69–0.74]; $P < .001$).
Conclusions: Less than half of the patients were compliant with osteoporosis therapy within one year after initiating oral bisphosphonates, and the likelihood of compliance was significantly lower by 29% among women with GI events.

1. Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Primarily occurring in postmenopausal women as they age and to a lesser degree in older men, osteoporosis is typically a disease without symptoms until a fracture occurs (Siris et al., 2001), with resultant pain, decreased quality of life, acute and sometimes chronic disability, and, in the case of hip fracture, an increase in mortality (Dempster, 2011; Adachi et al., 2010). The substantial personal and societal burden of osteoporotic fracture is accompanied by a large and rising economic burden. In the United States (US) alone, the direct medical costs of osteoporotic fracture were estimated at $16.9 billion in 2005 and are projected to rise to $25.3 billion by 2025 (Burge et al., 2007).

An estimated 30% of women and 19% of men 50 years and older in the US are at elevated risk of osteoporotic fracture and are considered eligible for pharmacologic treatment (Dawson-Hughes et al., 2012). There are several available therapies with proven efficacy for reducing fracture risk in patients with osteoporosis. Among them, the oral bisphosphonates, including alendronate, risedronate, and ibandronate, are the most commonly used agents. However, suboptimal compliance with osteoporosis therapies is a common and well-recognized problem in the real world of clinical practice, outside of clinical trials (Cramer et al., 2007; Kothawala et al., 2007; Li et al., 2012); and poor compliance results in increased risk of fracture, higher medical costs, increases in hospitalizations, and wasted medications (Halpern et al., 2011; Sampalis et al., 2011; Ross et al., 2011; Hadji et al., 2012). Improving compliance with osteoporosis therapies is thus an important goal for both policy makers and clinicians.

In randomized controlled trials, oral bisphosphonates are generally well-tolerated, with upper gastrointestinal (GI) events and discontinuation rates similar to those of placebo (Bauer et al., 2000; Liberman, 2006). The occurrence of GI events among patients using oral bisphosphonates is common in real world clinical practice (Hamilton

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http://dx.doi.org/10.1016/j.bonr.2015.10.006
2352-1872/

et al., 2003; Woo et al., 2010; Penning-van Beest et al., 2008) and it is often difficult to determine whether GI events are related to the use of oral bisphosphonates, other medication (e.g., NSAIDs), or are due to another new or preexisting GI condition. However, the understanding of the association between occurrence of GI events and compliance with osteoporosis therapy among patients using oral bisphosphonates, particularly among a US managed care population, is limited.

The objective of this study was to estimate the rate of GI events and the association between GI events and compliance with osteoporosis therapy among osteoporotic women in a US managed care population.

2. Methods

2.1. Data source

A retrospective cohort study was conducted using the i3 Invision Datamart, a large administrative claims database covering 45 million patients from geographically diverse areas in the US. Longitudinal de-identified patient information in the database includes demographic characteristics and claims data for outpatient visits, hospitalizations, and prescriptions. Disease diagnoses and comorbidities are coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (http://www.cdc.gov/nchs/icd/icd9cm.htm, n.d.); medications in pharmacy claims are identified using the National Drug Code Directory (NDC) (http://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm, n.d.).

2.2. Sample selection

To be included in the sample, a patient had to be female, aged 55 years or older, and had to be prescribed at least one oral bisphosphonate including alendronate, risedronate or ibandronate anytime from January 1, 2001 to December 31, 2010. Index drug was defined as the first oral bisphosphonate prescribed for a patient as the first oral osteoporosis treatment and the index date was defined as the date of the initiation of the oral bisphosphonate from January 1, 2001 to December 31, 2010. A patient also had to be continuously enrolled in the health plan for at least one year before (base year) and one year after index date (follow-up year). Patients who had a diagnosis of Paget's disease of bone (osteitis deformans; ICD-9-CM code 731.0) at any time in the database were excluded from the study, as were patients with a diagnosis of malignant neoplasm (ICD-9-CM codes, 140.xx to 208.xx, 230.xx to 239.xx, or 172.xx) anytime during the 2-year study period (Orsini et al., 2005). Patients who took any oral osteoporosis therapy during one year prior to index date were excluded.

2.3. Study variables

Compliance with osteoporosis treatment after initiation of an oral bisphosphonate was the outcome of interest in this study. We defined compliance with therapy as a medication possession ratio (MPR) of ≥0.8 (Siris et al., 2009). The MPR was calculated as the number of days' supply of all osteoporosis therapies received in the follow-up year divided by 365 days (Peterson et al., 2007).

GI events were identified using ICD-9 diagnosis codes of dysphagia; esophagitis; esophageal ulcer, stricture, perforation, and hemorrhage; gastroesophageal reflux disease (GERD); gastric ulcer; duodenal ulcer; peptic ulcer; acute gastritis; duodenitis; GI hemorrhage; and nausea and vomiting (Appendix). The GI events during the follow-up period could be recurrent or new. Osteoporotic fractures at baseline were identified from primary and/or secondary diagnoses based on inpatient and outpatient service claims during baseline year. Osteoporotic fractures included hip, vertebral, and non-vertebral fractures, including those of the pelvis, humerus, forearm, other femoral sites, tibia and fibula, rib, clavicle, scapula, and sternum. Fractures not considered as osteoporotic fractures were those of the hand, skull, digits, feet, and ankle and any open fractures (Diez-Perez et al., 2012).

2.4. Statistical analyses

Descriptive statistics were used to summarize patient characteristics at baseline. We compared characteristics of patients who had a recorded GI event with those who had no GI event during the follow-up year, using the χ^2 test for binary and categorical variables and Wilcoxon rank sum test for continuous variables.

Multivariate logistic regression was used to examine the association between GI events and compliance (outcome variable) within the follow-up year. The key independent variable in the model was the occurrence of GI events after initiation of an oral bisphosphonate during the follow-up year (1 year). Covariates in the model included age at the index date, presence of any osteoporotic fractures at baseline, occurrence of GI events at baseline, concomitant medication use at baseline (gastroprotective agents, nonsteroidal anti-inflammatory drugs [NSAIDs], corticosteroids, and estrogen), and comorbidities (inflammatory bowel disease, celiac disease, diabetes, inflammatory joint disease, depression, hypertension, urination problems, chronic kidney disease, hyperparathyroidism, vitamin D deficiency, and fatigue). In addition to the individual comorbidities, we included the Deyo-Charlson comorbidity index (CCI) score, a measure that has been adapted for use with administrative databases (Deyo et al., 1992) and is used to account for comorbidities based on the presence of 19 predefined comorbid conditions, with higher CCI score denoting greater risk of death from comorbid disease (Charlson et al., 1987). Effects of the likelihood of compliance on all independent variables were quantified and reported in terms of odds ratios (ORs) with 95% confidence intervals (CIs). For a continuous independent variable (e.g., CCI), an OR <1.0 indicates a lower likelihood of treatment compliance associated with the independent variable. For a binary or categorical independent variable (e.g., age group), an OR <1.0 indicates a lower likelihood of treatment compliance in comparison with the reference group (i.e., 0 for a binary variable). *P*-values were evaluated using Wald's tests and were considered statistically significant at a 5% level.

Furthermore, two sets of sensitivity analyses were conducted. One set of sensitivity analyses assessed the regression-adjusted association between GI event and compliance within the first 3 and 6 months of the follow-up year; the other set of sensitivity analyses examined the association between GI events and compliance using MPR ≥0.6 as the compliance threshold, a less stringent definition than in the main analysis (MPR ≥0.8). All statistical analyses were conducted using SAS software, version 9.3 (SAS Institute, Cary, NC).

3. Results

We identified 75,593 women who received at least one oral bisphosphonate from 2001 to 2010 after meeting selection criteria (Fig. 1). Patient baseline characteristics and the rate of post-index GI events have been previously reported (Modi et al., 2015). Briefly, the mean (SD) age of eligible women was 64.4 (8.4) years, 20,073 (26.6%) patients experienced at least one baseline GI event and 4531 (6.0%) patients had a recorded baseline osteoporotic fracture. A total of 21,142 (28.0%) patients experienced one or more GI events during the 1-year follow-up. Patients who experienced a GI event during the baseline year had a higher rate of GI events during the follow-up year (51.2% vs. 19.6%) as compared with those who did not (data not shown).

The distribution of patients by both compliance status (MPR ≥0.8 or MPR ≥0.6) and the presence/absence of a GI event during follow-up is shown in Table 1. The proportion of patients with MPR ≥0.8 was lower among patients who experienced a GI event compared with patients who did not experience a GI event (34.1% vs 44.3%, $P < 0.001$). The same pattern of lower compliance among patients with GI events

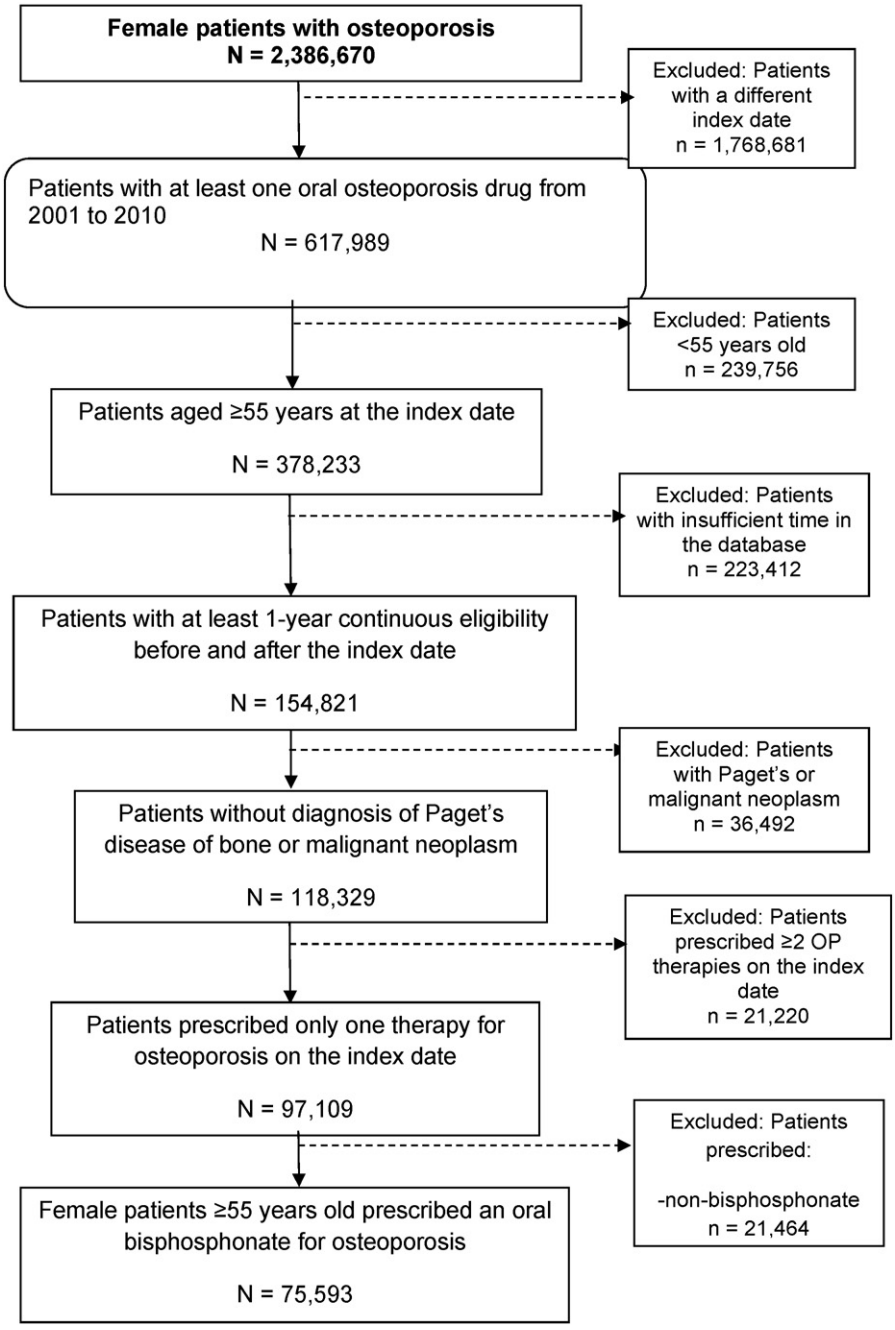

Fig. 1. Patient selection in the database.

was also evident using MPR ≥0.6 as the threshold for compliance: 48.5% of patients with GI events versus 58.0% of patients with no GI events had MPR ≥0.6 ($P < 0.001$) %). In addition, the mean MPR was significantly lower for patients with a GI event than for those with no GI event (0.55 vs. 0.62, $P < .001$). Among all 75,593 patients initiating oral bisphosphonates, irrespective of GI event status, a total of 31,306 (41.4%) patients (24,102 with no GI events and 7204 with GI events) had MPR ≥0.8.

Table 1
Compliance with oral bisphosphonate treatment among 75,593 female patients with and without GI events during the follow-up year.

	No GI event during follow-up year N = 54,451 (72%)	GI event during follow-up year N = 21,142 (28%)	*P*-value[a]
MPR, mean (SD)	0.62 (0.34)	0.55 (0.34)	<.001
MPR ≥0.8, n (%)	24,102 (44.3)	7204 (34.1)	<.001
MPR ≥0.6	31,605 (58.0)	10,243 (48.5)	<.001

[a] χ^2 test for binary and categorical variables and Wilcoxon rank sum test for continuous variables comparing patients with vs. without a GI event during the follow-up year.GI indicates gastrointestinal; MPR, medication possession ratio.

Table 2
Association between GI events and odds of compliance (MPR ≥0.8) with osteoporosis therapy among osteoporotic women during the follow-up year adjusted for patient baseline characteristics.

Effect	Odds ratio	(95% CI)	*P*-value
GI event during follow-up year	0.71	(0.69–0.74)	<.001
Age group (vs. 55–59 years)			<.001
60–69 years	1.06	(1.03–1.10)	
70–79 years	0.97	(0.93–1.02)	
80–89 years	0.97	(0.92–1.03)	
Osteoporotic fracture in baseline year	1.08	(1.05–1.11)	<.001
GI event in baseline year	0.88	(0.85–0.92)	<.001
Baseline medication use			
Gastroprotective agent	1.04	(0.995–1.09)	.087
NSAIDs	0.92	(0.89–0.96)	<.001
Corticosteroids	0.88	(0.84–0.92)	<.001
Estrogens	1.32	(1.27–1.37)	<.001
CCI score (higher vs. lower)	0.95	(0.93–0.97)	<.001
Comorbidity			
Inflammatory bowel disease	1.01	(0.86–1.18)	.89
Inflammatory joint disease	0.94	(0.91–0.98)	.003
Celiac disease	1.09	(0.84–1.42)	.51
Diabetes	0.85	(0.80–0.91)	<.001
Depression	0.79	(0.74–0.84)	<.001
Chronic kidney disease	1.07	(0.91–1.26)	.42
Hypertension	0.89	(0.86–0.92)	<.001
GI mucositis or urination problem	0.96	(0.91–1.02)	.19
Hyperparathyroidism	1.02	(0.85–1.22)	.84
Vitamin D deficiency	0.87	(0.74–1.02)	.08
Fatigue	0.85	(0.82–0.89)	<.001

CCI indicates Charlson comorbidity index; GI, gastrointestinal; MPR, medication possession ratio; NSAID, nonsteroidal anti-inflammatory drug.

The results of the logistic regression analysis examining the association between GI events during follow and the likelihood of MPR ≥0.8 are shown in Table 2. Patients with at least one GI event within the follow-up year were 29% less likely to be compliant with osteoporosis therapy (odds ratio [OR], 0.71; 95% confidence interval [CI], 0.69–0.74), as compared with patients who did not experience any GI event within the follow-up year. Other risk factors significantly associated with lower treatment compliance included the presence of GI events during baseline, a higher baseline CCI score, therapy with NSAIDs or corticosteroids during baseline and certain baseline conditions (inflammatory joint disease, diabetes, depression, hypertension, fatigue). Significantly better odds of compliance were evident for patients with baseline osteoporotic fracture or who were prescribed estrogen during baseline.

The results of a sensitivity analysis, in which data within the first 3 months after initiation of oral bisphosphonates were analyzed, are also consistent with those of the main analysis, showing that patients with at least one GI event during the first 3 months were 28% less likely to be compliant with osteoporosis therapy (odds ratio [95% CI], 0.72 [0.69–0.76]), as compared to patients who did not experience any GI event during the first 3 months after initiation of oral bisphosphonates (data not shown). The results of the sensitivity analysis in which data within the first 6 months after initiation of oral bisphosphonates were analyzed suggest that patients with at least one GI event during the first 6 months were 29% less likely to be compliant with osteoporosis therapy (odds ratio [95% CI], 0.71[0.68–0.74]), as compared to patients who did not experience any GI event during the first 6 months after initiation of oral bisphosphonates (data not shown). In addition, the sensitivity analysis in which compliance was defined as MPR ≥0.6 showed that patients experiencing at least one GI event during the first year after initiation of oral bisphosphonates were 26% less likely to be compliant with osteoporosis therapy (odds ratio [95% CI], 0.74[0.72–0.77]) as compared to patients who did not have any GI event within one year after initiation of oral bisphosphonates (data not shown). Results were consistent with the results of the main analysis in which compliance was defined as MPR ≥0.8.

4. Discussion

We found that 28% of women in this large observational study experienced GI events during their first year of osteoporosis therapy initiation with oral bisphosphonates and these women showed significantly lower likelihood of treatment compliance than women with no GI events during their first year of therapy. Other factors associated with significantly reduced likelihood of treatment compliance were a GI event during the baseline year and use of concomitant NSAIDs or corticosteroids at baseline. Overall, less than half (41%) of all women included in this study were compliant with their osteoporosis therapy during the follow-up year.

Our findings support the results of prior real-world studies investigating compliance with bisphosphonates and the occurrence of GI events. A similarly designed database study of 8822 new female users of bisphosphonates in The Netherlands found that GI medications prescribed for the first time during the follow-up year (indicative of a GI event) were independently associated with increased odds of non-compliance with bisphosphonates (Penning-van Beest et al., 2008). Likewise, in the Prospective Observational Scientific Study Investigating Bone Loss Experience (POSSIBLE US), women reporting GI side effects had significantly greater odds of therapy discontinuation at 6 and 12 months than those without GI side effects; moreover, GI side effects were more common among women prescribed bisphosphonates than other agents (Woo et al., 2010).

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 may be attributable to multiple factors including oral bisphosphonate use, an underlying condition or concomitant medication (e.g., NSAIDs, corticosteroids) that may cause or predispose osteoporotic women to GI problems (Vestergaard et al., 2010). The occurrence of GI events, regardless of whether the GI events were caused by use of bisphosphonates or by use of other medications, or concomitant medical conditions, was a risk factor for non-compliance with osteoporosis therapy after initiation of oral bisphosphonates.

In addition to GI events, certain baseline patient characteristics were independently associated with more modest reductions in the likelihood of compliance with osteoporosis therapy. These included older age, greater comorbid burden, certain medical conditions and use of specific medications. Previous studies have generally demonstrated greater compliance in older patients although the odds of improved compliance tended to diminish at age 65 and above (Penning-van Beest et al., 2008; Curtis et al., 2009; McCombs et al., 2004). Age may also be a proxy for higher comorbid burden and use of multiple medications. Our results showed a consistent negative association among other factors that may be linked with older age such as higher comorbidity score and NSAID use which compliments previous findings (Curtis et al., 2009; McCombs et al., 2004) although NSAID use has also been associated with higher odds of compliance (Penning-van Beest et al., 2008). Diabetes and glucocorticoid use have been linked with reduced compliance and persistence which is consistent with our results (Curtis et al., 2009; McCombs et al., 2004; Netelenbos et al., 2011). We also observed lower odds of compliance among patients with comorbid inflammatory joint disease, hypertension, depression or fatigue, which may be surrogates for higher overall disease burden. However, other factors that are unobservable in claims databases, such as patient beliefs regarding safety and efficacy, are also barriers to compliance with oral bisphosphonates (McHorney et al., 2007). The conflicting results in the literature are likely attributable in part to differences in study methodology but also suggest that the causes of poor compliance are multifactorial.

The results of this study indicate that less than half of women in a managed care population with osteoporosis comply with osteoporosis therapy during their first year after being prescribed an oral

bisphosphonate. In prior studies, factors associated with poor compliance included patients' failure to perceive increased risk of fracture, lack of satisfaction with treatment, a daily treatment regimen, and concern about side effects (Penning-van Beest et al., 2008; Barrett-Connor et al., 2012; Solomon et al., 2011; Siris et al., 2011; Sale et al., 2011). Our study results are similar to those of prior studies of medical conditions requiring chronic long-term therapy, for which suboptimal patient compliance with medications is a common problem, particularly with regard to conditions that are asymptomatic, such as osteoporosis before fracture and hypercholesterolemia before a cardiovascular event. A recent study estimated adherence to statin therapy among new statin users (which was calculated by dividing the total number of tablets dispensed during the 1 year follow-up after initiation of statin by the total number of days in the observation period) reported that the proportion of non-compliant patients ranged from 38.3% to 50.0% during the 1 year follow-up period (Lemstra and Blackburn, 2012). Similarly, Zhang et al. (Zhang et al., 2011) in their retrospective cohort study of 52,414 patients with type 2 diabetes, reported that only 52% of patients had a 2-year MPR >0.8 for statin therapy.

Ascertaining the factors associated with poor compliance with bisphosphonate therapy can help clinicians to identify and mitigate risk factors for patients who require closer monitoring and encouragement about the need for therapy. Better compliance with osteoporosis therapies is associated with greater reduction in fracture risk (Cotte et al., 2008; Patrick et al., 2010; Siris et al., 2006) and reduced mortality risk in women receiving osteoporosis therapy (Center et al., 2011). Moreover, economic modeling suggests that non-compliance is costly from the payer's and patients' perspective including direct health-care costs paid by health plans and individual patient's out-of-pocket contribution (Cotte and De Pouvourville, 2011; Hiligsmann et al., 2010). Improving compliance with osteoporosis therapy could reduce the incremental burden with respect to healthcare resource utilization and costs for health plans. Patient education about osteoporosis and fracture risk should be provided for patients prescribed osteoporosis therapy, particularly for those at risk of poor compliance, such as women with GI events at baseline. Moreover, the results of this study suggest that particular attention should be paid to patients who experience GI events during therapy, as well as those receiving concomitant NSAIDs or corticosteroids, who may be more likely to experience GI events.

4.1. Limitations

This analysis used administrative claims data on medication prescriptions and estimated MPR based on pharmacy claims and medical claims. We cannot be certain that dispensed medications were actually taken as prescribed; this drawback could result in overestimation of compliance. Moreover, information to fully characterize patients with regard to risk of a GI event or osteoporotic fracture (for example, bone mineral density and vitamin D levels) was not available from the database. There may also have been other unobserved patient characteristics that were not accounted for in the logistic regression model examining the association between GI events and compliance. For example, we excluded patients with evidence of use of any oral osteoporosis therapy any time prior to the index date during the study period in which patients were continuously enrolled in health plans in order to focus on patients with no prior exposure to oral bisphosphonate treatment. However, it is possible that some patients may have been treated with oral bisphosphonates before enrolling in the health plan or before the study period and prior experience with therapy may have influenced their degree of compliance during the follow-up period. However, we would expect that this potential influence would be limited to a small number of patients because previous research suggests that the large majority of patients who discontinue therapy and then re-initiate therapy do so within 1 year (Balasubramanian et al., 2013). Lastly, no temporal relationships between occurrence of GI events and discontinuation of bisphosphonates were considered in this analysis since only association was examined.

4.2. Conclusions

The results of this study indicate that less than half of women comply with osteoporosis therapy during their first year after being prescribed an oral bisphosphonate, and women who experience GI events have significantly lower odds of compliance. Further studies are needed to evaluate the burden of GI events on healthcare resource use and costs.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.bonr.2015.10.006.

Conflict of interest

This study was sponsored by Merck & Co., Inc., Kenilworth, NJ. Ethel S Siris has done consulting for Amgen, Eli Lilly, Merck, Novartis, AgNovos and Radius. Chun-Po Steve Fan is an employee of Asclepius JT LLC and is a paid consultant to Merck & Co., Inc. Xiaoqin Yang is an employee of Merck & Co., Inc. Shiva Sajjan, Shuvayu Sen and Ankita Modi are employees of Merck & Co., Inc. and have stock/stock options.

Acknowledgments

This study was funded by Merck & Co., Inc., Kenilworth, NJ, USA. Medical writing and editorial assistance was provided by Elizabeth V. Hillyer, DVM. This assistance was funded by Merck & Co.

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