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ORIGINAL ARTICLE

Compliance with drug therapy for postmenopausal osteoporosis

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Abstract
Introduction Patient compliance with pharmacotherapy for osteoporosis is typically poor in clinical practice; less frequent dosing with bisphosphonates may improve compliance.
Methods Using data from 49 US health plans, we identified all women aged ≥45 years with osteoporosis who initiated therapy with a bisphosphonate, calcitonin, estrogen, or raloxifene. Compliance was examined alternatively in terms of incidence of adherence failure (medication days <80% of possible) and persistence failure (gap in therapy ≥90 days), and was compared across treatment groups using Kaplan-Meier methods and Cox proportional hazards models.
Results The study population included 18,822 women, 48% of whom initiated weekly bisphosphonate therapy. Overall risk of adherence failure was 47% at 3 months, 70% at 1 year, and 84% at 3 years. Risk of persistence failure was 47% at 1 year, and 77% at 3 years. In multivariate analyses, risk of adherence failure was higher for calcitonin (hazard ratio=2.7 vs weekly bisphosphonate therapy, $p<0.01$), but comparable for all other therapies. Relative risks of persistence failure were generally similar.
Conclusions Approximately three-quarters of women who initiate osteoporosis drug therapy are non-adherent with treatment within 12 months, and almost 50% have discontinued such therapy by this time. Compliance with weekly bisphosphonate therapy is generally no better than that with osteoporosis medications requiring more frequent dosing.

Keywords Adherence · Compliance · Osteoporosis · Pharmacotherapy

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Introduction

Osteoporosis comprises a group of bone loss conditions characterized by a reduction in bone density and a consequent increased susceptibility to fracture [1]. Postmenopausal women and older men are principally affected. Although some cases of bone loss are a manifestation of other diseases (e.g., Cushing's syndrome or thyrotoxicosis) or an adverse effect of medical treatment (e.g., chronic glucocorticoid therapy, organ transplantation), most cases are not caused by other diseases or medical therapy. The most common fractures due to osteoporosis among persons–especially women–aged 45 years and older involve the hip, vertebrae, and distal radius; for women, the lifetime risk of a typical osteoporotic fracture has been estimated to be about 40% [2, 3].

A variety of medications-including bisphosphonates, calcitonin, estrogen, a selective estrogen receptor modulator (raloxifene), and an anabolic (teriparatide)-are currently available for the prevention and treatment of osteoporosis and, when used as recommended, have demonstrated efficacy against osteoporotic fracture [4]. Accumulating evidence suggests, however, that these agents are under-

utilized in clinical practice due to low rates of prescribing among persons at high risk of fracture, and also poor drug compliance among those who have been prescribed therapy [2, 5–12]. Numerous reasons are often cited for poor compliance, including the asymptomatic nature of osteoporosis and corresponding lack of symptomatic relief from therapy, the adverse effects and cost of medication, and the requirement of daily or every-other-day dosing for several agents [8].

The hypothesis that compliance may be greatly improved by reducing dosing frequency led to the development of weekly formulations of bisphosphonates, and has resulted in the recent availability of newer agents with even less frequent dosing. Recker and colleagues examined the relationship between dosing frequency and adherence with weekly versus daily bisphosphonate therapy [8]. While they report that adherence is slightly better with weekly than daily dosing, they conclude that it is inadequate with both regimens. Their study was limited, however, by an inability to control for certain factors that may influence compliance, such as history of fracture, and by a relatively short period of follow-up (i.e., one year) [13]. Also, Recker and colleagues did not examine adherence with osteoporosis therapies other than bisphosphonates (e.g., estrogen, calcitonin, raloxifene). We undertook the present study to expand knowledge in these areas.

Methods

Data source

Data were obtained from a large automated US health-care claims database (PharMetrics Patient-Centric Database), and spanned the period January 1, 1998 to December 31, 2003. The database comprises paid facility, professional-service, and retail (i.e., outpatient) pharmacy claims that were submitted to 49 US health plans providing commercial health maintenance organization, preferred provider organization, Medicare Risk, and indemnity products to 15 million persons annually. Approximately 4% of all patients in the database are aged 65 years or older, and 51% are female. Plan members reside throughout the US (Midwest: 35%, Northeast: 18%, South: 33%, West: 14%).

Data available for each facility and professional-service (i.e., medical) claim include dates and place of service, diagnoses (in International Classification of Diseases, Ninth Edition, Clinical Modification [ICD-9-CM] format), procedures performed/services rendered (in Health Care Financing Administration Common Procedure Coding System [HCPCS] format), quantity of services provided, and provider specialty. Data available for each retail pharmacy claim include the drug dispensed (in National Drug Code [NDC] format), the dispensing date, quantity dispensed, and number of days of therapy supplied. All medical and pharmacy claims include charged and paid amounts. Demographic and eligibility data for members are also available and include age, sex, geographic region, coverage type, and the dates of eligibility for plan benefits. Patient-level data can be arrayed in chronological order to provide a detailed longitudinal profile of all medical and pharmacy services used by each plan member.

All patient identifiers in the database have been fully encrypted, and the database is fully compliant with the Health Insurance Portability and Accountability Act of 1996 [14]. Since, "...subjects cannot be identified, directly or through identifiers linked to the subjects...", institutional review board (IRB) approval for this study was not sought [15].

Study population

The study population consisted of all women aged 45 years and older with osteoporosis who initiated therapy with a bisphosphonate (i.e., alendronate or risedronate), calcitonin (nasal or injection), estrogen (including estrogen-progesterone and estrogen-only products), or raloxifene (collectively, "study drugs") between July 1, 1998 and December 31, 2003. Women were considered to have initiated osteoporosis therapy if their first such prescription during the period of interest was preceded by a six-month period of continuous medical and drug benefits ("pretreatment period") without evidence of receipt of any study drug (or teriparatide). Subjects were classified into treatment groups based on the study drug first received; those initiating bisphosphonate therapy were further classified by formulation (i.e., weekly vs. daily dosing).

Presence of osteoporosis was ascertained on the basis of one or more medical claims with a diagnosis of osteoporosis (ICD-9-CM 733.00, 733.01) during the pretreatment period (or on the date of therapy initiation). Women with one or more medical claims with a listed diagnosis of breast cancer, cancer metastatic to bone, Paget's disease, or various secondary causes of osteoporosis (Cushing's disease, hyperthyroidism, Crohn's disease, rheumatoid arthritis, organ transplantation) during pretreatment (or on the index date) were excluded from the study population. Use of osteoporosis drug therapy was ascertained on the basis of medical and pharmacy claims with corresponding HCPCS and NDC codes, respectively.

Study measures

Compliance with osteoporosis drug therapy was assessed for each study subject from the date of therapy initiation through the date of health plan disenrollment, the date of switch to another osteoporosis drug (or formulation), or December 31,

2003, whichever occurred first. Duration of follow-up thus varied among subjects and was a maximum of 5.5 years; follow-up was 3 years or less for most subjects, however.

Compliance was examined in terms of adherence failure and persistence failure. Adherence was measured each day during follow-up based on the ratio of the cumulative number of therapy-days (for the study drug) to the cumulative number of elapsed calendar days (from therapy initiation); "adherence failure" was defined as a ratio less than 80%. Persistence was measured on a daily basis using the number of elapsed days from exhaustion of dispensed study drug ("Rx gap"); "persistence failure" was defined as an Rx gap of 90 days or more. For subjects who were hospitalized (or admitted to a skilled nursing facility on a short-term basis), adherence between date of admission and date of discharge was assumed to be 100%.

Statistical analyses

Demographic and clinical characteristics of study subjects in each treatment group were examined, including age, evidence of prior fracture, selected comorbid conditions, and pretreatment medical-care use and expenditures. Age was assessed as of the date of therapy initiation. Comorbidities (including cardiovascular disease, chronic pulmonary disease, diabetes, kidney disease, liver disease, malignant neoplasms, and mental disorders) and evidence of prior fracture (vertebrae, wrist, hip, and other sites of likely osteoporotic fracture [e.g., femur]) were ascertained on the basis of medical and pharmacy claims during pretreatment (or on the date of therapy initiation) with corresponding diagnosis, procedure, and/or drug class codes, as appropriate. Expenditures were tallied based on paid amounts on all medical and pharmacy claims. Tests of heterogeneity across treatment groups were undertaken using a one-way analysis of variance (ANOVA) for continuous variables, and chi-square test for categorical measures, as appropriate.

Kaplan-Meier methods were employed to compare crude (i.e., unadjusted) time to adherence failure and persistence failure, respectively, across treatment groups; a two-sided log-rank statistic was used to assess statistical differences. Cox proportional hazards models were employed to compare

Table 1 Characteristics of postmenopausal women initiating osteoporosis drug therapy

	Bisphosphonate					
	Daily (n=3,421)	Weekly (n=9,117)	Calcitonin (n=1,361)	Raloxifene (n=2,132)	Estrogen (n=2,791)	*p* value
Age[a], %						
<65	49.7	69.0	38.1	71.4	84.5	<0.001
65–74	24.1	14.1	22.8	16.0	9.5	
≥75	26.2	16.9	39.2	12.5	6.1	
Mean±SD	65.8±11.9	62.2±11.1	70.0±13.0	61.7±9.9	57.1±8.8	<0.001
Evidence of prior fracture[b], %						
Any	1.9	1.5	6.8	1.0	0.9	<0.001
Vertebral	0.5	0.3	3.7	0.3	0.2	<0.001
Wrist	0.1	0.1	0.4	0.0	0.1	0.027
Hip	0.9	0.7	1.9	0.5	0.3	<0.001
Other	0.6	0.6	1.6	0.2	0.5	<0.001
Comorbid conditions[b], %						
Cardiovascular disease	1.7	1.1	4.6	0.8	0.6	<0.001
Chronic pulmonary disease	1.5	1.0	4.0	0.6	0.6	<0.001
Diabetes	5.5	5.5	6.7	5.1	4.8	0.132
Kidney disease	0.1	0.0	0.3	0.0	0.1	0.007
Liver disease	0.1	0.0	0.3	0.0	0.1	<0.001
Malignant neoplasm	0.2	0.3	0.5	0.1	0.3	0.324
Mental disorders	27.1	27.7	36.0	26.5	29.1	<0.001
Medical-care[b], mean±SD						
No. of prescriptions	11.3±12.2	10.1±12.0	15.8±16.0	9.6±11.0	8.6±10.4	<0.001
No. of outpatient encounters	9.2±7.0	9.8±8.0	11.3±9.2	9.1±7.4	10.3±8.9	<0.001
No. of hospital admissions	1.4±0.8	1.4±0.8	1.7±1.1	1.2±0.7	1.3±1.0	<0.001
Total expenditures ($US)	2,477±6,079	2,723±7,389	4,940±11,369	2,216±4,719	2,529±5,344	<0.001

[a]As of index date
[b]Based on 6-month history period
SD: standard deviation

the risks of adherence failure and persistence failure, respectively, across treatment groups, controlling for differences in age, evidence of prior fracture, and presence of selected comorbid conditions; medical-care use and expenditures were not included because they were hypothesized to be highly collinear with each other and with the presence of comorbid conditions. Patients who did not experience the event of interest (i.e., adherence failure, persistence failure) prior to the end of follow-up period were censored as of the corresponding date. The proportionality of risks over time across treatment groups was assessed by including corresponding time-dependent covariates in the model. All analyses were conducted using SAS Proprietary Software, Release 8.2 (SAS Institute Inc., Cary NC).

Results

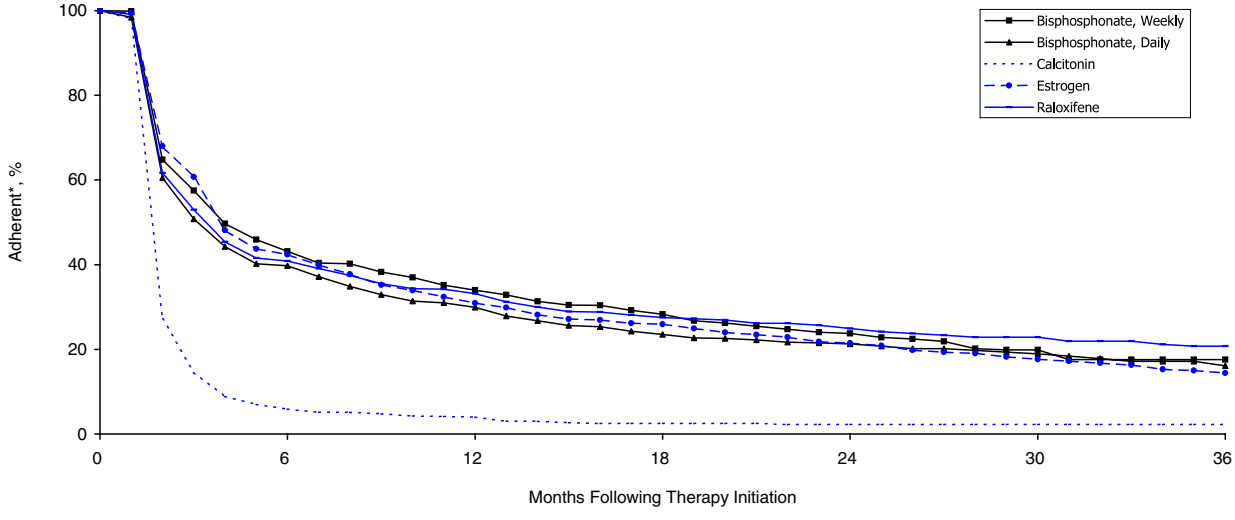
Patient characteristics

A total of 18,822 women aged ≥45 years were identified who initiated osteoporosis drug therapy during the period of interest; two-thirds received bisphosphonates (weekly formulations, 48% of total study population; daily formulations, 18%) (Table 1). Mean age was highest among those receiving calcitonin (70 years), and lowest among those receiving estrogen (57 years) ($p<0.01$ for test of heterogeneity across all treatment groups). Seven percent of calcitonin patients had evidence of fracture during the six-month period prior to therapy initiation, versus 1.9% and 1.5% of those initiating daily and weekly bisphosphonate therapy, respectively; the rate was about 1% among those receiving raloxifene and estrogen. (Such differences [i.e., in rates of pre-treatment fracture] across treatment groups may be partially explained by variation in patient age, although this relationship was not specifically examined.) There also were differences in comorbidities and medical-care use and expenditures across treatment groups.

Risks of adherence and persistence failure

Overall risk of adherence failure at three months was 47%; it was 70% at 1 year, and 84% at 3 years. Risk of adherence failure was consistently highest among patients initiating therapy with calcitonin (3 months: 85%; 1 year: 96%; 3 years: 98%); across the other treatment groups, failure rates ranged from 39–49% at 3 months, 66–70% at 1 year, and 79–86% at 3 years (Fig. 1). Overall risk of persistence failure was 47% at 1 year, and 77% at 3 years (Fig. 2). It was highest for calcitonin patients, but similar across the other treatment groups.

In multivariate analyses, the risk of adherence failure was higher for calcitonin versus weekly bisphosphonate therapy (hazard ratio [HR]=2.7, $p<0.01$) (Table 2), but comparable for all of the other therapies. Younger women, those with evidence of prior fracture, and women without

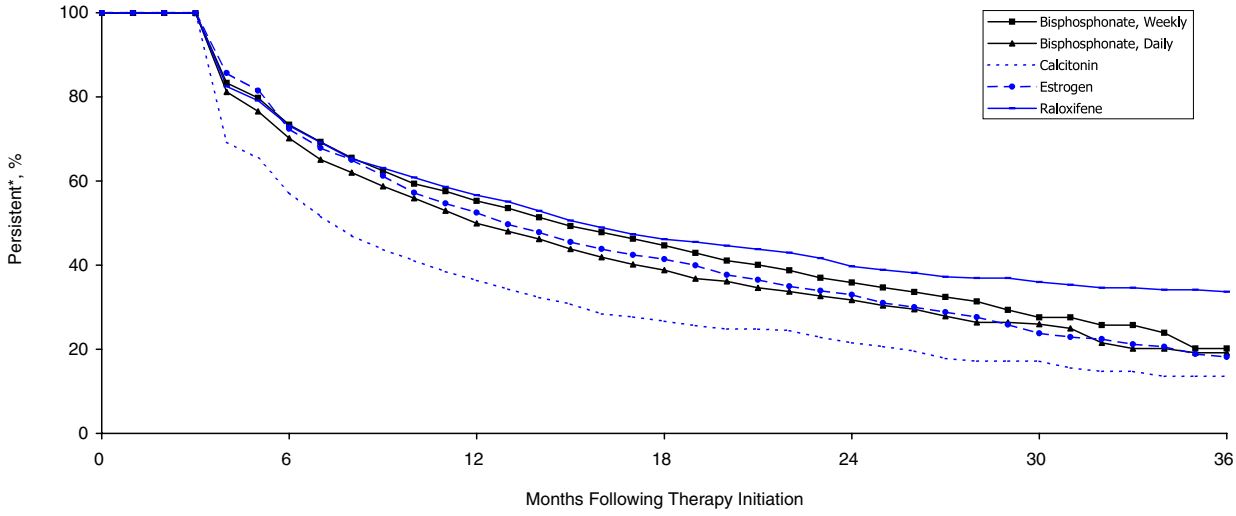


No. at Risk							
Bisphosphonate							
Weekly	9,117	2,576	1,289	615	226	29	6
Daily	3,421	911	396	176	87	37	14
Calcitonin	1,361	53	25	11	6	2	0
Estrogen	2,791	886	513	312	184	85	49
Raloxifene	2,132	614	362	212	131	78	46

p-value<0.001

*Adherent = 1 - adherence failure

Fig. 1 Time to adherence failure (adherence ratio <80%) with osteoporosis drug therapy in postmenopausal women



No. at Risk							
Bisphosphonate							
Weekly	9,117	4,314	2,028	923	326	42	6
Daily	3,421	1,559	656	282	128	55	16
Calcitonin	1,361	510	220	101	47	22	8
Estrogen	2,791	1,476	838	482	265	108	55
Raloxifene	2,132	1,077	602	343	193	111	67

p-value<0.001

*Persistent = 1 - persistence failure

Fig. 2 Time to persistence failure (Rx gap >=90 days) with osteoporosis drug therapy in postmenopausal women

Table 2 Time to adherence or persistence failure with osteoporosis drug therapy

	Adherence failure (adherence ratio <80%)			Persistence failure (Rx gap >=90 days)		
	HR[a]	95% CI[b]	*p* value	HR	95% CI	*p* value
Anti-osteoporosis medication						
Bisphosphonate-weekly (referent)	1.00	–	–	1.00	–	–
Bisphosphonate-daily	0.99	0.94–1.04	0.748	1.04	0.98–1.11	0.223
Calcitonin	2.67	2.50–2.85	<0.001	1.49	1.37–1.62	<0.001
Estrogen	1.02	0.97–1.08	0.477	1.17	1.09–1.25	<0.001
Raloxifene	0.95	0.90–1.01	0.124	0.92	0.85–0.99	0.027
Age						
<65 (referent)	1.00	–	–	1.00	–	–
65–74	1.17	1.11–1.23	<0.001	1.46	1.37–1.56	<0.001
≥75	1.23	1.17–1.29	<0.001	1.53	1.44–1.63	<0.001
Evidence of prior fracture						
Yes	0.81	0.70–0.94	0.004	0.76	0.63–0.92	0.006
No (referent)	1.00	–	–	1.00	–	–
Comorbid conditions						
Cardiovascular disease	1.11	0.95–1.29	0.202	1.15	0.94–1.40	0.180
Chronic pulmonary disease	1.07	0.90–1.26	0.455	1.22	0.99–1.51	0.066
Diabetes	1.13	1.05–1.22	0.002	1.09	0.99–1.21	0.080
Kidney disease	1.47	0.76–2.84	0.246	1.14	0.47–2.75	0.773
Liver disease	0.71	0.34–1.50	0.370	0.87	0.33–2.33	0.782
Malignant neoplasm	1.14	0.83–1.56	0.423	1.09	0.75–1.58	0.653
Mental disorders	1.13	1.09–1.18	<0.001	1.08	1.03–1.14	0.003

[a]HR: hazard ratio

[b]CI: confidence interval

particular comorbid conditions had lower risks of adherence failure versus the corresponding referent groups. Relative risks of persistence failure across treatment groups were generally similar to those for adherence failure. Tests of proportionality suggest that observed (relative) differences in risks of adherence or persistence failure between treatment groups generally decreased over time.

Discussion

Compliance with medications used to treat chronic diseases typically ranges from 50–60%; it is usually lower when a disease is asymptomatic, and/or when treatment confers bothersome side effects [10, 16]. It therefore is not surprising that 47% of postmenopausal women in our study were no longer adherent with therapy 3 months following initiation of treatment, and by the end of 1 year, nearly 70% were adherence failures. The percentage of women who were persistence failures, while lower, was still substantial (47% at 1 year). There thus appears to be a large cohort of patients who discontinue treatment soon after therapy initiation; among those who persist beyond this time point, the failure rate is much lower. With the exception of calcitonin, differences in failure rates across treatment groups were small; accordingly, little improvement in compliance seems to be conferred with the once-weekly formulation of bisphosphonate therapy versus other osteoporosis medications. In light of published studies suggesting that low compliance with osteoporosis drug therapy is associated with increased fracture risk, these data indicate that the large majority of osteoporotic women are not adequately protected against future fracture [9, 10]. The results of our study are largely consistent with those of prior research, despite various differences in study designs.

In the most recently published study, compliance was assessed among a group of Medicare patients (mean age, 80 years) in Pennsylvania who qualified for a state-run drug benefits program on the basis of annual incomes between $10,000 and $20,000 [17]. The decrease in compliance was greatest during the first 60 days of follow-up, and one year after initiating osteoporosis therapy, 45% of persons were not continuing to fill prescriptions. Recker and colleagues found that among women initiating daily or weekly bisphosphonate therapy, 87% and 75%, respectively, did not achieve adequate adherence (i.e., were adherence failures) defined as a medication possession ratio of 80% or greater during the one-year follow-up period [8]. In a study by McCombs et al., 35–53% of osteoporotic patients beginning estrogen, bisphosphonate, or raloxifene therapy received less than 3 months of their initial therapy over the following one-year period; 54–69% had 6 months or less [10]. Kayser et al. reported probabilities of therapy discontinuation over a two-year period of 56% for women starting raloxifene, and 72% for those beginning treatment with estrogen [11]. Another study found that 59–76% of postmenopausal women initiating estrogen therapy (irrespective of reason) discontinued within 12 months [18].

Lower failure rates (20–35%) have been reported in several studies. However, these studies are limited as to their generalizability because they either focused on a select group of patients (e.g., those recently sustaining an osteoporotic fracture, those with at least two prescriptions for the initial antiosteoporosis agent), had a relatively short follow-up period (e.g., less than 1 year), assessed adherence based on patient survey (which is known to result in upwardly biased estimates) rather than on prescription refill data, or included a small sample of patients [5, 19–21].

Several aspects of our study require further comment. First, although (with the exception of estrogen) the agents we studied are specific for osteoporosis, we required a diagnosis of osteoporosis (ascertained on the basis of ≥1 medical claims with the corresponding ICD-9-CM code) for study entry. In the case of estrogen, requirement of an osteoporosis diagnosis was necessitated by its widespread use for relief of menopausal symptoms. It should be noted that our study database includes the time period during which the findings of the Women's Health Initiative on estrogen use and selected health risks were reported, and thus women who were taking estrogen at the time of this report, and who otherwise would not have discontinued such therapy, may have done so in response to it, either independently, or on the advice of their physicians [22]. The precise magnitude of this effect in our study is unknown. In the case of other agents, requirement of an osteoporosis diagnosis excluded patients who received these agents for osteoporosis prevention (e.g., those with bone density measurements consistent with osteopenia); such an approach for sample selection has been employed in prior studies [9, 10]. Compliance may be even lower in patients taking osteoporosis agents prophylactically. Second, although there was statistically significant heterogeneity among the compliance rates for the different agents (in selected analyses), the actual differences are relatively small and were unlikely to be of clinical significance. In studies with large populations such as ours, small differences are frequently found to be statistically significant. Third, we focused on women with postmenopausal osteoporosis newly initiating drug therapy; this cohort probably represents only a fraction of those taking such medications. However, persons with prior prescriptions are of less interest in this type of study since, by definition, they are a more adherent group for whom the precise amount of time on medication may be unknown. Finally, our choice of 80% as the criterion for assessing adherence, and a prescription gap of 90 days for determin-

ing persistence, is somewhat arbitrary but is within the range of thresholds employed in prior studies [8, 9, 23, 24]. Results are robust, however, when varying the thresholds within reasonable limits.

There are several limitations to studies that assess the relationship between medical interventions and clinical outcomes based on automated health-care claims databases [25]. All such databases, for example, contain errors of omission and commission in coding. Moreover, for many studies based on claims data, information is not available for one or more clinically or economically important parameters (in the current study, bone mineral density, income levels, and out-of-pocket medication costs) and medical histories are left-censored (i.e., patients' experiences, such as fractures occurring before the period of interest are largely unobservable). The impact of these limitations on our study cannot be assessed.

In addition to these generic limitations, we point out one major limitation specific to our study and others measuring compliance using health-care claims data: it cannot be determined from data on prescription refills if the drug dispensed was actually taken, when it was taken, and how much was taken [22]. This limitation confers an upward bias to our estimates (i.e., if actual drug use could be observed, rates of compliance would be lower than those reported in this study). Finally, we could not assess compliance with teriparatide or ibandronate (a bisphosphonate), since sufficient data on their use were unavailable at the time of this study.

In summary, our results suggest that almost three-quarters of all women initiating osteoporosis drug therapy-regardless of the medication received-are no longer adherent with treatment 12 months following therapy initiation, and almost one-half have discontinued such therapy by this time. Notably, compliance with weekly bisphosphonate therapy appears to be generally no better than that with medications requiring more frequent dosing.

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