Factors Contributing to Compliance with Osteoporosis Medication

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Abstract

Background: Bisphosphonates are effective in the prevention and treatment of osteoporosis, yet their use is suboptimal.

Objectives: To measure bisphosphonate compliance among first-time users and identify factors associated with compliance.

Methods: We conducted a prospective follow-up of all women aged 45+ in the second largest health management organization in Israel who were prescribed bisphosphonates for the first time. The 4448 women were classified by drug dosage. Persistence and adherence measures of compliance were calculated for each woman over a 1 year period.

Results: Mean bisphosphonate persistence over a year was 216 days, with a mean medication possession ratio of 66%. Women whose medication was changed, whether from weekly to daily or daily to weekly, always had better persistence rates than those who consistently took the original dose. Persistence rates were as follows: 264 days for women who switched back and forth between daily and weekly doses, 229 days for those who switched from daily to weekly, 222 days for those who took the dosage weekly only, 191 days for those who switched to daily dosage, and 167 days for those who took the dosage daily only ($P < 0.001$). Switchers were also more likely to have adequate adherence rates (MPR ≥ 80%): 81.3%, 76.6%, 67.5%, 61.3% and 52.2% respectively ($P < 0.001$). More than 20% of women stopped taking their medication within the first month. Women with higher supplemental insurance (offering significant discounts for weekly dose medications) had better persistence rates: 221 vs. 208 days ($P = 0.03$). Younger women and women on national pension insurance had the lowest persistence rates: 204 and 209 days respectively.

Conclusions: While weekly bisphosphonate takers had better compliance rates, persistence and adherence rates were inadequate for all groups. Changing medication to meet the needs of the patient, discounting weekly medications, and providing follow-up within the first months of prescription may promote compliance.

IMAJ 2008;10:207–213

Osteoporosis has been defined as a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, resulting in increased bone fragility [1]. Its onset is insidious and its presence often has few, if any, symptoms. It has been estimated that 13–18% of women in the United States over the age of 50 have osteoporosis, and another 37–50% have osteopenia (precursor of osteoporosis) [2].

Although osteoporosis is not considered a directly life-threatening disease, it is a key risk factor for fragility fractures, particularly of the hip [3,4]. The 10 year risk of a fragility fracture in a 50 year old post-menopausal woman with osteoporosis is 5%. This risk increases to 20% by the age of 65 [4]. One in six patients aged 50–55 after hip fracture is discharged from the hospital to a nursing home, and this rate increases exponentially with increasing age [2]. Mortality rates are on average 20% higher within 1 year of hip fracture [1]. Despite these alarming figures, the perceived risks from osteoporosis among post-menopausal women are low [5,6].

Bisphosphonates are a first-line medication for the prevention and treatment of osteoporosis and have been shown to significantly reduce the risk of fracture [3,7-9]. However, bisphosphonates are costly, have significant side effects and interfere with daily life [5,6,10,11]. Bisphosphonates must be taken after an overnight fast with a glass of water at least 30 minutes before ingesting food, drink or medication. Patients are required to avoid the prone position for at least 30 minutes post-dose. Further, patients do not perceive any direct observed benefit from taking the medication [6].

Poor medication compliance is a key limiting factor in the prevention and treatment of chronic conditions [2,4,12]. Achieving compliance is even more difficult for a nearly asymptomatic condition such as osteoporosis, where the perceived risks are low and the 'costs' – both monetary and non-monetary – are high. Bisphosphonate compliance rates are poor, with weekly dose compliance rates better than daily dose rates but still suboptimal [13-17].

The estimated prevalence of osteoporosis for women over the age of 65 in Israel is 28% [18]. No national data are available for the incidence of hip fracture or bisphosphonate compliance. However, the hip fracture incidence rate reported in southern Israel is 1.5% for women aged 50 and older [19]. A 20% discontinuation rate for bisphosphonates within 6 months of prescription was found in another study in southern Israel [10]. The current study describes bisphosphonate compliance rates in a large health management organization in Israel, and identifies demographic and other characteristics associated with medication compliance.

Subjects and Methods

Data were collected from the Maccabi HealthCare Services database. Maccabi is the second largest HMO in Israel, providing health care coverage for over 1.7 million members. This database

MPR = medication possession ratio

HMO = health management organization

includes a complete and up-to-date registry of all HMO members, including medication purchases (updated daily), and medical and demographic characteristics.

Study population

The study population included all female members aged 45 and older who were current members of the HMO and had made their first bisphosphonate purchase between 1 May 2003 and 30 April 2004. "First purchase" was defined as the first purchase in this period, with no record of any prior purchase from 1 January 2000. The study period was defined as 1 year from the date of the first purchase for each member of the study population. Medications included were any bisphosphonate purchase (alendronate or risedronate) by the study group in the study period. Although other drugs (such as raloxifene) are available for the treatment and prevention of osteoporosis, this study focused on bisphosphonates alone as they are the drug group of first choice for the prevention of hip fractures. The study was approved by the Institutional Review Board of the HMO.

Medication compliance

Compliance is commonly measured in the literature [17,20] using the following two measures:

- The *medication possession ratio*, sometimes referred to as the adherence rate, is defined as the "number of supply days" per member in a 365 day period from date of first purchase, and is expressed as a percent of days in a year. The "number of supply days" is calculated as the number of purchases multiplied by the number of pills in the packet, and by the recommended dosage frequency. For example, if a woman purchased four packets of weekly bisphosphonate (where each packet contains four pills recommended to be taken once weekly) her MPR would be calculated as [(4 packets*4 pills*7 days)/365]*100. The assumption is made that any medication purchased is taken and at the recommended dose.
- The *persistence rate* is the number of consecutive supply days within a 365 day period from the date of the first purchase, allowing no more than a 30 day lapse between purchases. For example, if the same woman made her first and second purchases in May 2003, with only a 3 day gap between completion of the number of supply days of the first packet and purchase of the second packet, and her third and fourth purchases were in August of that same year, her persistence rate would be calculated as the number of days between her first purchase and the date when her last consecutive packet would have run out [(2 packets*4 pills*7 days)+3] = 59 days. The third and fourth packets would not be included in her persistence rate as these were not purchased consecutively.

Variables definition

Independent variables of interest included drug therapy group, age, immigrant status, socioeconomic status, and whether the member had higher level supplementary health insurance.

- *Drug therapy group*: The principal independent variable of this study was determined by categorizing each purchaser into one of five discrete groups: a) those who only purchased daily bisphosphonates during the study period, b) those who only purchased weekly bisphosphonates, c) those who at some point during their study period switched from daily to weekly bisphosphonate therapy, d) those who switched from weekly to daily, and e) those who made more than one change between daily and weekly therapies. This last group often switched several times and some even purchased both kinds of drug therapy on the same date.

- *Immigrant status*: We categorized the study population as either having immigrated to Israel from the former Soviet Union after 1990 or not. In 1990, immigration from the former USSR was such that within 1 year the Israeli population increased by 20%. Immigration rates have declined since then, although immigrants from the former USSR continue to arrive each month. This large subset of the population has been shown to differ in many respects to the host population – in terms of health risks and health behaviors, utilization of medical services and socioeconomic status [21].

- *Higher supplementary insurance*: The HMO currently offers two levels of supplemental insurance (with a relatively small difference in cost). The majority of women aged 45 and older (64%) had the higher level supplemental insurance. Only daily dose bisphosphonates are included in the basket of services that all HMOs in Israel must provide at minimal cost to patients. However, the higher insurance level offered by the HMO affords the member a 50% discount on bisphosphonate purchase. Therefore, women were characterized according to their level of supplemental insurance: i.e., having higher level supplemental insurance or not.

- *National Insurance pension*: A proxy variable for socioeconomic status divided the study population into two groups: those receiving national insurance pensions and those not.

- *Religiosity and population group*: Information on both variables was collected. However, the number of members in the key categories was so small that no further analysis was possible.

Statistical analysis

The relationship between each independent variable and the key independent variable – drug therapy group – was evaluated using chi-square. The association between each independent variable and both dependent variables – MPR and persistence – were measured using one-way ANOVA analysis. All the independent variables were then included in the multivariate analysis, using ANOVA with simple contrast analysis. All analyses were carried out using SPSS 14.0 for Windows.

Table 1. Bisphosphonate drug therapy group of 4448 first-time users aged 45+

	Drug therapy group (type of bisphosphonate purchased)					
	% daily only (N=1175)	% switch to daily (N=98)	% switch to weekly (N=292)	% weekly only (N=2,762)	% mixed (N=121)	Total (N=4,448) 100%
Age (yrs)						
45–54 *	17.5	2.2	7.7	69.6	3.0	969
55–64	22.5	1.5	6.4	67.0	2.6	1474
65–74	32.8	2.7	6.7	55.4	2.4	1319
75+	35.1	2.9	5.0	53.8	3.2	686
						$P < 0.001$**
New immigrant*						
No	15.7	2.1	6.4	73.3	2.4	3199
Yes	53.8	2.4	6.9	33.3	3.5	1249
						$P < 0.001$
Receives National Insurance pension						
No	15.7	1.8	6.6	73.6	2.2	3067
Yes	50.3	3.0	6.4	36.5	3.8	1381
						$P < 0.001$
Higher supplementary insurance**						
No	52.8	2.3	5.7	36.1	3.2	1104
Yes	17.7	2.2	6.8	70.7	2.6	3344
						$P < 0.001$
Region						
Northern	33.6	2.1	7.4	53.8	3.2	729
Eastern	19.2	1.4	6.0	69.6	3.9	720
Central	14.1	2.3	4.8	76.5	2.3	1231
Coastal (southern)	33.1	2.9	8.4	53.0	2.6	1234
Jerusalem	22.2	2.3	1.8	72.5	1.2	171
Southern	48.4	1.1	7.9	40.2	2.3	353
						$P < 0.001$

* Percent of row

** Pearson chi-square test

*** Immigrated from the former USSR and settled in Israel from 1990

**** Member has highest level of supplemental insurance and is therefore entitled to alendronate discount

Table 2. Association between independent variables and bisphosphonate compliance – univariate analysis

		Persistence (days)			MPR (% adherence)		
Independent variables	N= 4448	Mean (SD) 216 (149)	F	P	Mean (SD) 66 (36)	F	P
Drug therapy group							
Daily only	1175	167 (146)	44.9	< 0.001	52 (37)	71.9	< 0.001
Switched to daily	98	198 (143)			63 (32)		
Weekly only	2762	233 (147)			70 (35)		
Switched to weekly	292	237 (145)			79 (27)		
Mixed	121	268 (132)			83 (22)		
Age (yrs)							
45–54	969	215 (147)	2.5	0.056	66 (36)	1.9	0.128
55–64	1474	220 (149)			67 (36)		
65–74	1319	220 (150)			67 (36)		
75+	686	202 (151)			64 (37)		
New immigrant*							
No	3199	227 (148)	55.9	< 0.001	69 (36)	66.4	< 0.001
Yes	1249	188 (149)			59 (37)		
Receives National Insurance pension							
No	3067	227 (148)	50.0	< 0.001	69 (36)	60.2	< 0.001
Yes	1381	191 (149)			60 (37)		
Higher supplementary insurance**							
No	1104	187 (149)	52.1	< 0.001	58 (37)	73.5	< 0.001
Yes	3344	226 (148)			69 (36)		
Region							
Northern	729	210 (149)	3.6	0.003	66 (35)	6.2	< 0.001
Eastern	720	224 (147)			69 (35)		
Central	1241	227 (150)			69 (36)		
Coastal (southern)	1234	210 (150)			65 (36)		
Jerusalem	171	227 (150)			69 (36)		
Southern	353	192 (148)			58 (38)		

* From the former USSR and settled in Israel from 1990

** Member has highest level of supplemental insurance and is therefore entitled to alendronate discount

Results

Of the 4448 first-time bisphosphonate women users, the majority (63%) were in the 55–74 age range. Twenty-eight percent were new immigrants (compared to 32% in the entire HMO population for this age and gender group) and 31% received financial support from the government [Table 1]. Three-quarters of this group had higher supplemental insurance. Sixty-two percent of the study population purchased weekly bisphosphonates, with another 9% having switched to, or intermittently followed, the weekly treatment regimen. Just over a quarter (26%) of the women purchased daily bisphosphonates, with only 2% converting from a weekly to a daily dose. All of the independent variables were significantly associated with drug therapy group. Use of a daily bisphosphonate increased with increasing age and was more common among new immigrants (54%) than the rest of the population (16%) and among women of lower socioeconomic status (50% vs. 16% respectively). Those women who changed from weekly to daily doses were more likely to have a lower socioeconomic status (43% vs. 30%, $P = 0.008$).

In contrast, members with higher supplemental insurance were more likely to purchase the weekly bisphosphonates (71%) than those without such insurance (36%). Significant differences were found between regions, with the central and Jerusalem regions being more likely to purchase weekly bisphosphonates than in the peripheral regions.

Persistence

Women in this study population consistently purchased any kind of bisphosphonate medication for just over 7 months (216 ± 149 days). In the univariate analysis, women purchasing weekly bisphosphonate were significantly more likely to take the medication for longer (233 days) while daily-only users were likely to persist for less time (167 days, $P < 0.001$) [Table 2]. Forty-six percent of the women continued to take bisphosphonates for the whole year, with a 20% difference in 1 year persistence rates between women taking a weekly dose (51.7%) and those taking a
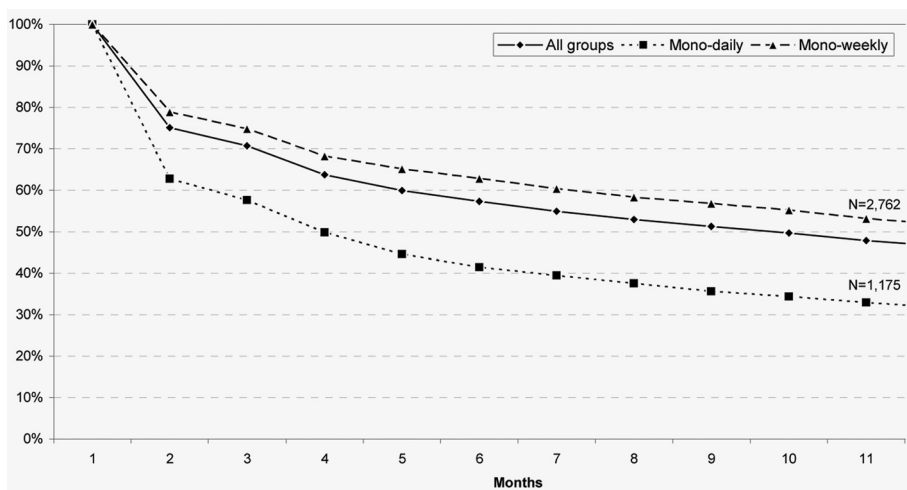
Figure 1. Percent of women persistently taking medication, by drug therapy group over time

Table 3. Association between characteristic variables and bisphosphonate compliance – multivariate analysis

Independent variables	N= 4448	Persistence (days) $r^2 = 0.048$				MPR (% adherence) $r^2 = 0.069$			
		Adj. mean*	P	F	P**	Adj. mean*	P	F	P**
Drug therapy group									
Daily only	1175	167	–	28.7	< 0.001	52.2	–	48.4	< 0.001
Switched to daily	98	191	0.132			61.3	0.01		
Weekly only	2762	222	< 0.001			67.5	< 0.001		
Switched to weekly	292	229	< 0.001			76.6	< 0.001		
Mixed	121	264	< 0.001			81.3	< 0.001		
Age (yrs)									
45–54	969	204	–	4.74	0.003	64.3	–	6.3	< 0.001
55–64	1474	215	0.07			67.2	0.05		
65–74	1319	228	< 0.001			71.0	< 0.001		
75+	686	213	0.23			68.7	0.02		
New immigrant*									
No	3199	219	–	2.08	0.15	68.5	–	0.8	0.385
Yes	1249	210	0.15			67.1	0.385		
Receives national insurance pension									
No	3067	221	–	3.99	0.046	69.2	–	3.9	0.049
Yes	1381	209	0.04			66.4	0.049		
Higher supplementary insurance**									
No	1104	208	–	4.60	0.032	65.5	–	9.2	0.002
Yes	3344	221	0.03			70.1	0.002		
Region									
Northern	729	214	–	.139	0.983	68.9	–	1.13	0.342
Eastern	720	215	0.98			68.6	0.85		
Central	1231	214	0.91			67.4	0.32		
Coastal (southern)	1234	214	0.90			68.0	0.57		
Jerusalem	171	221	0.57			69.9	0.76		
Southern	353	210	0.67			64.1	0.04		

*   Adjusted for all other variables in the model
**   *P* value of whole variable
***   From the former USSR, and immigrating to Israel in 1990
**** Member has highest level of supplemental insurance and is therefore entitled to bisphosphonate discount

daily dose (31.6%). The drop in compliance was most apparent in all groups between the first and second months of taking medication [Figure 1].

All other measures were associated with length of persistence in the univariate analysis. Those without higher supplemental insurance (187 days), new immigrants (188 days), those with lower socioeconomic status (191 days) and the 75+ age group (202 days) had lower persistence rates than their complementary counterparts. Women from the central and Jerusalem regions were more likely to have longer persistence rates than women from the periphery.

When all of the variables were entered into the multivariate analysis, most of the variables remained in the model, with the exception of immigrant status and region [Table 3]. However, the model only explained 4.8% of the variance. Trends for each significant variable were consistent with the findings in the univariate analysis, with the exception of age. When controlling for all other factors, the youngest age group (45–54 years) had the poorest persistence, with persistence increasing with increasing age until the 75+ age group where a drop in persistence was observed.

Women changing back and forth between daily and weekly regimens were likely to persist for an extra 97 days on average than women maintaining a daily-only bisphosphonate regimen. Women who maintained a weekly regimen were more likely to persist for an average of 55 days extra than the daily-only group, while women who switched from a daily to weekly regimen were more likely to persist even longer (an extra 62 days). Even women who switched from a weekly to a daily dose had on average a 24 day longer persistence. These findings were statistically significant ($P < 0.001$) and independent of all other variables in the model [Table 3].

MPR (adherence)
The average MPR of the first-time bisphosphonate user was 66% [Table 2]. Adherence rates, therefore, were

marginally higher than persistence rates. If women persisted to fill their prescriptions for an average of 7 consecutive months, their adherence to bisphosphonates over the year was 8 months on average. An MPR of 0.8 (≥ 80%) is commonly accepted in the literature as the cutoff point distinguishing between the compliant and non-compliant patient [3,6]. In the population studied 52.5% achieved an MPR of 80% or higher. Only 37% of the daily dose-only group had an MPR of ≥ 80%, while 43% of those who changed to a daily dose could be considered compliant by this definition. Weekly dose-only users were likely to be more compliant (58%), while 64% of those switching from daily to weekly dose had an MPR of ≥ 80%. Those who switched back and forth were the most likely to be compliant (65%).

Adherence rates in the univariate analysis were associated with all other variables. Women without higher supplemental insurance (58%), new immigrants (59%), women with lower socioeconomic status (60%) and women in the 75+ age group (64%) were all likely to have significantly lower adherence rates than their respective counterparts [Table 2]. Women from the southern region (the Negev) were particularly likely to have lower adherence rates than all other areas of Israel (58%).

Multivariate analysis revealed a similar picture to that of persistence rates. Drug therapy group, age, socioeconomic status and supplementary insurance were independently associated with adherence. Similarly, the only change in trend noted between univariate and multivariate analysis was for age. When controlling for all other variables, older women no longer had the poorest adherence rates. Rather, women in the youngest age group (45–54 years) were most likely to adhere poorly.

Potential differences in compliance between women taking risedronate vs. alendronate were also examined. Risedronate takers represented a small percentage (< 2%) of the study group. None of these women took risedronate exclusively over the year. No significant differences were found in persistence or adherence rates between these two groups ($P = 0.254$ and $P = 0.679$ respectively).

Potential differences in compliance between women taking generic vs. patented bisphosphonates were investigated. Weekly generic bisphosphonates were introduced late in the study period. (Only nine women were switched to these drugs). In contrast, the daily dose drugs purchased were almost exclusively generic (96% of daily dose takers). No significant differences in persistence or adherence rates were found between generic and patented daily dose takers ($P = 0.343$ and $P = 0.10$ respectively).

Discussion

Of all 4448 women in the HMO over the age of 45 for whom bisphosphonate therapy was prescribed, only 53% were compliant, with the average woman discontinuing treatment after 7 months. Women taking weekly dose bisphosphonates had better persistence and adherence rates than daily dose takers, although even among this group compliance rates were suboptimal. Unlike most other studies, those women whose dosage was changed over time were included for follow-up. We found that women who changed from a weekly to a daily regimen had better compliance rates than women who remained on a daily dose only. Women who switched from daily to weekly dose regimens had better compliance rates than women on a weekly dose only. These findings suggest that modification of medication, regardless of dosage type, may enhance compliance.

The low persistence and adherence rates found here are comparable with the findings of other studies. Cramer et al. [14] found good adherence rates (MPR ≥ 80%) of 55% for weekly bisphosphonate users, as compared to 40% for daily-only users (58% vs. 37% respectively in this study). Penning-van Beest and co-authors [13] reported a 1 year persistence rate of 43% for bisphosphonates in new users (46% in this study). Cramer et al. [17] reported an average persistence of 196 days (as compared to 216 days in this study).

Siris and team [3] found that women with an MPR lower than 50% had no appreciable advantage in fracture risk reduction. Between 50% and 75%, the probability of fracture declined, with an appreciable reduction in fracture risk found for women with an MPR of 75–80% and beyond. The mean MPR for women in the present study was 66%, with only 53% of women achieving an MPR of 80% or higher, suggesting that nearly half the women in the HMO were getting suboptimal protection against osteoporosis due to poor medication compliance.

We found that a large proportion of women stopped taking their medication after the first month of prescription. Similarly, Lo et al. [22] reported that 29% of the women in their study only filled a single prescription. Others report a significant drop in the first 3 months [5,13]. These findings provide a clear message to physicians prescribing these medications. Given the difficulties in taking the medication and possible side effects that may arise, new users need to be reviewed within 1–3 months of prescription, and again after 6 months to reinforce compliance (and minimize discontinuation typically found after 7 months).

The main factor associated with compliance was dosage frequency. Weekly users were significantly more likely to comply and to persistently purchase their medications than daily dose users. This finding is consistent with the literature [13-15,17] and reinforces the recommendation to initiate new users with a weekly regimen when possible. However, even among weekly dose users, only 58% had an MPR ≥ 80% and their average persistence time was just under 8 months. Efforts have been made to engineer a monthly dose (ibandronate) in the hope that monthly prescription will raise compliance to acceptable levels [6]. Ibandronate is available in Israel but its prescription is not currently authorized for the treatment and prevention of osteoporosis.

"Switchers" comprised nearly 12% of the study population, with those women switching from one dosage type to another, persisting longer than the group they changed from. This finding suggests that a change in medication to meet the specific needs of the patient may enhance compliance. Women who changed to a weekly dose may be more satisfied with the change, thus enhancing their compliance. Even those changing from a weekly dose to a daily dose did better than women taking a daily dose only. Those women who changed from weekly to daily were more

likely to have a lower socioeconomic status, suggesting that a change that met their financial needs may have impacted on compliance. A change in medication indicates at least a second visit to the physician regarding the medication first prescribed and reinforces the conclusions made earlier: physician monitoring and adaptation of the medication to the patient's needs play a positive role in augmenting compliance.

Increasing age was associated with increasing adherence and persistence when controlling for all other factors, until the age of 75. In the 75+ age group a drop in both measures was observed. Similar findings were reported in other studies [3,13]. However, while this oldest age group had the lowest compliance rates before controlling for other variables, this drop was less marked in the multivariate analysis, where the youngest age group was found to have the lowest compliance rates. This study identified two groups, therefore, at higher risk of poor compliance – the youngest and the oldest – but for apparently different reasons.

The youngest age group may feel less at risk of fracture and less likely to perceive the benefits of the medication. Gold and Silverman [5] pointed out that only after a second bone mineral density test (18–24 months after treatment commencement) would a patient gain any feedback regarding any medication-induced change. By that time, as our study has shown, most women – particularly in this age group – will have discontinued taking their medication.

The mechanisms undermining compliance among the eldest group of women (age 75+) are different. This group was more likely to have a low socioeconomic status and less likely to have supplemental insurance. These factors alone were found to decrease compliance. Beyond the impact of these measures, however, this age group had shorter persistence rates. We suggest that co-morbidities, more prevalent in this oldest age group, may play a modifying role in this group's compliance rates. Patients with co-morbidities may be selective in their medication purchase, prioritizing those medications for illnesses already acquired, than those requiring prevention.

Having the highest supplemental insurance, independent of socioeconomic status, had an impact on both persistence and adherence to bisphosphonate medication. Recognizing the advantages of the weekly dose, the HMO has been discounting once-weekly medications for those women with higher supplemental insurance since 2002. As of December 2006, these discounts were made available to all women in the HMO.

Although this comprehensive study was based on the entire relevant HMO population, limitations of the study warrant consideration. The final model explained a relatively small amount of the variance found, suggesting that other factors may play a role in compliance, such as concomitant use of hormone replacement therapies [22], a history of gastrointestinal upset in the past or as a result of taking bisphosphonates [10,13,22], having a bone mineral density test in the past [21,23], osteoporosis diagnosis, severity of osteoporosis, prior history of fracture [3], and high dose glucocorticoid exposure [22]. Another limitation was the lack of information regarding socioeconomic status. The "low" socioeconomic group identified here on the basis of govern-

ment subsidy underestimates the proportion of women for whom medication cost would be an issue.

It is likely that our findings underestimate the true compliance rates within the HMO for three reasons: firstly, those women who did not even purchase their first prescription are not included here. Secondly, the study assumes that all medications purchased were taken. Finally, a generous 30 days was allowed between purchases to calculate persistence.

We cannot assume that these findings are representative of post-menopausal women in Israel as a whole. Prevalence rates of osteoporosis in women aged 65+ in Israel and in the HMO are comparable (28% vs. 29% respectively). However, the average income of our HMO members is 19% higher than the national average [24]. We found a positive relationship between socioeconomic status and compliance, suggesting that compliance rates in Israel may be even lower than those found here.

The present study – based on 4448 women – confirms that post-menopausal women's compliance with bisphosphonate medications is poor. Compliance improves with prescription of weekly doses but is still inadequate. Age and socioeconomic factors play a significant role in compliance. Subsidization of weekly medications is a step in the right direction toward improving compliance. The role of the physician in reviewing the response to medication prescription at key points in time (after 1–3 and 6 months) is important in the promotion of compliance in this population group.

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Religion – freedom – vengeance – what you will. A word's enough to raise mankind to kill

Lord Byron (1788-1824), British Romantic poet and controversial figure. He is regarded as one of the greatest European poets and remains widely read. Lord Byron's fame rests not only on his writings but also on his life, which featured extravagant living, numerous love affairs, debts, and allegations of incest and sodomy. He was famously described by Lady Caroline Lamb as "mad, bad, and dangerous to know." Byron served as a regional leader of Italy's revolutionary organization the Carbonari in its struggle against Austria, and later travelled to fight against the Turks in the Greek War of Independence, for which the Greeks consider him a national hero. He died from a febrile illness in Messolonghi. His daughter Ada Lovelace, notable in her own right, collaborated with Charles Babbage on the analytical engine, a predecessor to modern computers.