Osteoporosis medication profile preference: results from the PREFER-US study

Thomas W. Weiss DrPH and Colleen A. McHorney PhD
Outcomes Research, Merck & Co., Inc., West Point, PA, USA

Abstract

Objective To assess patient preferences for two osteoporosis medications.

Design Women aged 50+ were surveyed via the Internet to assess preferences for two osteoporosis medication profiles. Drug A and Drug B, consistent with ibandronate and alendronate, respectively, differed by: time on market (recently vs. 10 years), dosing frequency (monthly vs. weekly), effectiveness (not proven vs. proven to reduce non-spine or hip fracture after 3 years) and dosing procedure (60 vs. 30 min wait before eating/drinking). Each profile had the same out-of-pocket costs, side-effects, potential for drug interaction and spine fracture efficacy. Patients force ranked and rated the importance of each attribute. Subgroup comparisons included diagnosed vs. at-risk respondents and treated vs. untreated respondents.

Results Among the 999 respondents, Drug B was preferred by 96%. Effectiveness was ranked as the most important determinant of preference (79% ranked it #1) compared with time on market (14%), dosing procedure (4%) and dosing frequency (3%). Effectiveness had the highest mean importance rating on a scale of 1 (extremely unimportant) to 7 (extremely important): mean (SD) = 6.1 (1.8), followed by time on market: 4.7 (1.7), dosing procedure: 4.6 (1.4) and dosing frequency: 4.5 (1.4). No significant differences in profile choice were found across study subgroups.

Conclusions The drug profile showing reductions in non-vertebral and hip fracture risk was chosen by almost all respondents. Drug effectiveness was the most important determinant of preference, while dosing frequency was the least important determinant. Incorporation of patient preferences in the medication decision-making process could enhance patient compliance and clinical outcomes.

Introduction

There are several FDA-approved medications on the market today for the prevention and treatment of post-menopausal osteoporosis. As a result, women with osteoporosis, and their doctors, have to decide on a given medication choice while weighing a number of crucial medication attributes, such as risks (i.e. safety, tolerability, adverse events and untoward quality-of-life sequelae), benefits (i.e. clinical effectiveness), convenience and costs. The most widely
prescribed medications in the US approved for the prevention and treatment of osteoporosis are the oral bisphosphonates, which include alendronate and risedronate (daily or weekly dosing) and ibandronate (monthly dosing). Other available osteoporosis therapies include oestrogen/hormone therapy (available in both oral and patch), calcitonin (nasal spray), teriparatide (injectable parathyroid hormone), raloxifene (daily oral selective oestrogen receptor modulator) and intravenous ibandronate.

Despite the demonstrated clinical benefits associated with bisphosphonate therapy, adherence is poor.\textsuperscript{1-10} Although it is difficult to average estimates across studies whose designs and operational definitions differ greatly, approximately one half of women discontinue prescription therapy for osteoporosis in the first 12 months.\textsuperscript{1-10} The reasons underlying medication non-adherence are multifactorial, involving both patients and doctors. Patient-level determinants of poor adherence in osteoporosis include side-effects (particularly upper gastrointestinal side-effects), patients’ lack of belief in the benefits of treatment, patients’ subjective assessment of the seriousness of osteoporosis, the asymptomatic nature of osteoporosis (until a fracture occurs), the complexity of the bisphosphonates treatment regimen, the need for long-term treatment and financial costs associated with treatment.\textsuperscript{11-13} Doctors, on the other hand, contribute to patients’ poor adherence by failing to adequately explain the benefits and side-effects of medications and failing to consider patients’ lifestyle and out-of-pocket costs of medication.\textsuperscript{14} Adding complexity to the problem, the ability of doctors to ascertain and improve non-adherence is poor.\textsuperscript{14} The clinical consequences of poor adherence are noteworthy: poor adherence with osteoporosis medications results in smaller increases in bone mass density\textsuperscript{15} and a greater risk of fracture.\textsuperscript{2,4,15–17}

It is likely that both patient adherence and patient satisfaction can be improved when doctors incorporate patient preferences into treatment decision-making. Patient preferences represent a ‘real-life’, omnibus valuation of various medication and/or treatment attributes, such as efficacy, tolerability, convenience, financial costs and ease of use, among others.\textsuperscript{18–21} In real life, patients are the ones who experience the inconvenience of treatment, their side-effects, their economic impact and their quality of life sequelae.\textsuperscript{18} If patients do not accept their treatment and do not persist with therapy, then clinical effectiveness is degraded and economic resources are wasted. Accounting for patient preferences is especially important when patients have chronic conditions and need to be informed partners in decision-making at almost every action point.\textsuperscript{22}

A variety of related terms (collaborative care, patient-centred care, shared decision-making) have been used to describe the processes of joint decision-making between the patient and healthcare provider. If patients are to participate in medication decisions, they must understand the potential benefits and risks associated with available medications as well as the potential impact of these medications on their everyday quality of life. If health-care providers are to embrace patient-centred care, they must understand patient preferences for their care. For doctors to make evidence-based decisions about medication choices with their patients, they must elicit from patients their preferences for the range of relevant medication attributes.\textsuperscript{18}

Given the recent proliferation of different prescription medications for osteoporosis, there is a pressing need for more information about patient preferences for different attributes of osteoporosis medications to facilitate the collaborative care process in osteoporosis care. The purpose of this research was to evaluate patient preferences for two osteoporosis medication profiles among post-menopausal women with osteoporosis or at risk for osteoporosis, whether or not they are currently receiving treatment. The results of this study may facilitate shared decision-making in osteoporosis care by providing clinicians insight into what medication attributes drive patients to prefer one osteoporosis medication over another. Such knowledge of patient preferences is especially relevant today because both primary and specialty care providers now have the option of offering
2 weekly and 1 monthly osteoporosis prescription medications to their patients for the prevention or treatment of osteoporosis.

**Research design and methods**

Over the past several years, weekly bisphosphonates (alendronate and risedronate) have become the mainstay of prescription osteoporosis therapy. In 2005, however, a once monthly bisphosphonate (ibandronate) entered the osteoporosis market. Recent literature has suggested that, in the absence of patient knowledge about medication attributes other than dosing frequency, osteoporosis patients tend to prefer a monthly dosing schedule.\(^\text{23}\) Further, some have hypothesized that monthly dosing should lead to better medication adherence,\(^\text{24}\) although this clearly remains an outstanding empirical research question.

It was on this foundation that we designed a study to elicit patient preference for two drug profiles similar to weekly alendronate and monthly ibandronate among post-menopausal women. The profiles were composed of four key osteoporosis medication attributes: (i) time on market; (ii) dosing frequency; (iii) drug effectiveness and (iv) dosing procedure. We used information from the peer-reviewed literature\(^\text{25–27}\) and the individual product inserts to build the profiles. Our specific aims were to determine: (i) which osteoporosis medication profile patients preferred and (ii) the importance patients assigned to four osteoporosis medication attributes when choosing between the two medication profiles.

**Sampling scheme and study cohort**

The sample consisted of a cohort of selected respondents to either the 2003 or the 2004 National Health and Wellness Survey (NHWS, http://www.nhwsurvey.com). The NHWS is a cross-sectional survey of adult consumers' (age 18+) attitudes, behaviours and treatment choices as they relate to health care. The NHWS is an Internet-based survey administered annually in the US by Consumer Health Sciences. Respondents for the survey were identified from a national Internet panel maintained by Harris Interactive (http://www.harrisinteractive.com). Additional methods of the PREFER-US study, specifically the sampling scheme and rationale, have been described in detail elsewhere.\(^\text{28}\) This study was approved by the Essex IRB.

The eligible study cohort consisted of women age 50 or older with osteoporosis or at risk for osteoporosis. Respondents who reported in the NHWS or the PREFER survey as having been diagnosed by a doctor as having osteoporosis were classified as ‘diagnosed’. Those not classified as diagnosed, but stated in the NHWS they were at risk or had a family history, were classified as ‘at risk’. Specifically, at-risk respondents stated ‘yes’ in the NHWS to ‘Do you think you are at risk for osteoporosis?’ or stated in the NHWS that they had a family history of osteoporosis.

Patients with a history of osteoporosis or at risk for osteoporosis were chosen for study because we believed that prescription osteoporosis medication choices would be relevant to them as it is likely that they would either be prior/current users of osteoporosis medication (i.e. diagnosed patients) or future users of osteoporosis medication (i.e. at-risk patients).

**Survey design and administration**

The PREFER survey was developed using input from four focus groups of women 50 years or older and from existing literature on patient preferences.\(^\text{28}\) Briefly, the survey consisted of the following: e-mail invitation and consent to participate in the study, demographic information, current prescription osteoporosis medication usage, items assessing self-reported convenience of taking osteoporosis medications and several item formats to assess preferences for osteoporosis medication attributes, including the medication profile that is the focus of this analysis. The entire survey was accessed and administered on-line. Additional details of the survey design can be found elsewhere.\(^\text{28}\)

Osteoporosis medication preferences were assessed by comparing the profiles of ‘Drug A’ and ‘Drug B’ (see Table 1). No brand names were
mentioned in the survey. The profile stated that the two medications had the same out-of-pocket costs, side-effects, potential for drug interaction and ability to reduce the risk of spine fracture. The profile also stated that the two drugs differed by the following attributes: time on market (recently vs. 10 years); dosing frequency (monthly vs. weekly); drug effectiveness (not proven vs. proven to reduce non-spine or hip fracture after 3 years); and dosing procedure (60 vs. 30 min wait after taking). These attributes are consistent with two osteoporosis medications currently on the market for the prevention and treatment of post-menopausal osteoporosis (ibandronate and alendronate, respectively).25–27

Change in bone mineral density (BMD) was not used to illustrate drug effectiveness for several reasons. First, from our focus group research, we learned that fractures and their consequences were better understood by women than clinical markers such as BMD, which only provides evidence of the antiresorptive activity of treatment.29 Secondly, the clinical literature in osteoporosis is divided on the issue of how much change in BMD accounts for observed fracture risk reduction during antiresorptive therapy.30,31 Finally, our use of fracture risk reduction to define the medication effectiveness attribute, rather than change in BMD, is consistent with previous research on osteoporosis treatment preferences.32

Respondents were asked to: (i) select between the two osteoporosis medication profiles; (ii) force-rank order, from 1 to 4, the four attributes according to their reason for selecting their preferred drug and (iii) separately rate the importance of each of the four attributes on a Likert-type scale from 1 (extremely unimportant) to 7 (extremely important) in determining their selection of their preferred drug. The primary research questions were: (i) when presented with two osteoporosis medication profiles, consistent with two available prescription treatment options, what is the preferred choice among women survey respondents with or at risk for osteoporosis; (ii) which particular medication attributes drove respondents’ drug profile choice and (iii) do drug profile preferences differ across patient subgroups?

Table 1 Medication profile comparison question

| Drug A | Drug B |
|--------|--------|
| How long the drug has been on the market | The drug has recently been introduced to the market | The drug has been on the market for 10 years |
| How often you take the drug | Once a month | Once a week |
| How effective the drug is in reducing the risk of fractures due to osteoporosis | Spine fracture: Proven to reduce the risk of having a spine fracture within 3 years | Spine fracture: Proven to reduce the risk of having a spine fracture within 3 years |
| Hip fracture: Not proven to reduce the risk of having a hip fracture |
| Procedure for taking the drug | Take it first thing in the morning and wait at least 60 min before lying down, drinking, eating or taking other prescription drugs | Take it first thing in the morning and wait at least 30 min before lying down, drinking, eating or taking other prescription drugs |

Based on the information presented in the table above, which drug would you prefer as a treatment for your bone health?

(Check only one box)

☐ Drug A  ☐ Drug B
Analytical approach

The primary outcome measure was the percentage of respondents that choose one or the other of the two medication profiles. The secondary outcomes were the forced ranking (heretofore called rankings) and the importance ratings of the four medication attributes. Analyses were conducted for the total sample and by subgroups (i.e. diagnosed vs. at risk for osteoporosis and treated vs. untreated for osteoporosis). Treatment was defined as current use of any of the following osteoporosis medications: risedronate, raloxifene, teriparatide, alendronate, calcitonin or ibandronate. We first used a chi-square with three degrees of freedom to test for difference in the rankings of the four medication attributes for the subgroup comparisons (diagnosed vs. at-risk and treated vs. untreated). When the overall chi-square was significant, we then used chi-square to investigate subgroup differences for each medication attribute by comparing the percentage in each subgroup that ranked the attribute as #1 vs. #2–4 combined.

The effects of age, race, education, income and prior fracture history on profile preference were also analysed using the chi-squared test.

Differences in mean importance ratings within a subgroup (e.g. diagnosed respondents) between the drug effectiveness attribute and each of the other three attributes were assessed separately for each attribute comparison by subtracting the rating score of drug effectiveness from the rating score for the other attribute. A paired t-test was then performed for this difference. Then, to determine differences in mean importance ratings between subgroups (e.g. diagnosed vs. at-risk) for each attribute, we used independent sample t-tests.

Results

Sample characteristics

We collected 999 responses after three full days of fielding. At the close of business of the third day of fielding, we exceeded our target sample size and stopped accepting questionnaires. As shown in Table 2, the mean age of respondents was 65, the vast majority were white (92%), and slightly over one-half were currently married. Slightly more the one-half (58%) were diagnosed with osteoporosis and somewhat less than one-half (42%) were currently being treated for osteoporosis.

There were 578 respondents diagnosed with osteoporosis and 421 respondents classified as at risk. Compared to those classified as at-risk, diagnosed respondents were slightly older, more likely to be widowed and retired, and less likely to have achieved a college education. Of the total sample, 421 respondents reported taking one or more prescription osteoporosis medications, and 578 reported taking no medication for osteoporosis. The treated sample was significantly older and more likely to be widowed and retired.

Preference of osteoporosis medication profile

The profile labelled ‘Drug B’ (designed to approximate alendronate) was preferred by 96% of respondents. In the subgroup analyses, Drug B was chosen by 95% of the diagnosed respondents, 97% of the at-risk respondents, 96% of the treated respondents and 96% of the untreated respondents. The profile preference was invariant across demographics and fracture history (data not shown).

Rankings and importance rating of prescription osteoporosis medication attributes

As shown in Table 3, 79% of the sample ranked drug effectiveness (e.g. ability to reduce the risk of fractures) as the #1 reason for preferring...
Drug B over Drug A, followed by time on market (14%), and dosing procedure (4%). Dosing frequency was the lowest ranked attribute, with only 3% of the sample ranking it as their #1 reason for choosing between the two drug profiles.

Figure 1a shows the comparison of the #1 ranked attributes for diagnosed vs. at-risk subgroups which were significantly different ($P = 0.04$). Comparing those diagnosed with osteoporosis vs. those at-risk, 81% and 77%, respectively, force ranked drug effectiveness as the #1 reason for choosing between the two profiles. Eleven percentage of the diagnosed group ranked time on market #1 vs. 17% of the at-risk group. The treated and untreated subgroups differed significantly ($P = 0.002$) in the #1 rankings of attributes (Fig. 1b). Among the treated, 83% ranked drug effectiveness as their #1 profile driver, while 76% of the untreated group ranked it as such. Nine percentage of the treated group ranked time on market #1 vs. 17% of the untreated.

As shown in Table 4 for the total sample, drug effectiveness had the highest percentage of ‘extremely important’ responses (68%) in

![Table 3: Forced ranking of osteoporosis medication profile attributes: total sample (n = 999)](image)

| Attribute*       | Forced rankings |
|------------------|-----------------|
|                  | 1st  | 2nd  | 3rd  | 4th  |
| Drug effectiveness (%) | 79   | 16   | 4    | 2    |
| Time on market (%)    | 14   | 33   | 16   | 38   |
| Dosing procedure (%)  | 4    | 27   | 32   | 36   |
| Dosing frequency (%)  | 3    | 24   | 48   | 24   |

*Attributes ordered from highest rank based on highest (#1) ranking to lowest (#4) rank.

![Figure 1](image)

**Figure 1** (a) #1 ranked attribute for osteoporosis medication profile by osteoporosis status. (b) #1 ranked attribute for osteoporosis medication profile by osteoporosis treatment status.

![Table 4](image)

**Table 4** Percentage distribution of importance ratings for osteoporosis medication profile attributes: total sample (n = 999)*

| Importance ratings† | Extremely important (%) | Very important (%) | Somewhat important (%) | Neither important nor unimportant (%) | Somewhat unimportant (%) | Very unimportant (%) | Extremely unimportant (%) | Mean (SD) | Median |
|---------------------|-------------------------|-------------------|------------------------|----------------------------------------|--------------------------|----------------------|--------------------------|-----------|--------|
| Drug effectiveness† | 68                      | 17                | 3                      | 1                                      | 0                        | 2                    | 9                        | 6.1 (1.8) | 7      |
| Time on market      | 15                      | 20                | 25                     | 15                                     | 11                       | 8                    | 5                        | 4.7 (1.7) | 5      |
| Dosing procedure     | 8                       | 21                | 31                     | 22                                     | 10                       | 7                    | 2                        | 4.6 (1.4) | 5      |
| Dosing frequency     | 7                       | 16                | 35                     | 20                                     | 11                       | 8                    | 3                        | 4.5 (1.4) | 5      |

*Percentages may not add to 100% due to rounding error. Attributes ordered from highest rating (based on % rating extremely important) to lowest rating.

†Drug effectiveness significantly different from time on market, dosing procedure and dosing frequency ($P < 0.0001$) for overall comparison.

†Scale ranges from Extremely Important (7) to Extremely Unimportant (1).
determining the profile choice, followed by time on market (15%). Dosing procedure and dosing frequency had the lowest percentages of ‘extremely important’ responses (8% and 7%, respectively) in determining the profile choice. For the total sample (Table 5), drug effectiveness had the highest mean importance rating (mean = 6.1, SD: 1.8), which was significantly higher than the other three attributes ($P < 0.0001$ for all paired comparisons). Significantly higher mean importance ratings for drug effectiveness relative to the other three attributes were invariant across subgroups ($P < 0.0001$).

The distributions of importance ratings for the dosing procedure attribute differed between the diagnosed and at-risk subgroups (data not shown). One-third (32%) of the diagnosed subgroup rated dosing procedure as ‘very’ or ‘extremely’ important compared with 23% of those at risk ($P = 0.005$). The distributions of importance ratings for the time-on-market and dosing-frequency attributes differed between the treated vs. untreated subgroups (data not shown). Less then one-third (29%) of treated respondents rated time on market as ‘very’ or ‘extremely’ important compared with 39% of those untreated ($P = 0.0009$). One-fifth (21%) of untreated respondents rated dosing frequency as ‘very’ or ‘extremely’ important compared with 27% of those treated ($P = 0.0009$).

**Discussion**

The past 16 years has been characterized as the ‘era of outcomes assessment’, in which the perspective of the patient – their quality of life, satisfaction with care and treatment preferences – has come to be regarded as a key component in understanding and monitoring the quality and effectiveness of medical care. Patient preference research, in particular, has burgeoned in the last few years for several reasons. For one, the number and types of pharmaceutical products have mushroomed in recent years, thereby offering payers, doctors and patients’ choices among drugs that may or may not differ substantially with respect to efficacy (depending on how efficacy is measured) but certainly differ on other attributes that matter to patients, such as convenience, costs and lifestyle disruption. Further, the Internet has made it easier for patients to readily access medically related information, including information on treatment options from online health information services, online support groups and direct-to-consumer prescription drug websites. Finally, direct-to-consumer advertising on television and in print has made patients more informed about treatment options for many conditions.

Recently, John Wennberg, one of the fathers of the outcomes movement, coined the term ‘preference-sensitive care’, which is clinical services where at least two valid alternative treatment strategies are available. In preference-sensitive decisions, the optimal choice depends on ‘patients’ values or preferences for the benefits and harms of each option’. While the patient outcomes movement has enlightened us about how satisfied patients are with their health care and their behavioural and emotional functioning, we still have much to learn about what aspects of treatment are important to patients and preferred by them. Across a wide variety of diseases, it has been asserted that fulfilment of patient preferences, in terms of medication and

| Attribute               | Diagnosed | At risk | Treated | Untreated |
|-------------------------|-----------|---------|---------|-----------|
| Drug effectiveness*     | 6.1 (1.9) | 6.1 (1.8)| 6.1 (1.9)| 6.1 (1.8) |
| Time on market\(\text{1}\) | 4.5 (1.7) | 4.9 (1.6)| 4.5 (1.6)| 4.8 (1.7) |
| Dosing procedure        | 4.7 (1.5) | 4.6 (1.3)| 4.7 (1.5)| 4.6 (1.4) |
| Dosing frequency        | 4.6 (1.5) | 4.5 (1.4)| 4.6 (1.5)| 4.5 (1.4) |

*Drug effectiveness significantly different from time on market, dosing procedure and dosing frequency ($P < 0.0001$) within each subgroup (i.e. diagnosed, at risk, treated and untreated).
\(\text{1}\)Time on market significantly different between diagnosed and at-risk and between treated and untreated groups ($P < 0.05$).
Scale ranges from Extremely Important (7) to Extremely Unimportant (1).
treatment attributes, could go far towards improving short-term adherence and long-term persistence with drug therapy.\textsuperscript{23,35,36} This is an issue of great consequence as medication non-compliance is widespread,\textsuperscript{37} costing patients and society billions in direct and indirect health-care costs,\textsuperscript{37} diminishing the impact of therapy on clinical and quality of life outcomes, and precipitating further morbidity and, sometimes, death.

Our preference study follows on the heels of dozens of others published in the literature. Assessment of patients’ treatment preferences have assumed many methodological forms, including standard survey-based ratings and rankings of preferences (like our study) and hypothetical treatment scenarios.\textsuperscript{38,39} Conjoint analysis and willingness-to-pay methods have also been used to study treatment preferences\textsuperscript{40,41} as well as preferences for different aspects of the processes of health-care delivery.\textsuperscript{42,43} Preference studies have been conducted in myriad therapeutic areas including, but not limited to, acne,\textsuperscript{44} allergic rhinitis (e.g. comparing different nasal sprays),\textsuperscript{45} asthma (e.g. comparing different inhalation therapies),\textsuperscript{46} diabetes (e.g. comparing different modes of insulin delivery),\textsuperscript{47} erectile dysfunction,\textsuperscript{48} GERD,\textsuperscript{49} glaucoma,\textsuperscript{50} HIV,\textsuperscript{51} insomnia,\textsuperscript{52} irritable bowel syndrome,\textsuperscript{53} migraine\textsuperscript{20} and osteoporosis (e.g. comparing drugs of the same class differing in dosing frequency\textsuperscript{23,54–56}).

In this study, 96% of sampled women with or at risk for osteoporosis chose the medication profile consistent with alendronate which, when compared with ibandronate, has a longer history on the market, data supporting overall effects on non-vertebral and hip fracture risk reduction,\textsuperscript{25,27} and a dosing procedure requiring less time, but with more frequent dosing. This finding was observed across subgroups defined by osteoporosis risk status and osteoporosis treatment status as well as by secondary demographic subgroups (i.e. age, race, education, income, prior fracture). Like preference studies in other diseases,\textsuperscript{20,36,57–61} we found drug effectiveness to be the #1 determinant of preferring the alendronate profile over the ibandronate profile, with 79% of the sample force ranking drug effectiveness as their #1 preference driver. Like preference studies in other diseases,\textsuperscript{62,63} we found that dosing frequency rated low in the drivers of patients’ treatment profile preference, with only 3% of the sample force ranking dosing frequency as their #1 preference driver. Our finding that almost all respondents preferred the drug profile with more evidence of fracture risk reduction, albeit with more frequent dosing, contrasts with studies showing that patients prefer less frequent dosing.\textsuperscript{23,54–56} In one such crossover study,\textsuperscript{23} patients were not informed about the key attributes of the medications they were taking and only reported preferences based on the frequency of dosing or tolerability.

Our findings using the methods of forced rankings were corroborated using importance ratings. Drug effectiveness had the highest percentage of extremely important responses (68%) compared with 15% for time on market, 8% for dosing procedure and 7% for dosing frequency. Combining the two most positive importance ratings (extremely and very), 85% of the sample rated drug effectiveness as extremely/very important compared with 35% for time on market, 29% for dosing procedure and 23% for dosing frequency. The mean importance rating was the highest for drug effectiveness (6.1), and it was significantly higher than those for time on market (4.7), dosing procedure (4.6) and dosing frequency (4.5). The mean importance rating for time on market was also significantly higher than that for dosing frequency.

We agree with the conceptualization of patient preferences as a value judgement from the patient point of view.\textsuperscript{64} As such, patient preference is a composite, patient-centred end point that incorporates numerous treatment and medication attributes,\textsuperscript{18–21} albeit not all of which are weighted equally by patients. Our use of two well-accepted methods – forced rankings and importance ratings – provided complimentary evidence of such unequal weighing.

The general limitations of our study design have been published elsewhere.\textsuperscript{28} In brief, our sample of responders had somewhat higher socioeconomic status than the non-responders.
or to the female population in the United States. The literature provides no guidance as to whether preferences for osteoporosis medications might vary as a function of socioeconomic status and whether different rankings and ratings would have been obtained with a sample more diverse in socioeconomic and ethnic characteristics. Given the overwhelming choice respondents made for Drug B, it is unlikely that these differences would have any appreciable impact on the study results. In addition, osteoporosis diagnosis and at-risk status were based on self-report rather than bone mineral density testing used in clinical trials. It may be that a small amount of misclassification occurred using self-reports. However, we do not think that this would have appreciably affected results given the very close similarity of results between those diagnosed vs. at risk and those treated vs. untreated.

Another potential limitation of the study is the presentation of the drug profiles. The attributes for each drug profile were presented in one fixed format (Table 1). We were careful to present the key medication attributes in a straightforward, easy to understand manner based on existing literature regarding the characteristics of each medication. In the interest of brevity, we excluded information on bone mineral density in the drug profiles. From our focus group research prior to survey development, patients were clearly more concerned with fracture risk reduction than with changes in bone mineral density. We do not believe that the addition of information on bone mineral density would change the conclusions of this study.

There are several clinical implications of our study. As echoed by clinician scholars across therapeutic areas, we believe that patient preferences provide a more ‘real-life’ perspective on medications and their attributes than is reflected by clinical trial data, or product inserts. As such, individual-level preference data could provide clinicians with real time/real life information on what matters to a patient and how much. For example, many of our focus group participants did not find the procedure associated with taking weekly bisphosphonates intrusive to their lifestyle because they built new habits around the requirements for taking it in the morning without food and remaining upright (e.g. taking the bisphosphonates and going for a morning walk or taking a shower). This observation underscores the fact that preferences are subjective (i.e. some patients find the bisphosphonate procedure quite arduous while others deem it undemanding) and can only be ascertained by direct elicitation. Further, preferences vary across patients, so it cannot be assumed that what is considered ‘inconvenient’ for Mrs Jones will be interpreted as ‘inconvenient’ for Mrs Smith. As importantly, there is a variance between patients’ and doctors’ perceptions of adherence barriers, with doctors overestimating the impact of doing frequency and pill burden on compliance and underestimating the influence of other medication attributes valued by patients.

The basis of clinical medicine is treating patients on an individual basis, but doctors often prescribe therapy based on traditional efficacy end points derived from group-level clinical trials. Tolerability and safety profiles are provided to patients and doctors, yet patient-derived information on convenience, ease of use, and subjective effectiveness ratings are rarely included in clinical trials and product inserts, even though these medication attributes influence patient perceptions of treatment acceptability and, ultimately, compliance and therapeutic success. As Dowson argues, ‘the most important question is not which prescription is best relative to another, but whether the chosen prescription provides the outcome desired by the patient and the health-care provider’. A patient-centred and preference-sensitive approach to medication decision-making would allow for tailoring various attributes of drug therapy to individual patient needs, particularly for disorders for which there is more than one drug of the same or similar class. Attention to patient preference for different drug attributes may be particularly important in asymptomatic conditions, like osteoporosis, where long-term therapy is required for stabilized or improved bone health and where patients may...
minimize their disease susceptibility (i.e. fracture risk) and perceive the drawbacks of therapy to exceed potential benefits.\textsuperscript{13,32}

The therapeutic success of any medication is dependent on the fidelity with which patients adhere to dosing procedure and instructions, and such fidelity is itself dependent on patient attitudes and beliefs about their disease and medication-taking in general as well as the aggregate acceptability of a regimen to them.\textsuperscript{45} Doctors may not be able to effectively or quickly change patient health and illness beliefs, but they may have the flexibility to prescribe medications that meet patients’ needs for pill size, dosing procedure, or dosing frequency or to prescribe medications that minimize unpleasant side-effects or life-style disruption. To reach these ends, though, doctors need to know what is important to patients, and the only way to achieve that end point to ask them. Hibbard\textsuperscript{66} recently argued that patient preferences should be considered as a ‘vital sign’ to be regularly monitored and attended to by doctors in clinical practice. Hibbard’s recommendation is synchronous with Don Berwick’s provocative patient-centred axiom – ‘nothing about me without me’.\textsuperscript{67} Recent research has demonstrated that not all patients wish to be the final arbiter of the medication decision; however, they do want to be engaged in the decision-making process by communicating beliefs, preferences and desired outcomes to their clinicians.\textsuperscript{68} Another recent study reported that about one half of patients wanted to leave final medical decisions to the clinician, but that 96% wanted to be offered choices and to be asked their opinion.\textsuperscript{69}

Numerous therapeutic options are currently available for the prevention and treatment of post-menopausal osteoporosis. Oral bisphosphonates are now available in daily, weekly and monthly dosing regimens. However, it would be both naive and premature to presume that monthly dosing will be a panacea for the long-standing problems of lack of adherence and persistence with therapy in osteoporosis. First, movement from daily to weekly dosing for osteoporosis has improved persistence rates\textsuperscript{3,6,7,9,70} although they still remain quite suboptimal even with weekly dosing. Secondly, when women are asked why they discontinue osteoporosis therapy, more often than not, they offer reasons other than mere dosing frequency, in particular upper gastrointestinal side-effects,\textsuperscript{11–13,71–73} safety concerns,\textsuperscript{13,71} medication costs\textsuperscript{11–13} and lack of motivation.\textsuperscript{13} Thirdly, although research has suggested that patients with osteoporosis have preferences for less frequent dosing,\textsuperscript{23,54–56} this research has been conducted largely within the context of open-label trials and without providing participants with information on how comparator medications do or do not differ on other medications attributes valued by patients, such as antifracture efficacy, side-effects and costs, among others. Finally, comprehensive reviews of the literature on the relationship between dosing frequency and a variety of health outcomes have been limited to studies of daily dosing, twice daily dosing and multiple daily dosing.\textsuperscript{74,75} Thus, it remains unknown from other diseases whether monthly dosing will indeed yield enhanced compliance or improved health outcomes in the prevention or treatment of post-menopausal osteoporosis.

It is clear that the personal and economic burden of osteoporosis is substantial, if not staggering, to patients, their families and society at large.\textsuperscript{76} In the US, doctors and patients are not at a loss for different choices of osteoporosis medications. Today’s challenge is to achieve reasonable persistence to a long-term medication regimen for a largely silent disease. Unfortunately, to date, we have been losing the persistence battle in osteoporosis. Payers, doctors and patients should openly welcome new advances in pharmaceutical therapy for osteoporosis because what may work for one patient may not work for another. At the same time, payers, doctors and patients may realize more gains from their investments in prescription osteoporosis therapy if a patient-centred and preference-sensitive approach to medication decision-making is embraced and compliance is ultimately enhanced.
Acknowledgement

This study was funded by Merck & Co., Inc., West Point, PA, USA.

References

1. Papaioannou A, Ioannidis G, Adachi JD et al. Adherence to bisphosphonates and hormone replacement therapy in a tertiary care setting of patients in the CANDOO database. *Osteoporosis International*, 2003; 14: 808–813.
2. McCombs J, Thiebau P, McLaughlin-Miley C, Shi J. Compliance with drug therapies for the treatment and prevention of osteoporosis. *Maturitas*, 2004; 48: 271–287.
3. Cramer JA, Amonkar MM, Hebborn A, Altman R. Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis. *Current Medical Research and Opinion*, 2005; 21: 1453–1460.
4. Huybrechts KF, Ishak KJ, Caro JJ. Assessment of compliance with osteoporosis treatment and its consequences in a managed care population. *Bone*, 2006; 38: 922–928.
5. Solomon DH, Avorn J, Katz JN et al. Compliance with osteoporosis medications. *Archives of Internal Medicine*, 2005; 165: 2414–2419.
6. Brankin E, Walker M, Lynch N, Aspray T, Lis Y, Cowell W. The impact of dosing frequency on compliance and persistence with bisphosphonates among postmenopausal women in the UK: evidence from three databases. *Current Medical Research and Opinion*, 2006; 22: 1249–1256.
7. Downey TW, Foltz SH, Boccuzzi SJ, Omar MA, Kahler KH. Adherence and persistence associated with the pharmacologic treatment of osteoporosis in a managed care setting. *Southern Medical Journal*, 2006; 99: 570–575.
8. Lo JC, Pressman AR, Omar MA, Ettinger B. Persistence with weekly alendronate therapy among postmenopausal women. *Osteoporosis International*, 2006; 17: 922–928.
9. Penning-van Beest FJ, Goetttsch WG, Erkens JA, Herings RM. Determinants of persistence with bisphosphonates: a study in women with postmenopausal osteoporosis. *Clinical Therapeutics*, 2006; 28: 236–242.
10. Weycker D, Macarios D, Edelsberg J, Oster G. Compliance with drug therapy for postmenopausal osteoporosis. *Osteoporosis International*, 2006; 17: 1645–1652.
11. Segal E, Tamir A, Ish-Shalom S. Compliance of osteoporotic patients with different treatment regimens. *The Israel Medical Association Journal*, 2003; 5: 859–862.
12. Zafra N, Liss Z, Peled R, Sherf M, Reuveni H. Incidence and causes for failure of treatment of women with proven osteoporosis. *Osteoporosis International*, 2005; 16: 1375–1383.
13. Rossini M, Bianchi G, Di Munno O et al. Determinants of adherence to osteoporosis treatment in clinical practice. *Osteoporosis International*, 2006; 17: 914–921.
14. Osterberg L, Blaschke T. Adherence to medication. *New England Journal of Medicine*, 2005; 353: 487–497.
15. Caro J, Ishak K, Huybrechts K, Raggio G, Naujoks C. The impact of compliance with osteoporosis therapy on fracture rates in actual practice. *Osteoporosis International*, 2004; 15: 1003–1008.
16. Weycker D, Macarios D, Edelsberg J, Oster G. Compliance with osteoporosis drug therapy and risk of fracture. *Osteoporosis International*, 2007; 18: 271–277.
17. Siris ES, Harris ST, Rosen CJ et al. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. *Mayo Clinic Proceedings*, 2006; 81: 1013–1022.
18. Salonen R. Drug comparisons: why are they so difficult? *Cephalalgia*, 2000; 20 (Suppl. 2): 25–32.
19. Dahllof C. Assessing patient preference in migraine treatment. *Cephalalgia*, 2001; 21: 791–795.
20. Loder E, Brandes JL, Silberstein S et al. Preference comparison of rizatriptan ODT 10-mg and sumatriptan 50-mg tablet in migraine. *Headache*, 2001; 41: 745–753.
21. Lainez M, Evers S, Kinge E et al. Preference for rizatriptan 10-mg wafer vs. eletriptan 40-mg tablet for acute treatment of migraine. *Cephalalgia*, 2006; 26: 246–256.
22. Bodenheimer T, Lorig K, Holman H, Grumbach K. Patient self-management of chronic disease in primary care. *Journal of the American Medical Association*, 2002; 288: 2469–2475.
23. Emkey R, Koltun W, Beusterien K et al. Patient preferences for once-monthly ibandronate vs. once-weekly alendronate in a randomized, open-label, cross-over trial: The Boniva Alendronate Trial in Osteoporosis (BALTO). *Current Medical Research and Opinion*, 2005; 21: 1895–1903.
24. Reginster JY, Rabenda V, Neuprez A. Adherence, patient preference and dosing frequency: understanding the relationship. *Bone*, 2006; 38 (4 Suppl. 1): S2–S6.
25. Cranney A, Wells G, Willan A et al. Meta-analyses of therapies for postmenopausal osteoporosis: II. Meta-analysis of alendronate for the treatment of postmenopausal women. *Endocrine Reviews*, 2002; 23: 508–516.
26. Chesnut C, Skag A, Christiansen C et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis.
27 Papapoulos SE, Quandt SA, Liberman UA, Hochberg MC, Thompson DE. Meta-analysis of the efficacy of alendronate for the prevention of hip fractures in postmenopausal women. Osteoporosis International, 2005; 16: 468–474.

28 Weiss T, Gold D, Silverman S, McHorney C. An evaluation of patient preferences for osteoporosis medications and their attributes: results from the PREFER-US Study. Current Medical Research and Opinion, 2006; 22: 949–960.

29 Marcus R, Wong M, Heath H III, Stock JL. Antiresorptive treatment of postmenopausal osteoporosis: comparison of study designs and outcomes in large clinical trials with fracture as an endpoint. Endocrine Reviews, 2002; 23: 16–37.

30 Hochberg MC, Greenspan S, Waisnich RD, Miller P, Thompson DE, Ross PD. Changes in bone density and turnover explain the reductions in incidence of nonvertebral fractures that occur during treatment with antiresorptive agents. The Journal of Clinical Endocrinology and Metabolism, 2002; 87: 1586–1592.

31 Delmas PD, Seeman E. Changes in bone mineral density explain little of the reduction in vertebral or nonvertebral fracture risk with anti-resorptive therapy. Bone, 2004; 34: 599–604.

32 Unson C, Siccion E, Gaztambide J, Gaztambide S, Mahoney Trella P, Prestwood K. Nonadherence and osteoporosis treatment preferences of older women: a qualitative study. Journal of Women’s Health, 2003; 12: 1037–1045.

33 Wennberg JE, Fisher ES, Skinner JS. Geography and the debate over Medicare reform. Health Affairs, 2002; Jul–Dec (Suppl Web Exclusives): W96–W114.

34 O’Connor AM, Llewellyn-Thomas HA, Flood AB. Modifying unwarranted variations in health care: shared decision making using patient decision aids. Health Affairs, 2004; (Suppl Web Exclusive): VAR63–VAR72.

35 Morin C, Gaudier B, Barry T, Kowatch R. Patients’ acceptance of psychological and pharmacological therapies for insomnia. Sleep, 1992; 15: 302–305.

36 Lipton R, Stewart W. Acute migraine therapy: do doctors understand what patients with migraine want from therapy? Headache, 1999; 39 (Suppl. 2): S20–S26.

37 DiMatteo MR. Variations in patients’ adherence to medical recommendations: a quantitative review of 50 years of research. Medical Care, 2004; 42: 200–209.

38 McQuellon R, Muss H, Hoffman S, Russell G, Craven B, Yellen S. Patient preferences for treatment of metastatic breast cancer: a study of women with early-stage breast cancer. Journal of Clinical Oncology, 1995; 13: 858–868.

39 Fraenkel L, Bogardus S, Concato J. Patient preferences for treatment of lupus nephritis. Arthritis and Rheumatism, 2002; 47: 421–428.

40 Singh J, Cuttler L, Shin M, Silvers J, Neuhauser D. Medical decision-making and the patient: understanding preference patterns for growth hormone therapy using conjoint analysis. Medical Care, 1998; 36: AS31–AS45.

41 Fraenkel L, Bodardus S, Wittink D. Understanding patient preferences for the treatment of lupus nephritis with adaptive conjoint analysis. Medical Care, 2001; 39: 1203–1216.

42 Morgan A, Shackley P, Pickin M, Braizer J. Quantifying patient preferences for out-of-hours primary care. Journal of Health Services Research and Policy, 2000; 5: 214–218.

43 Anderson G, Black C, Dunn E et al. Willingness to pay to shorten waiting time for cataract surgery. Health Affairs, 1997; 16: 181–190.

44 Kellett N, West F, Finlay AY. Conjoint analysis: a novel, rigorous tool for determining patient preferences for topical antibiotic treatment for acne. A randomised controlled trial. British Journal of Dermatology, 2006; 154: 524–532.

45 Bachert C, El-Akkad T. Patient preferences and sensory comparisons of three intranasal corticosteroids for the treatment of allergic rhinitis. Annals of Allergy, Asthma & Immunology, 2002; 89: 292–297.

46 Boulet LP, Cowie R, Johnston P, Krakovsky D, Mark S. Comparison of Diskus inhaler, a new multidose powder inhaler, with Diskhaler inhaler for the delivery of salmeterol to asthmatic patients. The Journal of Asthma, 1995; 32: 429–436.

47 Cappelleri J, Cefalu W, Rosenstock J, Kourides I, Gerber R. Treatment satisfaction in type 2 diabetes: a comparison between an inhaled insulin regimen and a subcutaneous insulin regimen. Clinical Therapeutics, 2002; 24: 552–564.

48 Sadeghi-Nejad H, Lim H, Long K, Gilhooly P. Assessment of the efficacy of viagra (sildenafil citrate) using the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS). Urologia Internationalis, 2003; 71: 100–102.

49 Johnson M, Guilford S, Libretto S. Patients have treatment preferences: a multicentre, double-blind, crossover study comparing rabeprazole and omeprazole. Current Medical Research and Opinion, 2002; 18: 303–310.

50 Schenker H, Maloney S, Liss C, Gormley G, Hartenbaum D. Patient preference, efficacy, and compliance with timolol maleate ophthalmic gel-forming solution vs. timolol maleate ophthalmic solution in patients with ocular hypertension or open-angle glaucoma. Clinical Therapeutics, 1999; 21: 138–147.
51 Beusterien KM, Dziekan K, Flood E, Harding G, Jordan JC. Understanding patient preferences for HIV medications using adaptive conjoint analysis: feasibility assessment. Value in Health, 2005; 8: 453–461.
52 Vincent N, Lionberg C. Treatment preference and patient satisfaction in chronic insomnia. Sleep, 2001; 24: 411–417.
53 Olden K, DeGarmo R, Jhingran P et al. Patient satisfaction with clesotran for the treatment of women with diarrhoea-predominant irritable bowel syndrome. American Journal of Gastroenterology, 2002; 97: 3139–3146.
54 Simon J, Lewiecki E, Smith M, Petruschke R, Wang L, Palmisano J. Patient preference for once-weekly alendronate 70 mg vs. once-daily alendronate 10 mg: a multicenter, randomized, open-label, crossover study. Clinical Therapeutics, 2002; 24: 1871–1886.
55 Kendler D, Kung AW, Fuleihan Gel-H et al. Patients with osteoporosis prefer once weekly to once daily dosing with alendronate. Maturitas, 2004; 48: 243–251.
56 Weiss M, Vered I, Foldes A, Cohen Y, Shamir-Elron Y, Ish-Shalom S. Treatment preference and tolerability with alendronate once weekly over a 3-month period: an Israeli multi-center study. Aging Clinical and Experimental Research, 2005; 17: 143–149.
57 Dahllof C. How to assess patient preference of migraine treatments. Cephalalgia, 1999; 19 (Suppl. 24): 2–6.
58 Salonen R, Ashford E, Gibbs M, Hassani H, The Sumatriptan Tablets S2CM11 Study Group. Patient preference for oral sumatriptan 25 mg, 50 mg, or 100 mg in the acute treatment of migraine: a double-blind, randomized, crossover study. International Journal of Clinical Practice, 1999; 105 (Suppl.): 16–24.
59 Kaliner M. Patient preferences and satisfaction with prescribed nasal steroids for allergic rhinitis. Allergy and Asthma Proceedings, 2001; 22 (6 Suppl. 1): S11–S15.
60 Johansson G, Stallberg B, Tornling G et al. Asthma treatment preference study. A conjoint analysis of preferred drug treatments. Chest, 2004; 125: 916–923.
61 Lambert N, Rowe G, Bowling A et al. Reasons underpinning patients’ preferences for various angina treatments. Health Expectations, 2004; 7: 246–256.
62 Miller L, Huffman H, Weidmer B, Hays R. Patient preferences regarding antiretroviral therapy. International Journal of STD & AIDS, 2002; 13: 593–601.
63 Moyle G. The Assessing Patients' Preferred Treatments (APPT-1) study. International Journal of STD & AIDS, 2003; 14 (Suppl. 1): 34–36.
64 Levine MN, Gafni A, Markham B, MacFarlane D. A bedside decision instrument to elicit a patient’s preference concerning adjuvant chemotherapy for breast cancer. Annals of Internal Medicine, 1992; 117: 53–58.
65 Dowson AJ, Tepper SJ, Dahllof C. Patients’ preference for triptans and other medications as a tool for assessing the efficacy of acute treatments for migraine. The Journal of Headache and Pain, 2005; 6: 112–120.
66 Hibbard JH. Moving toward a more patient-centered health care delivery system. Health Affairs, 2004; (Suppl Web Exclusive): VAR133–VAR135.
67 Davis K, Schoenbaum SC, Audet AM. A 2020 vision of patient-centered primary care. Journal of General Internal Medicine, 2005; 20: 953–957.
68 Belcher VN, Fried TR, Agostini JV, Tinetti ME. Views of older adults on patient participation in medication-related decision making. Journal of General Internal Medicine, 2006; 21: 298–303.
69 Levinson W, Kao A, Kuby A, Thisted RA. Not all patients want to participate in decision making. A national study of public preferences. Journal of General Internal Medicine, 2005; 20: 531–535.
70 Recker RR, Gallagher R, MacCosbe PE. Effect of dosing frequency on bisphosphonate medication adherence in a large longitudinal cohort of women. Mayo Clinic Proceedings, 2005; 80: 856–861.
71 Tosteson AN, Grove MR, Hammond CS et al. Early discontinuation of treatment for osteoporosis. American Journal of Medicine, 2003; 115: 209–216.
72 Hamilton B, McCoy K, Taggart H. Tolerability and compliance with risedronate in clinical practice. Osteoporosis International, 2003; 14: 259–262.
73 Turbi C, Herrero-Beaumont G, Acebes J et al. Compliance and satisfaction with raloxifene vs. alendronate for the treatment of postmenopausal osteoporosis in clinical practice: an open-label, prospective, nonrandomized, observational study. Clinical Therapeutics, 2004; 26: 245–256.
74 Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clinical Therapeutics, 2001; 23: 1296–1310.
75 Richter A, Anton SE, Koch P, Dennett SL. The impact of reducing dose frequency on health outcomes. Clinical Therapeutics, 2003; 25: 2307–2335.
76 Keen RW. Burden of osteoporosis and fractures. Current Osteoporosis Reports, 2003; 1: 66–70.