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ORIGINAL ARTICLE

An analysis of which anti-osteoporosis therapeutic regimen would improve compliance in a population of elderly adults

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ABSTRACT

Objective: Although medications to prevent osteoporotic fractures have been proven to be effective, compliance to these therapies is generally poor. Therapeutic regimens for different anti-osteoporotic medications differ widely and it is currently unknown which regimen would be most preferred by patients.

Research design and methods: We conducted a large, population-based study to discern which therapeutic attributes would be most preferable to a population representative of the age and sex distribution of patients with osteoporosis.

Results: Our study sample was restricted to persons aged 55 years and over and comprised 2485 individuals (mean age of 64.5 years). The study population was predominantly female (90.3%) and two-thirds of the respondents reported current daily medication use. Nearly half (45%) of the study population preferred to take medications daily, while one in five preferred weekly therapy and 30% preferred monthly therapy ($p < 0.0001$ for between proportion comparisons). When given the option of choosing between three different medication regimen scenarios, those subjects not currently using anti-osteoporotic medications preferred a theoretical regimen which was daily and did not involve subsequent fasting and maintaining an upright posture.

Conclusions: Our data suggest that compliance with osteoporotic medications could be improved if patients are able to choose a therapeutic regimen best suited to their particular needs. The majority of subjects preferred a drug which was taken daily and with minimal inconvenience, rather than a weekly drug with slightly more inconvenience. Given that most physicians currently prescribe anti-osteoporotic therapy as a weekly regimen, at the time of diagnosis physicians should ascertain which regimen would be most preferable to patients prior to initiating therapy.

Introduction

Osteoporosis is a serious medical condition which leads to a substantial increase in fractures and concomitant morbidity[1]. This increased propensity to fracture may result from a loss of bone mass, bone strength or a combination of these two factors[2]. Due to the rapid ageing of Western societies, and intensive research focused on osteoporosis over the past two decades, patients with osteoporosis and their care-givers have recently witnessed a dramatic increase in the number of therapies available for treatment of this debilitating disease.

The successful prevention of osteoporotic fractures involves first the identification of those at highest risk and the subsequent implementation of proven treatment strategies. The success of any chosen therapy

depends upon both its effectiveness and the patient's willingness to adhere to the therapeutic regimen. Thus compliance with treatment programs is essential to the successful treatment of osteoporosis, especially since osteoporosis is largely chronic and asymptomatic.

Recent randomized controlled trials have established the effectiveness of many therapies in the prevention of vertebral and hip fractures[3–7]. However, in a recent study of over 40 000 subjects, continuation of therapy for the treatment of osteoporosis was only 45.2% after one year[8]. Importantly, those who comply with therapy seem to experience a more profound improvement in bone mineral density (BMD)[9] and a decrease in rates of fracture[10].

The therapeutic regimen of different osteoporotic medications varies widely. Some therapies, such as strontium ranelate require the patient to take the medication each evening, two hours after food, prior to sleeping with half a glass of water. Other medications, such as bisphosphonates are taken in pill form, on an empty stomach with a full glass of water upon awakening and the patient is then to remain fasting and upright for at least 30 minutes. There are several options for bisphosphonate dosing frequency and these include daily, weekly, monthly oral regimens and a 3-monthly intravenous regimen. On the other hand, therapies such as selective oestrogen receptor modulators are used daily, without regard to meals. Thus, these different therapeutic regimens may have profound effects on compliance with anti-fracture therapy for individuals of differing age and circumstance.

Previous research has consistently demonstrated that compliance with bisphosphonate therapy can be improved by changing dosing frequency from once daily to once weekly[11–14]. Consequently, many clinicians have inferred that patients prefer once weekly dosing to once daily dosing for the treatment of osteoporosis. However, whether or not this preferred dosing frequency may be extrapolated from bisphosphonates to all other anti-osteoporotic therapies is unknown.

Given that anti-osteoporotic therapies vary widely in their dosing characteristics and little is known about which therapeutic factors would improve compliance, we undertook a survey of a large population of healthy men and women over the age of 55 to discern which therapeutic characteristics would be associated with improved compliance.

Patients and methods

Study population

The TwinsUK adult twin registry is an ongoing study investigating a wide range of age-related phenotypes including osteoporosis, obesity, diabetes, visual and cardiovascular disease (www.twinsUK.ac.uk) in men and women. This large, prospective, population-based study recruits healthy volunteers who are twins. The cohort is representative of singletons and of the UK general population for bone related traits and behaviours[15]. The study was approved by the Guy's and St. Thomas' Hospital Ethics Committee.

Questionnaire and statistical methods

A questionnaire was mailed to all available members of the TwinsUK adult twin registry. Subjects were blinded to the study hypothesis. All subjects aged 55 years and over were asked to answer questions relating to the therapeutic characteristics which would make a particular medical therapy most favourable for compliance. Vitamin and mineral supplements were not considered medications and reported separately. Alendronate and risedronate bisphosphonate medications were assumed to have been taken weekly.

Subjects were asked to state how often they would prefer to take a regular medication, if a medical condition required treatment. Further, to understand which therapeutic characteristics would alter this preference, subjects were then given three scenarios for drug regimen and asked to select which one was most preferable. The first scenario (Daily Therapy Scenario) was described as a medication 'To be taken once a day, this medication comes in the form of a sachet of tasteless powder which is diluted in half a glass of water and drunk before bedtime, at least two hours after eating'. The second scenario (Weekly Therapy Scenario) was described as 'Taken once a week, this medication is a tablet, which has to be taken with a full glass of water on an empty stomach first thing in the morning and at least 30 minutes before you have any food or drink. After taking the tablet you have to stand or sit upright for at least 30 minutes and not lie down until after you have eaten breakfast'. The final scenario (Monthly Therapy Scenario) was described as 'Taken once a month, this medication is a tablet, which has to be taken with a full glass of water on an empty stomach first thing in the morning and at least 30 minutes before you have any food or drink. After taking the tablet you have to stand or sit upright for at least 30 minutes and not lie down until after you have eaten breakfast'. Subjects were permitted to respond that they had no preference in the three types of therapy described. This analysis was then repeated after stratifying the overall population by current use of weekly anti-osteoporotic medications, non-weekly anti-osteoporotic medications and no current anti-osteoporotic medications. Finally, because one of the available osteoporotic therapies, strontium ranelate, requires that the medication be

taken with half a glass of water prior to bedtime, we hypothesized that since incontinence is more frequent in the elderly population, some of the elderly subjects may feel uncomfortable with taking water prior to sleeping and we consequently asked subjects their comfort level with taking water prior to sleeping.

Standard descriptive statistics of the study population were calculated. To detect differences in the proportion of respondents that preferred a specific therapy, an equality of proportions test was performed on categorical variables. All statistical manipulations were performed using Stata/SE 9.2 (College Station, TX, USA).

Results

The final study population was comprised of 2485 individuals, of whom, 90.3% were women. The response rate for our survey was 68.5%. All subjects were 55 years or older. The mean age of the sample was 64.5 years (range 55–89). Approximately two thirds (67.7%) of the study population used at least one medication per day, while approximately one in 10 (11.2%) took five or more medications per day. Fifteen per cent of the population had been previously diagnosed with osteoporosis and 10% of the overall study population was already using a medication to treat osteoporosis (Table 1).

When asked which frequency of dosing they preferred, if they were to be treated for a medical condition, nearly half (45%) of the respondents opted for daily medication, while once per week medication was favoured by one in five (20%) and 30.4% of respondents stated that they would prefer to take a medication monthly ($p < 0.0001$ for the difference of proportions between those who preferred daily dosing over each of the other regimen frequencies). The least popular dosing frequency was twice per day (Figure 1). Among those subjects already taking at least one other medication daily, without regard to type of medication, preference was again highest for daily medication use (Figure 2). Compared to those not using medications, those taking at least one medication per day were more likely to prefer daily dosing ($p < 0.001$) and less likely

Table 1. *Selected characteristics of study population*

	N = 2485
Age, years	64.5 (6.4)
Females, *n* (%)	2244 (90.3)
Number of medications taken daily, *n* (%)	
0	803 (32.3)
1	515 (20.7)
2	394 (15.9)
3	289 (11.6)
4	184 (7.4)
5+	278 (11.2)
Not reported	22 (0.9)
Use of supplements, *n* (%)	
Calcium	286 (11.5)
Vitamin D	130 (5.2)
Previous diagnosis of osteoporosis, *n* (%)	370 (14.9)
Use of osteoporotic medications, *n* (%)	239 (9.6)
Type of osteoporotic medication, *n* (%)	
Alendronate	133 (55.6)
Etidronate	18 (7.5)
Ibandronate	6 (2.5)
Raloxifene	17 (7.1)
Risedronate	66 (27.6)
Strontium ranelate	8 (3.3)
Teriparatide	2 (0.8)

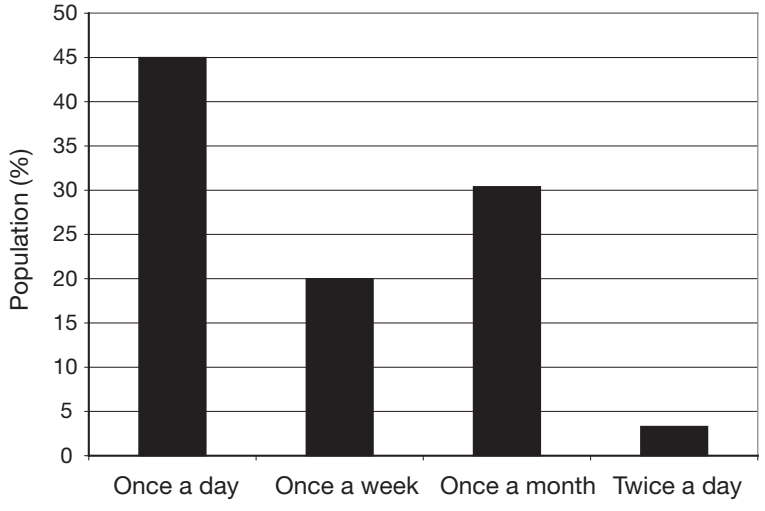

Figure 1. *Preferred frequency of medication regimen in study population (*N = *2485). The* p*-value for the difference of proportions between 'Once a Day' and each of the other dosing frequencies was* p < *0.0001*

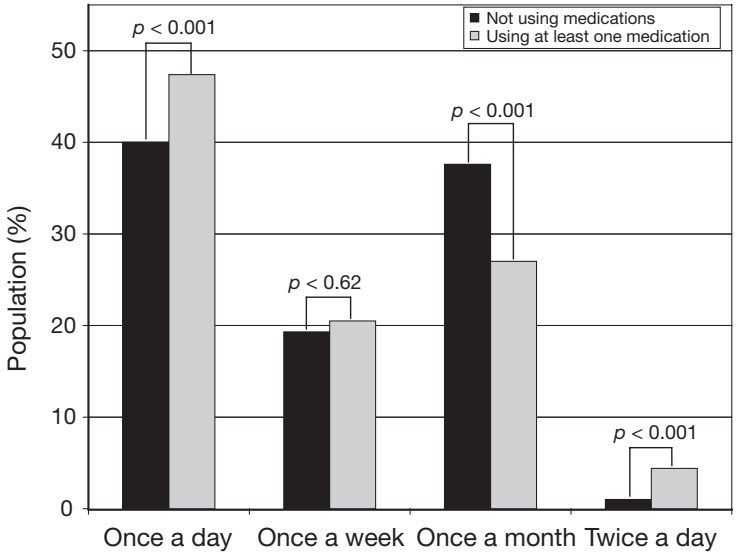

Figure 2. *Preference of frequency of medication frequency stratified by current medication users* (n = *1682) and those not using medications* (n = *803)*

to prefer monthly dosing ($p < 0.001$). These results were similar when responses were stratified by gender and age group (data not shown).

When the subjects were presented with three different scenarios for therapeutic regimens of a putative drug, the majority (59.5%) of respondents not already using anti-osteoporotic medications preferred daily therapy without having to remain fasting and upright after taking the medication compared with a weekly regime (preferred by 13.8% of this population) and monthly therapy (preferred by 13.0% of the population) which involved remaining fasting and upright after taking the medication ($p < 0.0001$) (Figure 3). Subjects already using non-weekly anti-osteoporotic medications had a similar preference pattern, while those already using weekly anti-osteoporotic medications preferred the weekly scenario (52.0%). Again there was no difference in preferred scenario when data were stratified by gender or age group (data not shown).

In our study population, over 85% of all men and women felt comfortable taking water prior to sleeping, and this proportion rose to 93% when women over the age of 75 were excluded (Figure 4).

Discussion

This large population-based study provides evidence that on average, persons aged 55 years and over prefer to take medications daily rather than weekly or monthly, especially if they are already taking other medication. Further, when asked about specific drug therapy regimens, a large proportion of respondents preferred a medication which does not require them to fast and remain upright after taking the medicine. Finally, very few subjects were uncomfortable with taking half a glass of water prior to bedtime. These results suggest that among subjects in the age-group most often afflicted with osteoporosis, daily therapy may be more preferable to weekly therapy, if there is little inconvenience associated with the taking of the medication. However, perhaps not surprisingly, those who have previously chosen either a daily or weekly anti-osteoporotic therapy seem content to continue with their prescribed regimen.

Given that osteoporosis is commonly an asymptomatic disease and successful treatment requires long-term adherence to therapy, potential improvements in compliance may have a large impact on the overall effectiveness of osteoporosis therapy. In addition, dual-energy X-ray absorptiometry (DEXA) scanning, which is used to diagnose osteoporosis, involves considerable costs, which may not be recuperated unless those subjects with osteoporosis receive and adhere to therapy to prevent osteoporotic fractures. Our results provide evidence that subjects currently not using anti-osteoporotic medications are most likely to prefer medications which are taken daily and impinge minimally on their daily routine. This would appear to contradict most previous research in the field of compliance with osteoporotic therapy which has focused on the utility of changing from daily bisphosphonate therapy to weekly bisphosphonate therapy. Although studies have demonstrated improved compliance with bisphosphonate therapy when it is used weekly[16,17], few studies have addressed whether compliance could be improved if therapeutic regimens were simplified. Consequently the improved

compliance noted in patients who use bisphosphonate therapy weekly rather than daily may be due to the particular inconveniences inherent to bisphosphonate use, rather than osteoporotic medications in general[18]. Thus while weekly dosing may be especially helpful if the medication is inconvenient to use, if the medication is relatively more convenient, subjects appear to prefer daily dosing.

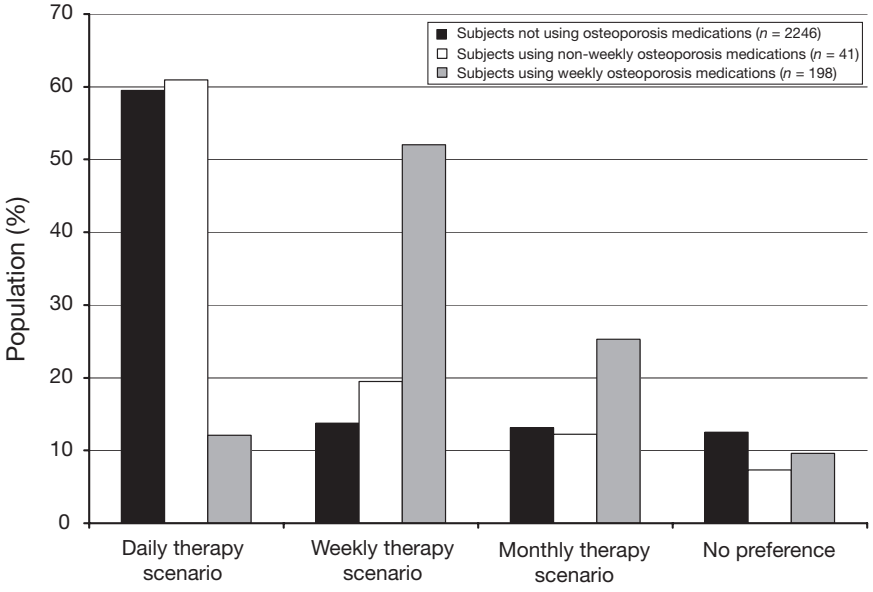

Figure 3. *Preference for medication scenario by current use of osteoporosis medications*

Where the daily therapy scenario was defined as 'To be taken once a day, this medication comes in the form of a sachet of tasteless powder which is diluted in half a glass of water and drunk before bedtime, at least two hours after eating'. The weekly therapy scenario was defined as 'Taken once a week, this medication is a tablet, which has to be taken with a full glass of water on an empty stomach first thing in the morning and at least 30 minutes before you have any food or drink. After taking the tablet you have to stand or sit upright for at least 30 minutes and not lie down until after you have eaten breakfast'. The monthly therapy scenario was defined as 'Taken once a month, this medication is a tablet, which has to be taken with a full glass of water on an empty stomach first thing in the morning and at least 30 minutes before you have any food or drink. After taking the tablet you have to stand or sit upright for at least 30 minutes and not lie down until after you have eaten breakfast'. The *p*-value for the difference of proportions between the daily therapy scenario and each of the other dosing frequencies in the subjects not using osteoporosis medications separately was $p < 0.0001$. Weekly osteoporosis medications included alendronate and risedronate. Non-weekly osteoporosis medications included etidronate, ibandronate, raloxifene, strontium and teriparatide

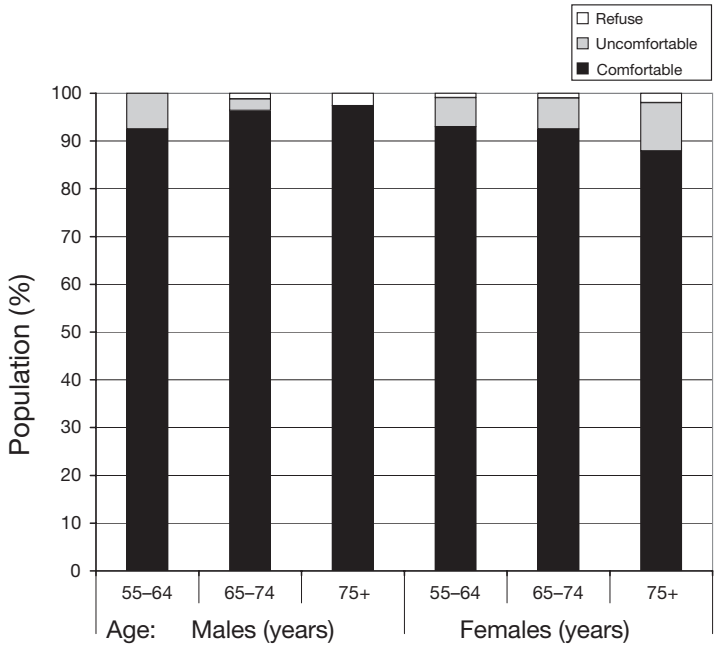

Figure 4. *Level of comfort with having half a glass of water before bedtime in study population (*N = *2485)*

Previous studies have indicated that compliance with anti-osteoporotic therapy is generally poor. A large health maintenance organization study found that compliance with treatment instructions for bisphosphonate therapy was low and that by 10 months after initiation of therapy, 46% of subjects had discontinued therapy[19]. Further, most women with osteoporosis rank drug effectiveness as the single most important attribute of an osteoporotic medication which would improve their compliance[20]. This makes patient discussion on the anti-fracture efficacy of the various treatment options an important consideration, in addition to discussion on the differences in dosage regimen. Previous randomized controlled trials have demonstrated that strontium ranelate is effective in the prevention of osteoporotic fractures[6,7] and have indicated that compliance with strontium ranelate is over 90%[21]. There are at present no real-life data comparing compliance with strontium ranelate and bisphosphonates outside of clinical trials.

There are several potential strengths and weaknesses to this our study. The size of our study and the fact that our population resembles that of the general United Kingdom population infers that our results may be generalizable[15]. Despite the fact that our study population consisted of twins, as these twins are similar to the general United Kingdom singleton population for musculoskeletal risk factors and rates of disease, it is unlikely there are any twin specific treatment preferences. This observational study can only offer insights into potential methods to improve compliance. The hypotheses generated from this study require testing within an experimental study design. In addition, not all of the subjects who answered our questionnaire suffered from osteoporosis. However, the age and sex distribution is similar to that of persons who have do osteoporosis. Finally, we did not collect data pertaining to once yearly therapy and we are therefore unable to compare preference for less frequent therapeutic regimens.

Conclusion

In conclusion, as with any therapeutic decision, physicians must involve the patient and ensure that the specific therapy for each patient is individually tailored to their preferences. This active participation in treatment decisions will likely improve compliance. Our results indicate that the most preferred therapy osteoporotic medication would be one which is taken daily and with minimal inconvenience. This is especially true among those subjects who are already taking medications other than anti-osteoporotic medications regularly. The choice of the patient may not be the one predicted by the prescribing physician as the circumstances and lifestyle of patients may be quite different. The message from this survey for the clinician is not to presume what your patients will prefer – it is best to describe the available options and allow them to make an informed choice.

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