**Title:** Patients’ preferences for anti-osteoporosis drug treatment: a cross-European discrete-choice experiment

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**Short title**

Patients’ preferences for osteoporosis therapy

**Abstract**

Objectives: To estimate the preferences of osteoporotic patients for medication attributes, and analyse data from seven European countries.

methods: A discrete choice experiment was conducted in Belgium, France, Ireland, the Netherlands, Spain, Switzerland and United Kingdom. Patients were asked to choose repeatedly between two hypothetical unlabelled drug treatments (and an opt-out option) that varied with respect to four attributes: efficacy in reducing the risk of fracture, type of potential common side-effects, mode and frequency of administration. In those countries in which patients contribute to the cost of their treatment directly, a fifth attribute was added: out-of-pocket cost. A mixed logit panel model was used to estimate patients’ preferences.

Results: In total 1,124 patients completed the experiment, with sample of between 98 and 257 patients per country. In all countries, patients preferred treatment with higher effectiveness and 6-monthly subcutaneous injection was always preferred over weekly oral tablets. In five countries, patients also preferred monthly oral tablet and yearly intravenous injections over weekly oral tablets. In the three countries where the out-of-pocket cost was included as an attribute, lower costs significantly contribute to the treatment preference. Between countries there were statistically significant differences for 13 out of 42 attribute/levels interactions.

Conclusions: We find statistically significant differences in patients’ preferences for anti-osteoporosis medications between countries, especially for the mode of administration. Our findings emphasize that international treatment recommendations should allow for local adaptation and that understanding individual preferences is important if we want to improve the quality clinical care for patients with osteoporosis.

**Key words**: Cross-Country Comparison; Discrete choice experiment; Drug treatment; Osteoporosis; Patients; Preferences.

**Introduction**

It is recognised that clinical and policy decision should include the patient’s perspective. Product development and acceptance could also benefit from knowledge about what patients value and prefer regarding their treatment (1). Patients’ preferences can also be useful for the appraisal of healthcare programs alongside the clinical, economic, social and ethical considerations. Recent examples include the attention to and inclusion of the patient’s perspective in health technology assessment, coverage decisions and clinical practice guideline development (2-4). Health professionals may find that knowledge of patients’ preferences and how patients value different aspects of care helps them to improve disease management. Patients who are more involved in decision-making could have better therapy adherence (5). In response, an increasing number of studies elicit patients’ preferences in the healthcare setting. In particular, the application of discrete choice experiments (DCEs) as a method to elicit patients’ preferences has increased in recent years (6, 7). A DCE is a stated-preference method in which respondents are asked to repeatedly choose between hypothetical treatments options that systematically differ in several attributes of interest, such as effectiveness, cost, side-effects, and mode of administration. DCEs are a useful method to quantify the relative importance of attributes and the trade-offs that respondents make between them (5).

Results from a recent DCE study (8) to assess the preferences of osteoporotic patients for drug treatment in Belgium suggest that osteoporotic patients preferred treatment modes of 6-month subcutaneous injection and oral monthly tablet, and disliked gastro-intestinal disorders as side-effects. In addition, patients were willing to trade treatment effectiveness or a personal monetary contribution for their preferred mode of administration.

Little is known about how comparable patients’ preferences are between countries. The previous study (8) was carried out in two osteoporosis centres in Belgium. An editorial accompanying the previous study (9) suggested that the generalizability of the results should be further investigated. We therefore extended the previous study to six additional Western European countries. The aim of this paper is to evaluate and compare the preferences of osteoporotic patients from several European countries for medication attributes. This study will therefore not only reveal if patients’ preferences differ between several countries but also provide further insights for policy makers and health professionals on generalizability of patients’ preferences for osteoporotic drug treatment.

**Methods**

We used a DCE to examine preferences for drug treatment among patients with, or at risk of, osteoporosis. In the DCE, patients were asked to make a series of hypothetical choices between two unlabeled drug alternatives that varied along several attributes of interest (and a no treatment option). State of the art methods recommended in DCE guidelines were used to select the attributes and levels, design the DCE and conduct the statistical analysis (5, 10). Details of the DCE development can be found in the previous publication (8), and access to the English language questionnaire is available online as an additional file (8). A brief description of the different components of the DCE is provided below.

**Attributes and levels**

The attributes included in the DCE were selected from the results of qualitative research (11, 12). Patient group discussions in Belgium and the Netherlands were used to prioritize a list of twelve, potentially, important osteoporosis drug therapy attributes. The list was based on existing literature and expert opinion. Patients identified five important attributes, and all were included in the DCE: effectiveness, side effects, mode and frequency of administration and, in Belgium, out-of-pocket cost (see table 1). The out-of-pocket cost attribute was only included in countries where patients pay out-of-pocket for osteoporotic treatment (i.e. Belgium, Ireland and Switzerland). Levels for each attribute were assigned based on current treatment using a literature review and expert opinion (n=5). For the side-effects attribute, the three levels were related to the nature of common side-effects.

**Experimental design**

The set of treatment options to be presented to the respondents was based on an experimental design. Specifically, we used a Bayesian efficient design to maximize the D-efficiency of the chosen choice sets using Ngene software (Version 1.1.1, <http://www.choice-metrics.com>). A Bayesian efficient design aims to maximize the precision of the estimated parameters of the attributes for a given number of choice tasks by incorporating *a priori* information about the sign and value of parameters. Parameter estimates derived from a pilot study (n=10) were used as *a priori* information to construct the choice sets. Fifteen choice tasks were created in which respondents were asked, in each case, to choose between two unlabelled drug alternatives (A and B) and a ‘no treatment’ option. The experimental design was restricted to include only realistic combinations of mode and frequency of administration. There was a small correlation between attributes in the experimental design because it was optimized on efficiency. One of the choice tasks was repeated at the end of the choice tasks to assess test-retest reliability of respondents’ choices. Each respondent therefore received 16 choice tasks. An example of a choice task is shown in Figure 1.

**Questionnaire, data collection and patients’ recruitment**

The questionnaire was paper-based. The attributes and levels were first described and an example of a completed choice task was included. After respondents had completed the 16 choice tasks, they were asked how difficult they found the tasks on a seven-point Likert scale. Data on patients’ demographics and socioeconomic characteristics and experiences with osteoporosis and treatments were also collected. Three versions of the questionnaire were designed that differed in attribute presentation to control for an attribute ordering effect.

The questionnaire was developed in English by a working group that included a patient, DCE experts and clinical experts. This version was approved by two native English speakers who are osteoporosis experts. The questionnaire was translated into three languages (French, Spanish and Dutch) by a medical translation company specialising in patient reported outcome measures translation (Pharma Quest Ltd, Oxford, UK). The four languages covered the languages spoken across the countries in our sample. Each language version was checked and approved by at least two native speakers. The English survey was pilot tested (n=15) to check for any problems with interpretation and face validity; only minor changes to layout were made.

The study was conducted in seven European countries Belgium, France, Ireland, the Netherlands, Spain, Switzerland and United Kingdom between March and October 2012. The analysis for Belgian patients has been published previously (8). Patients with, or at risk for, osteoporosis to whom medication (or lifestyle changes) was at least proposed were consecutively recruited during outpatients’ clinics. The questionnaire was completed by the patient at the clinic, or at home and returned in a postage-paid envelope. Calculation of optimal sample sizes was not possible as it depends on the true values of the unknown parameters estimated in the DCE (13). Hence, a minimum of 100 patients per country was targeted, which was sufficient based on common rules-of-thumb for minimum sample size (14).

Approval for this study was obtained from the Medical Ethics Committee of the Academic Hospital Maastricht and Maastricht University. A team from this university coordinated the project. Participants gave informed written consent according to the 1964 Helsinki declaration. Additional local ethics approval was obtained from those participating centers that required ethics approval for a DCE study, i.e. the Research Ethics Committee of the Sligo University Hospital, the Southampton Joint Ethics Committee, the CEIC-Parc de Salut Mar (Committee of Ethics and Clinical Investigation) and the *'Commission cantonale d'éthique de la recherche'* (CCER) of Geneva.

**Statistical analyses**

Data analysis was carried out using Nlogit software, version 5.0. Data of patients who completed less than five choice sets were excluded. To allow for preference heterogeneity within each country, a mixed logit model was estimated (15). This model is based on the assumption that parameters are randomly distributed in the population and captures heterogeneity by estimating the standard deviation of the parameter’s distribution. We used a *panel* mixed logit model to account for the panel nature of the data as each patient completed 15 choice sets.

The following utility model was estimated for each country *c*:

*Vij =* β0 + (β1+η1i) efficacyj + (β2+η2i) costj

+ (β3+η3i)oral\_1mj + (β4+η4i) sub\_3mj + (β5+η5i) sub\_6mj + (β6+η6i)int\_3mj

+ (β7+η7i)int\_1yj + (β8+η8i)flusymptj + (β9+η9i) skinreactj + *ε*ijt

Where *V* represents the systematic relative utility, β0 is the constant reflecting the average preference for selecting treatment relative to no treatment across the different choice sets, β1-β9 are coefficients of the attributes levels indicating the relative preference for each attribute level and η1i-η9i are error terms capturing individual-specific unexplained variation around the mean. Effects coding was used to describe the categorical variables (mode and frequency of administration, and side-effects). Using effect coding, mean attributes are normalized to zero and preference weights are relative to the mean effect of the different levels of the attribute. A positive sign for a given level therefore indicates a level has a positive effect on utility compared to the mean effect of the attribute. If the 95% confidence interval around two levels did not overlap, the differences between the preference weights were considered as statistically different. Although the attributes ‘efficacy in reducing the risk of future fractures’ and ‘out-of-pocket contribution’ are presented as discrete levels in the experiment, they were coded as continuous variables in the model with a linear specification, allowing willingness to pay estimates and providing a better model fit. .

We took preference heterogeneity into account by specifying all parameters as random parameters. The random parameters for the cost and efficacy were drawn from a log-normal distribution in order to constrain the parameter on the negative and positive scale, respectively (15). All other random parameters were drawn from a normal distribution. If the standard deviation of the random parameters is significantly different from zero, this is interpreted as evidence of significant preference heterogeneity for the attribute within the population. The estimation was conducted by using 2000 Halton draws. Model fit was assessed using log-likelihood, McFadden’s pseudo-R² and Akaike Information Criterion (AIC).

Two subgroups analyses were conducted to investigate potential differences between countries. We wish to allow preferences to be systematically different in countries with the cost attribute (Belgium, Ireland and Switzerland) and in countries without (France, the Netherlands, Spain, United Kingdom). To assess if preferences are significantly different between countries within each subgroup (with and without a cost attribute),a joint model was estimated using interaction terms to capture potentially systematic differences in preference between countries. Preferences are considered to vary across countries within a subgroup if the parameters estimated for the interaction terms are statistically different from zero (5% level). To take scale heterogeneity into account and thus to control for the fact that differences between countries can also be due to difference in the unobserved error scale a normally distributed random component was added for each country dummy (16). This allows us to test if a significant difference in the interaction terms reflects a systematic difference in preference, and not merely a difference in the scale of the random error between countries.

In addition, at the country level we analysed the impact of previous fractures on patients’ preferences that was shown to be a relevant covariate in previous research (8, 17, 18). To assess the significance of the differences between patients with and without previous fractures, a joint model per country was estimated using interaction terms. A normally distributed random component was added for the dummy variable designed for previous fractures.

**Results**

**Patients’ characteristics**

A total of 1,201 questionnaires were returned. Of these, 1,124 questionnaires were sufficiently completed (i.e. at least 10 choice tasks completed) and included in the analysis, with sample between 98 and 257 patients per country. The respondents had a mean age of 65.0 years and 85.3% were female. Of all respondents, 73.9% were diagnosed with osteoporosis, 52.1% had a prior fracture and 55.4% received osteoporosis drug treatment. Socio-demographics and health characteristics are shown in Table 2 by country. A total of 85.2% of the respondents (country range: 80.9%-89.4%) selected the same alternative in the test–retest exercise. On average the task was seen as relatively easy, with an average score of 3.04 (country range: 2.62-3.41) based on responses to a seven-point scale (1 for extremely easy and 7 for extremely difficult). Both test-retest reliability and the perceived level of task difficulty are in line with previous studies (19)

**Patients’ preferences**

The panel mixed logit model results are presented in Table 3. The estimated coefficients for efficacy and costs (when included) were statistically significant in all countries. The positive sign of the efficacy parameter indicates that treatment utility increases with higher treatment efficacy and the negative sign of the cost parameter indicates that respondents prefer to pay less for treatment.

In all countries, patients preferred a 6-monthly subcutaneous injection over weekly oral tablets (see Figure 2). In most countries, patients also preferred a monthly oral tablet and/or yearly intravenous injections over weekly oral tablets. In all countries, except Switzerland where no statistical differences were observed, patients disliked being at risk of gastro-intestinal disorders more than being at risk of skin reactions and flu-like symptoms. The two parameters for the side-effects attribute had a positive sign, indicating that patients disliked being at risk of gastro-intestinal disorders more than being at risk of skin reactions and flu-like symptoms. Standard deviations parameters were significant for most of the attributes in all countries, indicating the presence of preference heterogeneity between patients and hence variations in the importance of the attributes/levels.

There were statistical significant differences for 13 out of 42 attribute/levels interactions between countries (Table 4). Countries with the largest sample were used as reference, i.e. Belgium for countries with the cost attribute and the Netherlands for those without, respectively. In comparison to Belgium, patients in Ireland had a significant stronger preference for intravenous every three months or yearly, and preferred being at risk for flu-like symptoms and skin reactions compared to gastrointestinal disorders. In Switzerland, a significantly higher value was attached to subcutaneous every 6 months and yearly intravenous compared with Belgium, while monthly oral tablet was significantly less preferred.

In comparison to the Netherlands, patients in France, UK and Spain are found to have only a few significant interactions differences. For example, in the UK, monthly oral tablet was significantly less preferred while intravenous every 3 months was significantly more preferred. Efficacy was less preferred in France and Spain than in the Netherlands.

The presence of previous fractures significantly reduced the importance of the cost attribute in two of the three countries with a cost attribute (see Supplementary Table online). In Belgium and Switzerland, patients with previous fractures are willing to pay more for osteoporosis medication than patients without fractures. In countries without the cost attribute, the presence of a previous fracture was shown to positively and significantly affect the importance of drug effectiveness, with the exception of France.

**Discussion**

This study used a DCE to evaluate the preferences of patients with, or at risk of, osteoporosis for medication attributes in seven European countries. In line with a previous study conducted in Belgium only (8), osteoporotic patients across Europe trade between attributes when making treatment choices and all attributes were significant and thus important for patients’ decisions. As expected, patients preferred higher efficacy and lower costs; and mode of administration was an important attribute for patients (17, 20). In all countries, patients preferred on average 6-month subcutaneous injection compared to weekly oral tablet, and in some countries, patients also preferred monthly oral tablet or yearly intravenous compared to weekly oral tablets.

To the best of our knowledge, this study is one of the first DCE studies that elicit preferences across several countries (21) and therefore provides information on the comparability of patients’ preferences across countries, and the first to do so for osteoporosis. Our study suggests that patients’ preferences for osteoporosis drug therapy are the same on many key attributes between several European countries although some statistical differences between countries were observed for a small number of attributes, especially modes of administration. Depending on policy objectives, this may imply that a pan-European policy could be promoted or that local differences in policy may be facilitated. Further work on the transferability of patients’ preferences between countries would be needed to assess whether the individual patients’ characteristics or system level factors, such as jurisdiction, affect preferences. Of note, in this study we did not investigate the underlying drivers of preference differences between countries. Notwithstanding, this study’s finding emphasize that international treatment recommendations should allow for local adaptation and highlight the importance of accounting for individual preferences in policies that aim to improve the quality clinical care for patients with osteoporosis. Our study revealed that the effect of one covariate (previous fractures) on preferences was not the same across countries. Previous fractures only affected the cost attribute in countries where patients pay out-of-pocket, but affected preferences for treatment effectiveness in countries with no out-of-pocket payment. This trend was not found in all the countries. Transferring the impact of covariates on preferences between countries could be uncertain.

The substantive results from this international study could be very useful for health professionals and decision makers, especially given the poor adherence to weekly oral regimens which substantially affect the clinical and economic burden of these medications (22, 23). Our study suggests that in all countries patients preferred on average 6-month subcutaneous injection compared to a weekly oral tablet, and in some countries, they also preferred monthly oral tablet or yearly intravenous compared to a weekly oral tablet. Treatment that is in line with what patients prefer would increase patient satisfaction with, as well as trust in, care, and potentially lead to improved adherence (5). We also found that preferences elicited at the group level show large variance around the estimated coefficients, indicating heterogeneity in preferences between patients. For clinical practice, this indicates that tools are needed to reveal individual patients’ preferences and to support shared-decision making. These tools should balance drug effectiveness against patients’ beliefs and preferences (17). Several decision aids are already available in osteoporosis to support the decision to start an oral bisphosphonate or not, or to select an appropriate medication (24-26). The use of decision aids has the potential to be cost-effective (27) and our results suggest that tailoring treatments to individual patients can increase their satisfaction with the treatment. As such, our findings might assist decision makers to identify treatments that are more likely to be cost-effective in practice (9).

Our study has some limitations. First, although we used a rigorous method to define attributes and levels, some decisions were made to focus on specific aspects of the research question. We focused on the nature of common side-effects and not on their frequency or more severe but rare side-effects. Rare adverse events such as osteonecrosis of the jaw and atypical femoral fracture (28) could occur with osteoporosis medications. They are infrequent in all categories of osteoporosis medications and therefore patients’ preferences would probably not differentiate between drugs for this reason. Alarming information in the media on these side effects could perhaps however influence patients’ choice and leads to subjective perception. A second potential limitation is that data collection was performed in 2012 and treatment patterns could have changed since then. Temporal variations in preferences need to be better understood, particularly as patients’ preferences could change over the course of treatment (9). Third, we did not incorporate all types of osteoporosis medications in our study and focused on common osteoporosis medications. By example, the daily subcutaneous injection of teriparatide (only prescribed under specific conditions for patients with severe osteoporosis), or the oral administration of a dissolved powder (strontium ranelate) were not included. Fourth, in most countries in our research, the study was only conducted in one centre and we therefore acknowledge that the data may not be generalizable to all individuals from the country. Fifth, despite the care taken in translation and adaptation of the survey instrument including the use of medical translation company specialising in the translation of patient reported outcome measures and further check and approbation of two native speakers per version, the questionnaire was not back-translated. It is therefore possible that patients’ understanding of the descriptions slightly differ between language versions. Sixth, while DCEs are widely used, an inherent limitation is that respondents are evaluating hypothetical medications. Therefore, what respondents declare they will do may potentially be different from what they would actually do if faced with the choice in real life. Some studies about the external validity of DCEs have already been conducted in healthcare (28, 29) but not yet in the field of osteoporosis. Previous studies suggested that predicted and actual treatment choices could differ at the individual level and that further work needs to be done to understand reasons for these differences(29, 30). Combining stated preference with actual choice data in osteoporosis would therefore be interesting in the future (9). Seventh, the a-prior information to construct the choice sets was derived from a pilot study using 10 patients from one country. Though this is a relatively small number, the results of this pilot were consistent with expectations and guided the subsequent design of the main experiment. To maintain consistency across countries the same design was used in all countries. Potentially more efficient designs could have been obtained at the individual country level, but this would have restricted the comparability of the task between countries. Finally, although we assessed the impact of previous fractures on patients’ preferences on a country basis, our aim was not to assess the impact of additional characteristics of the individual patient as covariates on the preferences. Previous studies (12, 18) reported that preferences could differ between populations and that factors such as age, gender, income, education and prior fractures could affect preferences for osteoporosis medications. Further work at a country level is needed to assess if preferences for attributes and levels may not differ according to a number of factors such as age and gender.

In conclusion, this study provides evidence that across seven western European countries osteoporotic patients are willing to trade efficacy or to pay money for preferred mode of administration, and that on average patients preferred 6-monthly subcutaneous injection over weekly oral tablets. In addition, our study suggests that the preferences of patients for many attributes of osteoporotic drug therapy are similar across seven European countries, but that only for levels of some attributes, significant differences were observed. The heterogeneity of preferences within each country highlights the importance of incorporating preferences of individual patients in clinical decision making to improve osteoporosis care.

**Acknowledgements**

We would like to thank all participating centres: the Unit for Osteoporosis and Metabolic Bone from Ghent University Hospital (Belgium); the University Center for Investigation in Bone and Articular Cartilage Metabolism in Liege (Belgium); the Fracture Clinic of the Maastricht University Medical Center (Netherlands); the Bone Unit of Paris Descartes University, Paris (France); The North Western Rheumatology Unit, Our Lady’s Hospital, Manorhamilton and the Sligo University Hospital (Ireland); the Musculoskeletal Research Unit and RETICEF from the Universitat Autònoma de Barcelona (Spain); the Division of Bone Diseases from the Geneva University Hospitals (Switzerland); the MRC Lifecourse Epidemiology Unit from the University of Southampton (United Kingdom) for helping us in data collection; Ed Porquie, our patient partner; Wafa Ben Sedrine, Ivette Essers and Wilco Tilburgs for data entry and all the patients for their participation.

**Funding**

This work was supported by Amgen. The funding agreement between Maastricht University and Amgen ensured the authors’ independence in designing the study (including selection of attributes and levels), interpreting the data, and writing and publishing the report. Other participating centres were compensated by Maastricht University for their participation in the study.

**References**

1. Ijzerman MJ, Steuten LM. Early assessment of medical technologies to inform product development and market access: a review of methods and applications. Applied health economics and health policy 2011;9(5):331-47.

2. Kreis J, Schmidt H. Public engagement in health technology assessment and coverage decisions: a study of experiences in France, Germany, and the United Kingdom. Journal of health politics, policy and law 2013;38(1):89-122.

3. Menon D, Stafinski T. Role of patient and public participation in health technology assessment and coverage decisions. Expert Rev Pharmacoecon Outcomes Res 2011;11(1):75-89.

4. Dirksen CD. The use of research evidence on patient preferences in health care decision-making: issues, controversies and moving forward. Expert Rev Pharm Out 2014;14(6):785-94.

5. Bridges JF, Hauber AB, Marshall D, Lloyd A, Prosser LA, Regier DA, et al. Conjoint analysis applications in health--a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force. Value Health 2011;14(4):403-13.

6. Clark MD, Determann D, Petrou S, Moro D, de Bekker-Grob EW. Discrete choice experiments in health economics: a review of the literature. PharmacoEconomics 2014;32(9):883-902.

7. de Bekker-Grob EW, Ryan M, Gerard K. Discrete choice experiments in health economics: a review of the literature. Health economics 2012;21(2):145-72.

8. Hiligsmann M, Dellaert BG, Dirksen CD, van der Weijden T, Goemaere S, Reginster JY, et al. Patients' preferences for osteoporosis drug treatment: a discrete-choice experiment. Arthritis research & therapy 2014;16(1):R36.

9. Laba TL. Using Discrete Choice Experiment to elicit patient preferences for osteoporosis drug treatments: where to from here? Arthritis research & therapy 2014;16(2):106.

10. Lancsar E, Louviere J. Conducting discrete choice experiments to inform healthcare decision making: a user's guide. Pharmacoeconomics 2008;26(8):661-77.

11. Coast J, Al-Janabi H, Sutton EJ, Horrocks SA, Vosper AJ, Swancutt DR, et al. Using qualitative methods for attribute development for discrete choice experiments: issues and recommendations. Health Econ 2012;21(6):730-41.

12. Hiligsmann M, van Durme C, Geusens P, Dellaert BG, Dirksen CD, van der Weijden T, et al. Nominal group technique to select attributes for discrete choice experiments: an example for drug treatment choice in osteoporosis. Patient Prefer Adherence. 2013;7:133-9

13. de Bekker-Grob EW, Rose JM, Donkers B, Essink-Bot ML, Bangma CH, Steyerberg EW. Men's preferences for prostate cancer screening: a discrete choice experiment. British journal of cancer 2013;108(3):533-41.

14. de Bekker-Grob EW, Donkers B, Jonker MF, Stolk EA. Sample Size Requirements for Discrete-Choice Experiments in Healthcare: a Practical Guide. The patient 2015;8(5):373-84.

15. Hensher D, Rose J, Greene W. Applied choice analysis: a primer. Cambridge, UK. Cambridge University Press 2007.

16. Swait J, Louviere J. The Role of the Scale Parameter in the Estimation and Comparison of Multinomial Logit-Models. J Marketing Res 1993;30(3):305-14.

17. Hiligsmann M, Bours SP, Boonen A. A Review of Patient Preferences for Osteoporosis Drug Treatment. Current rheumatology reports 2015;17(9):61.

18. Silverman S, Calderon A, Kaw K, Childers TB, Stafford BA, Brynildsen W, et al. Patient weighting of osteoporosis medication attributes across racial and ethnic groups: a study of osteoporosis medication preferences using conjoint analysis. Osteoporos Int. 2013 Jul;24(7):2067-77.

19. Ryan M, Gerard K, Amaya-Amaya M: Using Discrete Choice Experiments to Value Health and Health Care. Dordrecht: Springer; 2008.

20. Bansback N, Trenaman L, Harrison M. How important is mode of administration in treatments for rheumatic diseases and related conditions? Current rheumatology reports 2015;17(6):514.

21. Hifinger M, Hiligsmann M, Ramiro S, Watson V, Severens JL, Fautrel B, et al. Economic considerations and patients' preferences affect treatment selection for patients with rheumatoid arthritis: a discrete choice experiment among European rheumatologists. Annals of the rheumatic diseases 2016. [Epub ahead of print]

22. Hiligsmann M, McGowan B, Bennett K, Barry M, Reginster JY. The clinical and economic burden of poor adherence and persistence with osteoporosis medications in Ireland. Value in health 2012;15(5):604-12.

23. Hiligsmann M, Rabenda V, Bruyere O, Reginster JY. The clinical and economic burden of non-adherence with oral bisphosphonates in osteoporotic patients. Health policy 2010;96(2):170-7.

24. Hiligsmann M, Ronda G, van der Weijden T, Boonen A. The development of a personalized patient education tool for decision making for postmenopausal women with osteoporosis. Osteoporosis international 2016;27(8):2489-96

25. LeBlanc A, Wang AT, Wyatt K, Branda ME, Shah ND, Van Houten H, et al. Encounter Decision Aid vs. Clinical Decision Support or Usual Care to Support Patient-Centered Treatment Decisions in Osteoporosis: The Osteoporosis Choice Randomized Trial II. PloS one 2015;10(5):e0128063.

26. Montori VM, Shah ND, Pencille LJ, Branda ME, Van Houten HK, Swiglo BA, et al. Use of a decision aid to improve treatment decisions in osteoporosis: the osteoporosis choice randomized trial. The American journal of medicine 2011;124(6):549-56.

27. Penton H, Hiligsmann M, Harrison M, Reginster JY, Boonen A, Bansback N. Potential cost-effectiveness for using patient decision aids to guide osteoporosis treatment. Osteoporosis international 2016;27(9):2697-707

28. Rizzoli R, Reginster JY, Boonen S, Breart G, Diez-Perez A, Felsenberg D, et al. Adverse reactions and drug-drug interactions in the management of women with postmenopausal osteoporosis. Calcified tissue international 2011;89(2):91-104.

29. Krucien N, Gafni A, Pelletier-Fleury N. Empirical Testing of the External Validity of a Discrete Choice Experiment to Determine Preferred Treatment Option: The Case of Sleep Apnea. Health economics 2015;24(8):951-65.

30. Lancsar E, Swait J. Reconceptualising the external validity of discrete choice experiments. PharmacoEconomics 2014;32(10):951-65.

**Tables**

Table 1: List of attributes and levels

|  |  |
| --- | --- |
| Efficacy in reducing the risk of future fractures | 20% |
|  | 30% |
|  | 40% |
|  | 50% |
| Possible side effects (affecting 1 in 50 patients) | Gastro-intestinal disorders |
|  | Flu-like symptoms |
|  | Skin reactions |
| Mode of administration | Oral tablet |
|  | Subcutaneous injection |
|  | Intravenous injection |
| Frequency of administration | Weekly |
|  | Monthly |
|  | Every 3 months |
|  | Every 6 months |
|  | Yearly |
| Cost to you (per month) | €5 |
|  | €15 |
|  | €25 |
|  | €40 |
|  | €60 |

Table 2: Patients’ characteristics

|  |  |  |
| --- | --- | --- |
|  | **Countries with cost attribute** | **Countries without cost attribute** |
|  | **Belgium****(n=257)** | **Ireland (n=200)** | **Switzerland (n=98)** | **France (n=100)** | **Netherlands (n=188)** | **Spain (n=183)** | **UK** **(n=100)** |
| Age (years, mean ±SD) | 67.1±10.4 | 63.9±11.9 | 62.6±9.3 | 67.8±11.0 | 65.3±11.9 | 59.2±9.8 | 71.1±8.4 |
| Female gender | 83.3% | 86.8% | 81.1% | 88.4% | 78.1% | 91.1% | 91.9% |
| Educational level |  |  |  |  |  |  |  |
|  Primary | 8.4% | 19.4% | 10.2% | 5.3% | 12.7% | 23.4% | 3.0% |
|  Some high school | 35.9% | 25.0% | 15.3% | 31.6% | 36.4% | 10.8% | 55.0% |
|  High school graduate | 30.3% | 29.6% | 36.7% | 14.7% | 28.8% | 32.9% | 20.0% |
|  College or University | 25.5% | 26.0% | 37.8% | 48.4% | 22.0% | 32.9% | 22.0% |
| Diagnosis of osteoporosis | 89.8% | 45.9% | 93.3% | 94.7% | 70.0% | 54% | 93% |
|  Years since osteoporosis (mean ±SD) | 8.9±6.1 | 5.4%±5.1 | 7.4±5.7 | 9.0±8.8 | 4.7±5.6 | 8.9±10.5 | 8.8±6.5 |
| With prior fracture(s) | 52.5% | 45.3% | 53.7% | 71.2% | 61.6% | 33.8% | 60.2% |
| Patients on osteoporotic treatment | 69.8% | 37.8% | 74.4% | 65.6% | 50.7% | 38.2% | 65.3% |
| Administration mode of current treatment |  |  |  |  |  |  |  |
|  Oral | 72.2% | 41.3% | 65.7% | 75.4% | 73.5% | 86.0% | 81.5% |
|  Subcutaneous | 15.4% | 42.7% | 11.4% | 1.9% | 15.7% | 4.0% | 6.1% |
|  Intravenous | 12.4% | 16.0% | 22.9% | 22.6% | 10.8% | 10.0% | 12.3% |
| Test-retest | 85.2% | 89.4% | 81.6% | 88.9% | 93.6% | 80.9% | 84.0% |
| Task difficulty (range 1-7) | 3.35 | 2.66 | 2.94 | 2.77 | 3.41 | 3.05 | 2.62 |

Table 3. Results from the panel mixed logit model

|  |  |  |
| --- | --- | --- |
|  | **Countries with the cost attribute** | **Countries without the cost attribute** |
| **Attributes and levels** | **Belgium** | **Ireland** | **Switzerland** | **France** | **Netherlands** | **Spain** | **UK** |
|  | **Coef (SD)** | **Std Devs$** | **Coef** | **Std Devs** | **Coef** | **Std Devs** | **Coef** | **Std Devs** | **Coef** | **Std Devs** | **Coef** | **Std Devs** | **Coef** | **Std Devs** |
| Constant | 1.97\*\*\* (0.06) |  | 2.25\*\*\* (0.08) |  | 0.11 (0.13) |  | -1.45\*\*\* (0.20) |  | -1.62\*\*\* |  | 0.77\*\*\* (0.05) | **-** | -1.57\*\*\* (0.03) | **-** |
| Efficacy (1% risk reduction) | 0.04\*\*\* (0.01) | 1.38\*\*\* | 0.05\*\*\* (0.01) | 1.37\*\*\* | 0.10\*\*\* (0.02) | 1.24\*\*\* | 0.08\*\*\* (0.02) | 1.07\*\*\* | 0.07\*\*\*(0.01) | 0.83\*\*\* | 0.05\*\*\* (0.01) | 1.33\*\*\* | 0.11\*\*\* (0.01) | 1.58\*\*\* |
| Cost per month (€1 or CHF1) | -0.04\*\*\* (0.01) | 1.38\*\*\* | -0.01\*\*\* (0.00) | 1.51\*\*\* | -0.03\*\*\* (0.01) | 1.16\*\*\* | --- | --- | --- | --- | --- | --- | --- | --- |
| Mode of administration |
|  Weekly oral tablet (Reference level) | -0.20 | - | -0.27 | - | -0.55 | - | -1.02 | - | -0.29 | - | -0.54 | - | -0.50 | - |
|  Monthly oral tablet | 0.38\*\*\* (0.06) | 0.16 | 0.01 (0.08) | 0.09 | 0.07 (0.14) | 0.65\*\*\* | 0.74\*\*\* (0.12) | 0.21 | 0.64\*\*\* (0.12) | 0.88\*\*\* | 0.14\*\* (0.07) | 0.04 | 0.62\*\*\* (0.13) | 1.00\*\*\* |
|  Subcutaneous 3- month | -0.08 (0.07) | 0.33\*\* | -0.28\*\*\* (0.09) | 0.47\*\*\* | -0.02 (0.14) | 0.31 | 0.16 (0.12) | 0.24 | -0.02 (0.12) | 0.76\*\*\* | -0.01 (0.07) | 0.18 | 0.15 (0.17) | 0.44\*\* |
|  Subcutaneous 6-month | 0.40\*\*\* (0.08) | 0.12 | 0.19\* (0.11) | 0.46\*\*\* | 0.53\*\* (0.22) | 1.05\*\*\* | 0.39\* (0.23) | 1.14\*\*\* | 0.48\*\*\* (0.18) | 1.41\*\*\* | 0.40\*\*\* (0.11) | 0.64\*\*\* | 0.86\*\*\* (0.21) | 1.36\*\*\* |
|  Intravenous 3-month | -0.38\*\*\* (0.09) | 0.56\*\*\* | -0.04 (-0.10) | 0.20 | -0.54\*\* (0.24) | 0.86\*\* | -0.65\*\*\* (0.27) | 1.09\*\*\* | -1.13\*\*\* (0.18) | 1.25\*\*\* | -0.31\*\* (0.13) | 0.46\*\* | -1.32\*\*\* (0.26) | 0.92\*\*\* |
|  Intravenous yearly | -0.12 (0.10) | 0.57\*\*\* | 0.39\*\*\* (0.11) | 0.23 | 0.50\* (0.27) | 1.29\*\*\* | 0.38 (0.24) | 0.97\*\*\* | 0.32\*\*\* (0.16) | 1.03\*\*\* | 0.32\*\*\* (0.10) | 0.39\*\*\* | 0.18 (0.24) | 1.83\*\*\* |
| Side-effects |
|  Gastro-intestinal disorders (reference level) | -0.41 | - | -1.18 | - | -0.33 | - | -0.71 | - | -1.02 | - | -0.18 | - | -1.50 | - |
|  Flu-like symptoms | 0.26\*\*\* (0.05) | 0.42\*\*\* | 0.67\*\*\* (0.10) | 0.77 | 0.17 (0.12) | 0.66\*\*\* | 0.43\*\*\* (0.12) | 0.87\*\*\* | 0.63\*\*\* (0.11) | 0.98\*\*\* | 0.05 (0.05) | 0.39\*\*\* | 1.08\*\*\* (0.11) | 1.40\*\*\* |
|  Skin reactions | 0.15\*\*\* (0.06) | 0.45\*\*\* | 0.51\*\*\* (0.09) | 0.74 | 0.16\* (0.09) | 0.46\*\*\* | 0.28\*\*\* (0.12) | 0.80\*\*\* | 0.39\*\*\* (0.09) | 0.89\*\*\* | 0.12\*\*\* (0.04) | 0.22\*\*\* | 0.42\*\*\* (0.10) | 0.58\*\*\* |
| Pseudo R-squared | 0.39 | 0.49 | 0.39 | 0.44 | 0.38 | 0.30 | 0.49 |
| Log likelihood | -2540.61 | -1674.04 | -968.98 | -907.54 | -1891.87 | -2063.56 | -838.14 |

\* P<0.10, \*\* P<0.05, \*\*\* P<0.01

$ Std Dev values correspond to the random component of the model coefficients (as opposed to the standard deviations of the coefficients themselves reported as SDs)

Table 4: Interaction models to assess differences between countries with and without cost attributes.

|  |  |  |
| --- | --- | --- |
| **Attributes and levels** | Countries with cost (reference = Belgium) | Countries without cost (reference = Netherlands) |
|  | Ireland | Switzerland | France | Spain | UK |
| Constant |  |  |  | + |  |
| Efficacy (1% risk reduction) |  | - | - | - |  |
| Cost per month (€1 or CHF1) |  |  | --- | --- | --- |
| Mode of administration |  |  |  |  |  |
|  Monthly oral tablet |  | - |  |  | - |
|  Subcutaneous 3-month |  |  |  |  |  |
|  Subcutaneous 6-month |  | + |  |  |  |
|  Intravenous 3-month | + |  |  |  | + |
|  Intravenous yearly | + | + |  |  |  |
| Side-effects |  |  |  |  |  |
|  Flu-like symptoms | + |  |  |  | - |
|  Skin reactions | + |  |  |  |  |

+ above average reference country, - below average reference country (P<0.05)

--- no cost attribute in these countries

**Legends for illustrations**

Figure 1: Attributes and levels and example choice set of DCE experiment

No legend

Figure 2: Preferences of osteoporotic patients for mode of administration per country

SC subcutaneous, Int Intravenous, OT oral tablet, W weekly, M monthly, Y yearly

**DISCLOSURE STATEMENT**

JYR has received research grant and/or consulting fees from Servier, Novartis, Negma, Lilly, Wyeth, Amgen, GlaxoSmithKline, Roche, Merckle, Nycomed-Takeda, NPS, IBSA Genevrier, Theramex, UCB, Asahi Kasei, Endocyte, Merck Sharp and Dohme, Rottapharm, Teijin, Teva, Analis, NovoNordisk, Ebewee Pharma, Zodiac, Danone, Will Pharma, Meda, Bristol Myers Squibb, Pfizer, Organon, Therabel, Boehringer, Chiltern, Galapagos. SG has received lecture fees from Amgen or paid advisory board from UCB. AD-P has been speaker or advisor for Amgen, Lilly, MSD, UCB, Active Life Scientific. RR has received Consulting fees or paid advisory boards from Radius Health, Labatec, Danone, Nestlé. BW has received speaker fees and paid advisory boards from Abbvie, Pfizer, Merck Sharp and Dohme, Menarini and Novartis Pharmaceuticals. The remaining authors state that they have no competing interests.

**KEY MESSAGES**

* Osteoporotic patients are willing to pay for their preferred mode of administration
* Significant heterogeneity in patients’ preferences for osteoporotic drug treatment and country differences are observed.