# Stated preferences for persistence with medications: A discrete choice experiment (DCE)

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**Abstract**

**Aim:** To examine patients' stated preferences for persistence with medications.

**Method:** A 4-attribute DCE (mild side-effects, potentially life-threatening side-effects, dose frequency, treatment benefits) with 3-levels identified from literature and expert opinion was developed using a fractional factorial design. Scenarios were folded into nine forced binary choices: Which medicine would you be most likely to continue taking? The survey was translated, piloted and approved for eleven European countries. Target sample was 323 patients prescribed anti-hypertensives per country, recruited by posters in community pharmacies or general practices. Results were analysed in STATA using a random effects logit model.

**Results:** 2856 patients across Austria (n=323), Belgium (n=180), England (n=323), Germany (n=265), Greece (n=289), Hungary (n=323), Netherlands (n=237), Poland (n=323) and Wales (n=323) completed the online questionnaire. In eight countries, all four attributes were statistically significant in influencing patients' choice to persist with treatment ($p<0.01$). Probability of treatment benefit was not significant in Greece ($p=0.57$). Patients were willing to forego improvements in treatment benefits in order to: reduce the risk of ADR, reduce the frequency of dose, and reduce the risk of mild ADRs. They were also willing to forego reduction in risk of common, mild ADR to avoid severe (but rare) ADR and to move to a less frequent dosing schedule. With the exception of Austria ($p<0.05$), there was no evidence from other counties that self-reported adherence influences stated preferences to persist.

**Conclusion:** Persistence is associated with a willingness to trade potential benefits, harms, and convenience. The total utility produced by different combinations of these attributes may have value in assessing patients' likelihood of persisting with medicines, and in the personalisation of medicines, or formulations thereof, to maximise persistence. Further analysis is necessary to compare results across countries.

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**Introduction**

Lack of persistence with medications for chronic diseases has a significant health and economic impact (1). Consequently, there is widespread recognition that further research into the factors that influence patients' decisions not to persist with therapy is warranted (2). Although there are a number of studies in the psychosocial and biomedical literature (3), the application of behavioural economic models to adherence to medications has been limited (4) and mainly focused on single determinants such as cost (consumer demand theory) and time (time preference) (3,5,6). There has been limited research on choice behaviour and the trade-offs patients make in their decision to continue taking a medicine over time.

The current study makes use of stated preference methods (7) with the design of a discrete choice experiment (DCE), consistent with Lancaster's economic theory of value (8). DCE is an attribute-based survey measure in which the utility of goods and services (medicines) is described by attributes and levels. This method assumes people have clear preferences for one good over another and are able to choose between them rationally. Choices reveal information about the relative importance of each attribute, willingness to trade among attributes, and the total utility score that is generated by different combinations of these attributes. Stated preference methods represent a particularly effective method of eliciting preferences regarding health processes and outcomes, that have gained extensive use in several contexts (9,10,11). Previous studies have successfully assessed patients' preferences for medicines using DCE (12-23), but only one study has made specific reference to adherence. In patients with T2DM, Hauber et al. (2009) asked respondents to indicate how likely they would be to miss or skip a dose of their preferred therapy and report that medication-related weight gain and cardiovascular risk are significant predictors of non-adherence.

This study aims to explore how people value the key attributes of medicines in their decision to persist with therapy and to examine the trade-off between benefit, harm and convenience; using a discrete choice experiment within an online survey of medicines use by adult patients prescribed medication for hypertension in 11 European countries.

**Method**

We invited ambulatory, adult patients with hypertension from 11 European countries to participate in an online questionnaire, however only nine countries (Austria, Belgium, England, Germany, Greece, Hungary, Netherland, Poland, and Wales) reached the DCE target sample of 100 patients within the timeframe of the study. Recruitment was via community pharmacies (Austria, Belgium, England, Germany, Greece, Netherlands, Poland, Wales), GP surgeries (Poland, Hungary), hypertension clinics (Hungary), advertisements placed in the press (England, Wales), and online patient support groups (Poland). The survey was administered online, anonymously through SurveyMonkey®. To reduce the chance of multiple responses, the survey was set up to allow one entry per Internet Protocol address. Patient information sheets, consent forms and eligibility checks, were provided online. Ethical approval was obtained from all relevant committees. The questionnaire was piloted extensively in England, Poland and Wales; the revised version was then piloted in every country in all relevant languages.

Inclusion criteria were patients who consented and self-reported as being: aged 18 years or above, with ≥3 months diagnosis of hypertension, currently receiving prescribed antihypertensive medication, and personally responsible for administering their medications. Respondents declaring a psychiatric disorder or those living in a nursing home (or similar facility) were excluded.

*Design of the DCE:* Attributes and levels included in the discrete choice experiment (Table 1) were derived from the literature reporting previous DCE studies (12-23) and known factors that influence adherence (25,26). A pragmatic approach was taken to select attributes and levels that would remain meaningful across different countries, languages and medications.

The choice of levels for each attribute was based on clinical evidence on the effects of commonly used treatments for the management of chronic diseases (26); they were set at plausible values with a range sufficient to model future possibilities, encourage respondents to trade, and limit potential dominance. Each attribute was set to have the same number of levels (27).

The DCE contained two value attributes: treatment benefit and risk of common, mild ADR, to allow comparison between attributes of benefit and harm across countries using marginal rates of substitution (MRS). Cost was not considered as an attribute due to the heterogeneity in drug pricing mechanisms and prescription charge policies across and within participating countries.

The number of possible questions in the DCE is given by the number of levels raised to the power of the number of attributes. A DCE with four attributes each with four levels will results in 256 possible scenarios, requiring a minimum of 128 choice sets. This would pose too great a burden on respondents, and so a fractional factorial design was selected with 9 profiles from a published design catalogue (28). Binary choices were created using the methods of Street and Burgress (2007) (29). The attribute and question order was randomised from that of the design catalogue, to avoid left or right hand bias. The first choice is shown in Figure 1.

The survey included background questions to ascertain participant demographics, use of medicines, self-rated health (30). Self-reported adherence was also measured, using the Morisky questionnaire (31) which categorises participants as being non-adherent if they respond with a "yes" to at least one of four items e.g. "do you ever forget to take your high blood pressure medicine?". A battery of health psychology measures followed the DCE, the results of which are reported elsewhere (*ABC project final report, forthcoming*).

There is no formal sample size calculation for a DCE, however a minimum of 30 respondents is recommended. Assuming 30% of patients are classed as non-adherent by Morisky score, the minimum sample size was set at 100 respondents per country to enable sub-group analysis by adherence score.

The discrete choice experiment was translated and back-translated into the appropriate languages (including a Welsh option for participants in Wales). The appropriate words to describe potentially life-threatening ADRs were identified using terminology included in Summaries of Product Characteristics, which is standardised across Europe, in which adverse reactions are listed according to frequency. The labels for frequencies of 1/100, 1/1,000 and 1/10,000 were used as levels in the experiment.

*Data analysis:*

We imputed missing demographic data using chained equations in STATA Version 10 (StataCorp LP) (32), and created 25 data sets for each country. Cross country comparisons of demographics, medicines use, and health status were performed in SPSS Version 19 on each set and imputation-specific coefficients were pooled according to Rubin's rules (33). In order to satisfy the assumptions of independent observations, missing DCE choices were not imputed and only complete cases were analysed.

Results of the discrete choice experiment were analysed in STATA using a random effects logit model that allowed for repeated observations from the same respondent. Numerical attributes, treatment benefit and mild ADR, were included in the base case analysis as a linear continuous variable. Categorical attributes, frequency of dose and risk of severe ADR, were effects coded. To explore the assumption of linearity we plotted the resulting size of the attribute against the level of each categorical attribute. The marginal rates of substitution were calculated for numerical attributes Subgroup analyses were performed to assess the influence of adherence to medications. Log likelihood ratio tests of restricted and unrestricted models were calculated using a 5% level of significance (6 degrees of freedom). Further analysis is planed to establish a multi-level model for Europe.

**Preliminary Results**

A total of 2630 adults from 11 countries completed the questionnaire. The analysis was restricted to nine countries that reached the target sample size and to individuals within those countries who responded to at least one of the nine choice sets within the experiment (n=2403/2586). Participants' characteristics for the countries included in the analysis are presented in Table 2. Country comparison using chi-squared tests and ANOVAs showed significant differences among countries for all demographics. Participants from the Netherlands were the most adherent to antihypertensive therapy, with 15.5% classed as non-adherent according to the Morisky score. This was followed by patients from Germany (27.8%), Austria (32.1%), Belgium (33.9%), England (36.6%), Wales (37.1%), Poland (48.6%), Greece (48.6%), and Hungary where the majority of participants were non-adherent (70.9%).

*Importance and strength of attributes*

Tables 3 to 11 show the results of the regression analyses for the base case of individual countries. The signs of the β-coefficients for statistically significant attributes were consistent across countries and with a priori hypotheses. All four attributes were statistically significant in eight out of the nine countries ($p<0.01$). This indicates that the probability of treatment benefit; dose frequency; risk of common, mild ADRs; and, risk of rare but severe ADRs, are all important to participants in their stated choice to continue taking a medicine, with the exception of Greece where the probability of benefit did not have a significant influence.

*Subgroup analysis*

All four attributes remained statistically significant for adherent and non-adherent samples in Austria, England, Germany, Netherlands, Poland and Wales ($p<0.01$). The results for the adherent sample suggest dose is not important in Belgium (BD $p= 0.066$, QDS $p=0.061$), Greece (BD $p=0.077$) and Hungary (BD $p=0.10$). This was also the case for the non-adherent sample in Germany (BD $p=0.125$) and Netherlands (BD $p=0.435$, QDS $p=0.859$). Benefit remained not significant for both samples in Greece (adherent $p=0.841$, non-adherent $p=0.578$). Log likelihood ratio tests comparing the base case 'restricted' model (all cases) with the unrestricted model for subgroups (adherent and non-adherent) indicated that in all countries, except Austria, there is no evidence that the restricted model is statistically different from the unrestricted model (Table 12). In Austria, the non-adherent sample had stronger preferences for probability of severe ADRs (uncommon to very rare) and dose frequency (four to once a day).

*Comparing preferences within and across countries*

Table 13 presents the marginal rates of substitution (MRS) using treatment benefit as the value attribute for the base case. Participants across countries had similar preferences: the MRS values across countries suggest that patients were willing to forego improvements in treatment benefits in order to: reduce the risk of ADR (e.g. -63% Germany, -34% Netherlands, -20% England). They are also willing to give up treatment benefit to reduce the frequency of dosing (e.g. -13% Hungary to move from four times to once daily) and to

reduce a fraction of the risk of mild ADRs (e.g. Wales -0.9%). They were also willing to forego a reduction in risk of mild ADR to avoid severe ADR and to move to a lower dosing schedule.

Tables 14 and 15 show the marginal rates of substitution using treatment benefit as the value attribute for the adherent and non-adherent sub-groups. Preferences varied slightly and inconsistently for each model. Dose frequency became the most important attribute relative to benefit in the adherent sample for Austria; and for the non-adherent sample in England. This was caused by the non-adherent sample having a smaller negative preference for severe ADRs (36% in base case to 31% in adherent model); and the non-adherent sample having a stronger preference for once a day dosing (18% in the base case to 30% in the non-adherent model), in Austria and England respectively.

Tables 16 shows the marginal rates of substitution using mild ADRs as value attribute. The marginal rates of substitution for mild ADR suggest participants are willing to give up a potential reduction in mild ADR to move from an uncommon to very rare risk of severe side-effects (e.g. Greece willing to give up a 42% improvement in risk of mild side-effects. This is followed by dose frequency, the size of this trade varied from -74% Austria to -22% Belgium.

Tables 17 and 18 present the marginal rates of substitution using mild ADRs as the value attribute and the estimated coefficients for the adherent and non-adherent sub-groups, respectively.

**Discussion**

The preliminary results of the study suggest that, in addition to treatment benefits, patients place a high value on reducing the risk of severe (but relatively rare) ADR and frequency of dose when choosing to continue taking a medicine. Persistence is therefore associated with the willingness to trade potential benefits, harms, and convenience. The total utility produced by different combinations of these attributes may have value in assessing patients' likelihood of persisting with medicines, and in the personalisation of medicines, or formulations thereof, to maximise persistence.

There are a number of published DCEs that have successfully assessed patient preferences for different medicines (12-23). These have variously included measures of health outcome

(beneficial and/or adverse effects) and probability of outcome occurrence which define 'risk'. Patients have been shown in these studies to make trade-offs between treatment harms and the benefits associated with treatment. In their assessment of patients' preferences for characteristics associated with treatments for osteoarthritis, Ratcliffe et al. (13) reported that respondents were relatively more concerned about the risk of serious ADRs (even with a very low probability) than mild to moderate ADRs (at a much higher probability). This study is consistent with our findings. Hauber et al. (2009) reported that medication-related weight gain and cardiovascular risk has significant negative effects on likely medication adherence. The direction of effect is also consistent with that observed here, although it should be noted that our focus was on persistence with medication, whereas Hauber et al. asked how likely participants would be to miss or skip doses of each medication.

In a study specifically designed to assess attitudes towards risk and patient treatment preferences, Fraenkel et al (15) concluded that patients' relative risk-attitudes are related to their treatment preferences, and that differences in risk-attitude helped explain the inter-patient variability in treatment preferences. We hypothesised that adherence to medication (concurrent behaviour) would affect persistence with medication (stated preference to continue taking a medicine); but there was no evidence that the restricted model was statistically different from the unrestricted model for the majority of countries. Only in Austria could the hypothesis be accepted at p=0.05. Further cross-country comparisons are necessary to explore influences on the selected attributes, such as the number of prescribed doses, health status, and patient demographic characteristics.

*Strengths and limitations*

To our knowledge this is the first study of preferences for persistence with medication to survey a large multi-national sample. The DCE was generic and used European Medicines Agency data and terminology where possible to enable general application.

There were a number of limitations. First, respondents were asked about their persistence with therapy, assuming that patients would initiate dosing. The forced choice design confounds this as the participant has no option but to select a medicine to continue with the questionnaire which may have affected their responses. Second, it is acknowledged that

trading multiple probabilities is cognitively challenging (35) although to address and hopefully minimise this, the DCE was piloted extensively and used two methods of displaying risk: (i) the pictogram was intended to aid in interpretation and also to minimise the loss of any meaning during translation. Positive and negative effects were also colour coded with green figures representing benefit and red figures portraying harm. (ii) The information was described in absolute frequencies. Literature suggests that respondents find it much easier to understand than presenting probabilities in the form of 1 in X chance (36). The length of the survey (155 items) represents a further limitation, however it should be noted that the DCE was purposely put towards the beginning of the survey before the participant was asked to complete any items that may have conditioned their choice.

*Next steps*

This paper represents work in progress. The preliminary analysis reported here has been conducted to: (i) explore numerical and effects coding of the attributes; (ii) calculate the results at an individual country level, and (iii) commence cross-country comparisons. The next stages are to: (i) calculate and compare 95% confidence intervals for attributes and marginal rates of substitution (generated by 1000 bootstrap replications); (ii) conduct a multi-level analysis to gain preferences for Europe; and (iii) perform further sub-group analyses of age, gender, medicines use, optimism and time preference. Finally, and following the publication of the results of the complete DCE data, we will explore the use of imputed missing data in DCE analysis.

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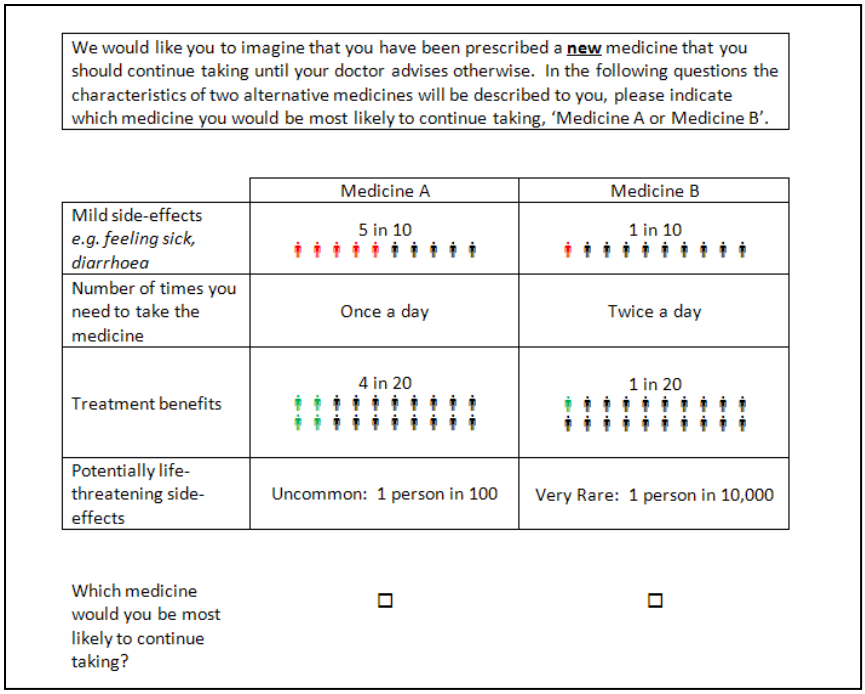


*Figure 1.* Example of a pair wise choice question

*Table 1*. Attribute names and descriptions

| Attribute name | Attribute description | Level description | Level coding for analysis | Effects coding for testing |
|---|---|---|---|---|
| Benefit | Treatment Benefits | 1 in 20<br>2 in 20<br>4 in 20 | 5<br>10<br>20 | Benefit_L0<br>Benefit_L1<br>Benefit_L2 |
| Dose | Number of times you need to take the medicine | Once a day<br>Twice a day<br>Four times a day | Dose (base)<br>_BD<br>_QDS | Dose (base)<br>_BD<br>_QDS |
| Mild ADR | Mild side-effects e.g. feeling sick, diarrhoea | 1 in 10<br>3 in 10<br>5 in 10 | 10<br>30<br>50 | Mild_L0<br>Mild_L1<br>Mild_L2 |
| Severe ADR | Potentially life-threatening side-effects | Very rare: 1 person in 10,000<br>Rare: 1 person in 1,000<br>Uncommon: 1 person 100 | Severe (base)<br>_rare<br>_uncommon | Severe (base)<br>_rare<br>_uncommon |

ADR, Adverse drug reaction.

*Table 2*. Selected demographic data and cross country comparison

| Group | Subgroup | Austria | Belgium | England | Germany | Greece | Hungary | N'lands | Poland | Wales | *Chi sq/f* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Response | Survey / DCE (%) | 323/312 (95.59%) | 180/165 (91.67%) | 323/292 (90.40%) | 265/248 (93.58%) | 289/280 (96.89%) | 323/321 (99.38%) | 237/207 (87.34%) | 323/263 (81.42%) | 323/315 (97.52%) | |
| Adherence | Non-adherent | 109 (33.96%) | 66 (37.71%) | 130 (41.27%) | 87 (32.71%) | 144 (50%) | 226 (70.19%) | 56 (24.24%) | 176 (56.41%) | 121 (37.93%) | 185.52*** |
| | Adherent | 212 (66.04%) | 109 (62.29%) | 185 (58.73%) | 179 (67.29%) | 144 (50%) | 96 (29.81%) | 175 (75.76%) | 136 (43.59%) | 198 (62.07%) | |
| Age | Mean (95% CI) | 60.10 (58.77-61.43) | 57.46 (55.70 – 59.21) | 59.69 (58.59 – 60.78) | 56.85 (55.40 – 58.31) | 63.82 (62.49 – 65.15) | 58.30 (56.87 – 59.74) | 58.24 (59.98 – 59.50) | 54.32 (53.02 – 55.63) | 60.96 (59.78 – 62.14) | 16.3701*** |
| Gender | Male | 177 (55.14%) | 114 (65.14%) | 179 (56.83%) | 115 (43.23%) | 115 (39.93%) | 143 (44.41%) | 119 (51.52%) | 147 (47.12%) | 200 (62.70%) | 65.890*** |
| | Female | 144 (44.86%) | 61 (34.86%) | 136 (43.17%) | 151 (56.77%) | 173 (60.07%) | 179 (55.59%) | 112 (48.48%) | 165 (52.88%) | 119 (37.30%) | |
| Education | School | 121.9 (37.98%) | 6 (3.43%) | 109.4 (34.73%) | 48.2 (18.12%) | 149.9 (52.05%) | 254.0 (78.88%) | 5 (2.16%) | 161.7 (51.83%) | 95 (29.78%) | 546.644*** |
| | Higher | 199.1 (62.02%) | 169 (96.57%) | 205.6 (65.27%) | 217.8 (81.88%) | 138.1 (47.95%) | 68.0 (21.12%) | 226 (97.84%) | 150.3 (48.17%) | 224 (70.22%) | |
| Total Income (deciles) | 1-4 | 100.1 (31.18%) | 14.4 (8.23%) | 81.4 (25.83%) | 103.3 (38.83%) | 137.2 (47.62%) | 93.4 (29.01%) | 35.6 (15.41%) | 56 (17.95%) | 90.5 (28.37%) | 314.371*** |
| | 5-7 | 115.4 (35.95%) | 15.4 (8.80%) | 91 (28.88%) | 86.7 (32.59%) | 86 (29.85%) | 85.3 (26.49%) | 41.1 (17.79%) | 76.8 (24.62%) | 91 (28.53%) | |
| | 8-10 | 61.5 (19.16%) | 116.6 (66.63%) | 106.7 (33.86%) | 42 (15.79%) | 31.7 (11.00%) | 61 (18.94%) | 110.7 (47.92%) | 112.8 (36.15%) | 98.9 (31.00%) | |
| | Not willing to provide | 44 (13.71%) | 28.6 (16.34%) | 36 (11.42%) | 34 (12.78%) | 33.2 (11.52%) | 82.3 (25.56%) | 43.6 (18.87%) | 66.4 (21.28%) | 38.6 (12.10%) | |

| Group | Subgroup | Austria | Belgium | England | Germany | Greece | Hungary | N'lands | Poland | Wales | *Chi sq/f* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Health Status | Poor | 23.2 (7.23%) | 4 (2.29%) | 10 (3.17%) | 5 (1.88%) | 0 (0.00%) | 26 (8.07%) | 4 ( 1.73%) | 22 (7.05%) | 13 (4.08%) | 318.352*** |
| | Fair | 94.3 (29.38%) | 25 (14.29%) | 52 (16.51%) | 80 (30.08%) | 92.3 (32.05%) | 127.2 (39.50%) | 48.2 (20.87%) | 129 (41.35%) | 51 (15.99%) | |
| | Good | 129.4 (40.31%) | 75 (42.86%) | 118 (37.46%) | 139 (52.26%) | 140.6 (48.82%) | 132.7 (41.21%) | 110.6 (47.88%) | 133 (42.63%) | 114.1 (35.77%) | |
| | Very good | 74.1 (23.08%) | 71 (40.57%) | 135 (42.86%) | 42 (15.79%) | 55.1 (19.13%) | 36.1 (11.21%) | 68.2 (29.52%) | 28 (8.97%) | 140.9 (44.17%) | |
| Number of conditions | Mean (95% CI) | 2.85 (2.59 – 3.11) | 2.29 (2.10 – 2.48) | 2.30 (2.16 – 2.43) | 2.14 (1.98 – 2.31) | 2.83 (2.62 – 3.04) | 2.85 (2.68 – 3.03) | 2.08 (1.92 - 2.24) | 2.13 (2.01 – 2.26) | 2.42 (2.26 – 2.58) | 12.8779*** |
| Number of different meds per day | Mean (95% CI) | 4.41 (4.05-4.77) | 3.56 (3.20 - 3.92) | 3.87 (3.60 – 4.13) | 3.40 (3.12 – 3.67) | 4.34 (3.96 – 4.72) | 5.15 (4.79 – 5.52) | 3.40 (3.06 – 3.75) | 4.14 (3.84 – 4.43) | 3.85 (3.58 – 4.11) | 11.7401*** |
| Number of tablets per day | Mean (95% CI) | 5.56 (5.00-6.13) | 3.80 (3.34 – 4.25) | 4.96 (4.48 – 5.44) | 3.96 (3.60 – 4.33) | 5.04 (4.55 – 5.52) | 7.44 (6.90 – 7.98) | 4.40 (3.53 – 5.26) | 3.31 (2.97 – 3.65) | 5.03 (4.50 – 5.55) | 21.7029*** |
| Frequency of taking medications | Once a day | 114.6 (35.70%) | 122.9 (70.23%) | 217 (68.89%) | 98 (36.84%) | 51.2 (17.78%) | 54 (16.77%) | 154.7 (66.97%) | 127.1 (40.74%) | 237 (74.29%) | 545.521*** |
| | Twice a day | 110 (34.27%) | 33.1 (18.91%) | 62 (19.68%) | 125 (46.99%) | 112.2 (38.96%) | 155.3 (48.23%) | 55.2 (23.90%) | 137.5 (44.07%) | 47 (14.73%) | |
| | Three or more times a day | 96.4 (30.03%) | 19 (10.86%) | 36 (11.43%) | 43 (16.17%) | 124.6 (43.26%) | 112.7 (35.00%) | 21.1 (9.13%) | 47.4 (15.19%) | 35 (10.97%) | |
| Number of items prescribed | Mean (95% CI) | 4.49 (4.04-4.93) | 3.24 (2.87 – 3.61) | 4.00 (3.66 – 4.33) | 2.65 (2.38 – 2.91) | 4.23 (3.85-4.62) | 4.69 (4.33-5.06) | 2.58 (2.29 - 2.88) | 3.83 (3.53 – 4.13) | 4.26 (3.78 – 4.74) | 14.7883*** |

*Table 3.* Results of the random-effects logit regression model for Austria

| Attribute | Coef | Std Err | P value | 95% CI | | MRS (%) Benefit | MRS (%) Mild AE |
|---|---|---|---|---|---|---|---|
| Benefit | 0.033 | 0.005 | 0.000 | 0.024 | 0.042 | | -2.21 |
| Dose OD | | | | | | 33.48 | -74.00 |
| _BD | -0.405 | 0.066 | 0.000 | -0.534 | -0.277 | -12.11 | 26.76 |
| _QDS | -0.715 | 0.069 | 0.000 | -0.850 | -0.580 | -21.38 | 47.24 |
| Mild AE | -0.015 | 0.002 | 0.000 | -0.018 | -0.012 | -0.45 | |
| Severe AE | | | | | | 15.10 | -112.14 |
| _rare | -0.490 | 0.063 | 0.000 | -0.613 | -0.366 | -14.65 | 32.37 |
| _uncommon | -1.208 | 0.062 | 0.000 | -1.329 | -1.087 | -36.10 | 79.78 |
| _cons | 0.509 | 0.060 | 0.000 | 0.390 | 0.628 | | |
| | | | | | | | |
| No. of obs = | 2847 | | | | | | |
| No. of groups = | 321 | | | | | | |
| Wald chi2(6) = | 499.020 | | | | | | |
| Log likelihood = | -1527.236 | | | | | | |

*Table 4.* Results of the random-effects logit regression model for Belgium

| Attribute | Coef | Std Err | P value | 95% CI | | MRS (%) Benefit | MRS (%) Mild AE |
|---|---|---|---|---|---|---|---|
| Benefit | 0.046 | 0.007 | 0.000 | 0.032 | 0.059 | | -1.67 |
| Dose OD | | | | | | 13.34 | -22.31 |
| _BD | -0.277 | 0.091 | 0.002 | -0.456 | -0.097 | -6.08 | 10.16 |
| _QDS | -0.331 | 0.097 | 0.001 | -0.520 | -0.141 | -7.27 | 12.15 |
| Mild AE | -0.027 | 0.002 | 0.000 | -0.032 | -0.023 | -0.60 | |
| Severe AE | | | | | | 12.47 | -66.29 |
| _rare | -0.540 | 0.090 | 0.000 | -0.717 | -0.364 | -11.87 | 19.85 |
| _uncommon | -1.264 | 0.083 | 0.000 | -1.426 | -1.102 | -27.77 | 46.44 |
| _cons | 0.443 | 0.073 | 0.000 | 0.299 | 0.586 | | |
| | | | | | | | |
| No. of obs = | 1540 | | | | | | |
| No. of groups = | 175 | | | | | | |
| Wald chi2(6) = | 353.390 | | | | | | |
| Log likelihood = | -776.959 | | | | | | |

*Table 5.* Results of the random-effects logit regression model for England

| Attribute | Coef | Std Err | P value | 95% CI | | MRS (%) Benefit | MRS (%) Mild AE |
|---|---|---|---|---|---|---|---|
| Benefit | 0.047 | 0.005 | 0.000 | 0.038 | 0.056 | | -1.66 |
| Dose OD | | | | | | 17.89 | -29.77 |
| _BD | -0.310 | 0.065 | 0.000 | -0.439 | -0.182 | -6.61 | 10.99 |
| _QDS | -0.530 | 0.069 | 0.000 | -0.666 | -0.395 | -11.29 | 18.78 |
| Mild AE | -0.028 | 0.002 | 0.000 | -0.031 | -0.025 | -0.60 | |
| Severe AE | | | | | | 7.12 | -44.58 |
| _rare | -0.306 | 0.064 | 0.000 | -0.432 | -0.181 | -6.52 | 10.85 |
| _uncommon | -0.953 | 0.057 | 0.000 | -1.065 | -0.841 | -20.28 | 33.74 |
| _cons | 0.321 | 0.053 | 0.000 | 0.217 | 0.425 | | |
| | | | | | | | |
| No. of obs = | 2716 | | | | | | |
| No. of groups = | 315 | | | | | | |
| Wald chi2(6) = | 583.010 | | | | | | |
| Log likelihood = | -1439.548 | | | | | | |

*Table 6.* Results of the random-effects logit regression model for Germany

| Attribute | Coef | Std Err | P value | 95% CI | | MRS (%) Benefit | MRS (%) Mild AE |
|---|---|---|---|---|---|---|---|
| Benefit | 0.024 | 0.006 | 0.000 | 0.013 | 0.035 | | -0.93 |
| Dose OD | | | | | | 30.79 | -28.68 |
| _BD | -0.281 | 0.080 | 0.000 | -0.437 | -0.125 | -11.86 | 11.05 |
| _QDS | -0.448 | 0.080 | 0.000 | -0.605 | -0.291 | -18.93 | 17.63 |
| Mild AE | -0.025 | 0.002 | 0.000 | -0.029 | -0.022 | -1.07 | |
| Severe AE | | | | | | 30.13 | -85.74 |
| _rare | -0.688 | 0.074 | 0.000 | -0.832 | -0.544 | -29.06 | 27.06 |
| _uncommon | -1.491 | 0.069 | 0.000 | -1.626 | -1.356 | -63.00 | 58.68 |
| _cons | 0.557 | 0.056 | 0.000 | 0.448 | 0.666 | | |
| | | | | | | | |
| No. of obs = | 2322 | | | | | | |
| No. of groups = | 266 | | | | | | |
| Wald chi2(6) = | 600.990 | | | | | | |
| Log likelihood = | -1112.026 | | | | | | |

*Table 7.* Results of the random-effects logit regression model for Greece

| Attribute | Coef | Std Err | P value | 95% CI | | MRS (%) Benefit | MRS (%) Mild AE |
|---|---|---|---|---|---|---|---|
| Benefit | -0.003 | 0.005 | 0.570 | -0.012 | 0.007 | | 0.11 |
| Dose OD | | | | | | -368.18 | -40.94 |
| _BD | -0.222 | 0.073 | 0.002 | -0.365 | -0.079 | 80.71 | 8.98 |
| _QDS | -0.790 | 0.067 | 0.000 | -0.921 | -0.658 | 287.47 | 31.97 |
| Mild AE | -0.025 | 0.002 | 0.000 | -0.028 | -0.021 | 8.99 | |
| Severe AE | | | | | | -92.31 | -51.05 |
| _rare | -0.229 | 0.065 | 0.000 | -0.356 | -0.102 | 83.32 | 9.27 |
| _uncommon | -1.032 | 0.057 | 0.000 | -1.144 | -0.920 | 375.71 | 41.78 |
| _cons | 0.610 | 0.051 | 0.000 | 0.511 | 0.709 | | |
| | | | | | | | |
| No. of obs = | 2558 | | | | | | |
| No. of groups = | 288 | | | | | | |
| Wald chi2(6) = | 560.930 | | | | | | |
| Log likelihood = | -1329.795 | | | | | | |

*Table 8.* Results of the random-effects logit regression model for Hungary

| Attribute | Coef | Std Err | P value | 95% CI | | MRS (%) Benefit | MRS (%) Mild AE |
|---|---|---|---|---|---|---|---|
| Benefit | 0.037 | 0.004 | 0.000 | 0.028 | 0.045 | | -2.25 |
| Dose OD | | | | | | 18.76 | -42.17 |
| _BD | -0.204 | 0.061 | 0.001 | -0.323 | -0.085 | -5.56 | 12.49 |
| _QDS | -0.484 | 0.063 | 0.000 | -0.608 | -0.360 | -13.20 | 29.68 |
| Mild AE | -0.016 | 0.001 | 0.000 | -0.019 | -0.013 | -0.44 | |
| Severe AE | | | | | | 12.42 | -83.66 |
| _rare | -0.439 | 0.059 | 0.000 | -0.555 | -0.323 | -11.98 | 26.93 |
| _uncommon | -0.925 | 0.053 | 0.000 | -1.030 | -0.821 | -25.23 | 56.73 |
| _cons | 0.400 | 0.052 | 0.000 | 0.299 | 0.501 | | |
| | | | | | | | |
| No. of obs = | 2892 | | | | | | |
| No. of groups = | 322 | | | | | | |
| Wald chi2(6) = | 465.860 | | | | | | |
| Log likelihood = | -1655.287 | | | | | | |

*Table 9.* Results of the random-effects logit regression model for Netherlands

| Attribute | Coef | Std Err | P value | 95% CI | | MRS (%) Benefit | MRS (%) Mild AE |
|---|---|---|---|---|---|---|---|
| Benefit | 0.041 | 0.006 | 0.000 | 0.030 | 0.053 | | -1.70 |
| Dose OD | | | | | | 18.61 | -31.56 |
| _BD | -0.321 | 0.082 | 0.000 | -0.481 | -0.160 | -7.79 | 13.21 |
| _QDS | -0.445 | 0.088 | 0.000 | -0.617 | -0.274 | -10.82 | 18.35 |
| Mild AE | -0.024 | 0.002 | 0.000 | -0.028 | -0.020 | -0.59 | |
| Severe AE | | | | | | 14.25 | -81.92 |
| _rare | -0.562 | 0.080 | 0.000 | -0.718 | -0.406 | -13.66 | 23.15 |
| _uncommon | -1.426 | 0.080 | 0.000 | -1.584 | -1.268 | -34.66 | 58.77 |
| _cons | 0.416 | 0.080 | 0.000 | 0.258 | 0.574 | | |
| | | | | | | | |
| No. of obs = | 1982 | | | | | | |
| No. of groups = | 231 | | | | | | |
| Wald chi2(6) = | 422.630 | | | | | | |
| Log likelihood = | -1004.578 | | | | | | |

*Table 10.* Results of the random-effects logit regression model for Poland

| Attribute | Coef | Std Err | P value | 95% CI | | MRS (%) Benefit | MRS (%) Mild AE |
|---|---|---|---|---|---|---|---|
| Benefit | 0.029 | 0.005 | 0.000 | 0.020 | 0.038 | | -1.70 |
| Dose OD | | | | | | 39.46 | -67.24 |
| _BD | -0.335 | 0.067 | 0.000 | -0.466 | -0.204 | -11.62 | 19.80 |
| _QDS | -0.802 | 0.071 | 0.000 | -0.942 | -0.662 | -27.84 | 47.44 |
| Mild AE | -0.017 | 0.002 | 0.000 | -0.020 | -0.014 | -0.59 | |
| Severe AE | | | | | | 18.38 | -87.63 |
| _rare | -0.513 | 0.065 | 0.000 | -0.641 | -0.385 | -17.79 | 30.32 |
| _uncommon | -0.969 | 0.061 | 0.000 | -1.088 | -0.850 | -33.63 | 57.32 |
| _cons | 0.434 | 0.063 | 0.000 | 0.311 | 0.557 | | |
| | | | | | | | |
| No. of obs = | 2563 | | | | | | |
| No. of groups = | 312 | | | | | | |
| Wald chi2(6) = | 429.450 | | | | | | |
| Log likelihood = | -1424.027 | | | | | | |

*Table 11.* Results of the random-effects logit regression model for Wales

| Attribute | Coef | Std Err | P value | 95% CI | | MRS (%) Benefit | MRS (%) Mild AE |
|---|---|---|---|---|---|---|---|
| Benefit | 0.033 | 0.005 | 0.000 | 0.024 | 0.042 | | -1.03 |
| Dose OD | | | | | | 26.07 | -26.74 |
| _BD | -0.338 | 0.069 | 0.000 | -0.473 | -0.203 | -10.24 | 10.51 |
| _QDS | -0.523 | 0.068 | 0.000 | -0.656 | -0.389 | -15.82 | 16.23 |
| Mild AE | -0.032 | 0.002 | 0.000 | -0.035 | -0.029 | -0.97 | |
| Severe AE | | | | | | 14.07 | -47.74 |
| _rare | -0.432 | 0.065 | 0.000 | -0.560 | -0.305 | -13.10 | 13.43 |
| _uncommon | -1.105 | 0.057 | 0.000 | -1.217 | -0.992 | -33.44 | 34.31 |
| _cons | 0.452 | 0.054 | 0.000 | 0.346 | 0.558 | | |
| | | | | | | | |
| No. of obs = | 2857 | | | | | | |
| No. of groups = | 319 | | | | | | |
| Wald chi2(6) = | 672.770 | | | | | | |
| Log likelihood = | -1445.957 | | | | | | |

*Table 12.* Likelihood ratio test of restricted versus unrestricted models by country

| Country | Log likelihood Statistic | | | | $\chi^2(6)$ |
|---|---|---|---|---|---|
| | Restricted Model | *Adherent sample* | *Non-adherent sample* | Unrestricted Model[$] | |
| Austria | -1527.2358 | -1038.1682 | -474.1814 | -1512.3496 | -14.8862* |
| Belgium | -776.9588 | -496.5495 | -273.1393 | -769.6887 | -7.2700 |
| England | -1439.5476 | -869.3357 | -561.5467 | -1430.8824 | -8.6652 |
| Germany | -1112.0260 | -755.4037 | -353.1628 | -1108.5665 | -3.4596 |
| Greece | -1329.7951 | -656.8962 | -668.3347 | -1325.2309 | -4.5642 |
| Hungary | -1655.2865 | -466.8842 | -1183.6113 | -1650.4955 | -4.7910 |
| Netherlands | -1004.5783 | -768.4440 | -228.8163 | -997.2602 | -7.3181 |
| Poland | -1424.0272 | -611.4951 | -808.9726 | -1420.4676 | -3.5596 |
| Wales | -1445.9567 | -869.0246 | -572.4723 | -1441.4969 | -4.4598 |

[$] Sum of the log likelihood of adherence and non-adherent models.

* Statistically significant at $p<0.05$

*Table 13.* Marginal rates of substitution using treatment benefit (%) as value attribute: *Base case*

| Attribute | Austria | Belgium | England | Germany | Greece | Hungary | Netherlands | Poland | Wales |
|---|---|---|---|---|---|---|---|---|---|
| Dose OD | 33.484 | 13.342 | 17.895 | 30.790 | -368.182 | 18.755 | 18.615 | 39.456 | 26.067 |
| _BD | -12.108 | -6.077 | -6.605 | -11.860 | 80.708 | -5.556 | -7.794 | -11.619 | -10.244 |
| _QDS | -21.376 | -7.265 | -11.290 | -18.931 | 287.475 | -13.199 | -10.821 | -27.837 | -15.823 |
| Mild AE | -0.452 | -0.598 | -0.601 | -1.074 | 8.992 | -0.445 | -0.590 | -0.587 | -0.975 |
| Severe AE | 15.098 | 12.467 | 7.121 | 30.129 | -92.309 | 12.423 | 14.246 | 18.378 | 14.070 |
| _rare | -14.645 | -11.869 | -6.520 | -29.056 | 83.317 | -11.978 | -13.657 | -17.791 | -13.095 |
| _uncommon | -36.097 | -27.772 | -20.281 | -62.996 | 375.711 | -25.232 | -34.664 | -33.633 | -33.443 |

*Table 14.* Marginal rates of substitution using treatment benefit (%) as value attribute: *Adherent sample*

| Attribute | Austria | Belgium | England | Germany | Greece | Hungary | Netherlands | Poland | Wales |
|---|---|---|---|---|---|---|---|---|---|
| Dose OD | 31.371 | 11.763 | 12.385 | 39.273 | -663.809 | 20.458 | 21.181 | 51.462 | 31.400 |
| _BD | -10.583 | -5.743 | -4.199 | -15.019 | 129.627 | -4.923 | -8.325 | -13.449 | -12.944 |
| _QDS | -20.788 | -6.020 | -8.186 | -24.255 | 534.183 | -15.535 | -12.857 | -38.013 | -18.456 |
| Mild AE | -0.447 | -0.733 | -0.496 | -1.143 | 17.109 | -0.420 | -0.489 | -0.959 | -1.241 |
| Severe AE | 14.220 | 16.143 | 5.293 | 37.572 | -192.433 | 13.637 | 13.229 | 24.804 | 18.846 |
| _rare | -13.773 | -15.410 | -4.797 | -36.429 | 175.324 | -13.217 | -12.740 | -23.845 | -17.605 |
| _uncommon | -30.982 | -32.577 | -16.687 | -72.558 | 834.869 | -29.029 | -31.265 | -46.943 | -43.458 |

*Table 15.* Marginal rates of substitution using treatment benefit (%) as value attribute: *Non-adherent sample*

| Attribute | Austria | Belgium | England | Germany | Greece | Hungary | Netherlands | Poland | Wales |
|---|---|---|---|---|---|---|---|---|---|
| Dose OD | 38.203 | 14.867 | 29.456 | 18.320 | -294.175 | 18.013 | 5.693 | 34.183 | 21.304 |
| _BD | -15.123 | -5.792 | -11.801 | -6.981 | 69.435 | -5.781 | -4.636 | -10.811 | -7.869 |
| _QDS | -23.079 | -9.075 | -17.655 | -11.339 | 224.740 | -12.231 | -1.057 | -23.371 | -13.435 |
| Mild AE | -0.439 | -0.420 | -0.817 | -0.951 | 6.811 | -0.452 | -1.070 | -0.422 | -0.720 |
| Severe AE | 15.611 | 8.016 | 10.885 | 19.188 | -63.897 | 11.801 | 19.891 | 15.622 | 9.374 |
| _rare | -15.172 | -7.597 | -10.069 | -18.237 | 57.086 | -11.349 | -18.821 | -15.200 | -8.654 |
| _uncommon | -44.751 | -22.323 | -27.801 | -48.464 | 240.214 | -23.544 | -52.159 | -27.906 | -23.660 |

*Table 16.* Marginal rates of substitution using mild AE (%) as value attribute: *Base case*

| Attribute | Austria | Belgium | England | Germany | Greece | Hungary | Netherlands | Poland | Wales |
|---|---|---|---|---|---|---|---|---|---|
| Benefit | -2.210 | -1.672 | -1.663 | -0.931 | 0.111 | -2.248 | -1.695 | -1.704 | -1.026 |
| Dose OD | -74.000 | -22.311 | -29.766 | -28.679 | -40.945 | -42.170 | -31.560 | -67.238 | -26.742 |
| _BD | 26.759 | 10.162 | 10.987 | 11.046 | 8.975 | 12.492 | 13.214 | 19.800 | 10.509 |
| _QDS | 47.240 | 12.149 | 18.779 | 17.633 | 31.969 | 29.678 | 18.346 | 47.438 | 16.233 |
| Severe AE | -112.141 | -66.287 | -44.580 | -85.741 | -51.048 | -83.663 | -81.924 | -87.634 | -47.744 |
| _rare | 32.366 | 19.847 | 10.845 | 27.064 | 9.266 | 26.931 | 23.154 | 30.318 | 13.434 |
| _uncommon | 79.775 | 46.440 | 33.735 | 58.677 | 41.782 | 56.732 | 58.771 | 57.315 | 34.309 |

*Table 17.* Marginal rates of substitution using mild AE (%) as value attribute: *Adherent sample*

| Attribute | Austria | Belgium | England | Germany | Greece | Hungary | Netherlands | Poland | Wales |
|---|---|---|---|---|---|---|---|---|---|
| Benefit | -2.237 | -1.364 | -2.014 | -0.875 | 0.058 | -2.379 | -2.047 | -1.043 | -0.806 |
| Dose OD | -70.167 | -16.050 | -24.947 | -34.359 | -38.799 | -48.668 | -43.355 | -53.678 | -25.306 |
| _BD | 23.671 | 7.836 | 8.458 | 13.139 | 7.577 | 11.712 | 17.039 | 14.029 | 10.432 |
| _QDS | 46.496 | 8.214 | 16.488 | 21.220 | 31.223 | 36.957 | 26.316 | 39.650 | 14.874 |
| Severe AE | -100.103 | -65.476 | -43.272 | -95.350 | -59.045 | -100.499 | -90.073 | -73.836 | -49.212 |
| _rare | 30.805 | 21.026 | 9.662 | 31.871 | 10.248 | 31.442 | 26.078 | 24.872 | 14.189 |
| _uncommon | 69.298 | 44.450 | 33.610 | 63.479 | 48.798 | 69.057 | 63.996 | 48.964 | 35.024 |

*Table 18* Marginal rates of substitution using mild AE (%) as value attribute: *Non-adherent sample*

| Attribute | Austria | Belgium | England | Germany | Greece | Hungary | Netherlands | Poland | Wales |
|---|---|---|---|---|---|---|---|---|---|
| Benefit | -2.276 | -2.384 | -1.225 | -1.052 | 0.147 | -2.213 | -0.935 | -2.370 | -1.389 |
| Dose OD | -86.941 | -35.440 | -36.071 | -19.264 | -43.194 | -39.859 | -5.321 | -81.005 | -29.590 |
| _BD | 34.417 | 13.808 | 14.451 | 7.341 | 10.195 | 12.793 | 4.333 | 25.621 | 10.930 |
| _QDS | 52.524 | 21.632 | 21.620 | 11.923 | 32.998 | 27.066 | 0.988 | 55.385 | 18.660 |
| Severe AE | -136.370 | -71.321 | -46.376 | -70.138 | -43.652 | -77.211 | -66.339 | -102.152 | -44.881 |
| _rare | 34.527 | 18.109 | 12.330 | 19.177 | 8.382 | 25.113 | 17.590 | 36.021 | 12.020 |
| _uncommon | 101.843 | 53.212 | 34.045 | 50.961 | 35.271 | 52.099 | 48.749 | 66.131 | 32.862 |