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What influences persistence with medicines? A multinational discrete choice experiment of 2549 patients

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Title: What influences persistence with medicines? A multinational discrete choice experiment of 2549 patients

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SUMMARY

Aim: To examine patients' stated preferences to persist with medicines and to explore the influence of psychosocial and sociocognitive factors.

Methods: Community-dwelling, hypertensive patients recruited from 9 European countries were invited to complete a discrete choice experiment (DCE) with attributes for treatment benefits, mild yet common adverse drug reactions (ADR), rare but potentially life-threatening ADR and dosing frequency. Patients responded to the binary-choice of which medicine would they be most likely to continue taking. Data were analysed using a random effects logit model.

Results: 2549 patients from Austria (n=321), Belgium (n=175), England (n=315), Germany (n=266), Greece (n=288), Hungary (n=322), Netherlands (n=231), Poland (n=312) and Wales (n=319) completed the DCE. All attributes significantly influenced patients' stated preference to persist with medications ($p<0.05$). Patients were willing to accept decreases in treatment benefits of: 50.6 percentage points (95%CI: 46.1-57.9) for a very rare (as opposed to rare) risk of severe ADR; 28.3 percentage points (95%CI: 25.2-33.1) for a once-daily instead of twice-daily dosing; and 0.74 percentage points (95%CI: 0.67-0.85) for a 1% point reduction in mild ADR. Models accounting for psychosocial and sociocognitive characteristics were significantly different from the base case.

Conclusion: Patients' intention to persist with treatment was associated with their willingness to trade potential benefits, harms, and dosing frequency. Psychosocial and sociocognitive factors influenced the extent of trading. The utility model may have value in assessing patients' likelihood of persisting with medicines, and to tailor treatment to maximise persistence.

What is known about this subject?

1. Persistence with medicines can be considered as an outcome of a conscious decision patients make about whether the continued taking of the medication will increase their utility
2. Discrete choice experiments of implementation of dosing have found that patients are willing to accept adverse events in exchange for increase benefit.

What this study adds

1. Within our multinational DCE, hypertensive patients' intentions to persist with medication were influenced by treatment benefit, harm and dosing frequency
2. Psychosocial and sociocognitive factors changed the extent to which trade-offs were made among these attributes
3. The findings may have value in assessing patients' likelihood of persisting with medicines, and in the development of adherence-enhancing interventions

INTRODUCTION

Medication adherence encompasses the processes of initiation, implementation of dosing and persistence [1]. Reduced persistence with prescribed treatment is prevalent, with median length of time between patients' initiation of treatment for chronic diseases and their last dose being typically in the order of 1 year [2], despite failure to continue treatment having a detrimental effect on health [3]. Reasons for the premature discontinuation of medicines are varied, and include factors related to patients, such as their beliefs and socioeconomic characteristics; the condition and its treatment; healthcare professionals and health systems [3,4]. There is emerging evidence of the role of behavioural economic theories in explaining patients' choice to persist with their prescribed medicines [5]. This is based on a notion that persistence with medications may be an outcome of a decision patients consciously make about whether the continued taking of their medication will increase their utility [6]. That is, if patients' utility (satisfaction) is maximised through taking their medications, their likelihood of persisting increases; but conversely if patients maximise their utility by not taking their medications, they will discontinue treatment.

Patients' utility may be examined using stated preference techniques, such as the discrete choice experiment (DCE) [7]. DCEs are an attribute-based survey measure underpinned by a Lancastrian view of utility which contends that goods and services (or medicines in this case) can be described by their characteristics or attributes and that the utility yielded by a medicine is a function of its various attributes [8]. Choices reveal information about the relative importance of each attribute, willingness to trade them, and total utility which patients aim to maximise.

DCEs represent a particularly effective method of eliciting preferences regarding health processes and outcomes that have gained extensive use in several contexts, including patients' preferences for medicines [9,10], but few empirical studies have made specific reference to the process of adherence to medication [11-13]. Hauber et al [11] conducted a study of treatment preferences and adherence to oral glucose-lowering agents amongst individuals with type 2 diabetes and found that while patients were willing to accept some adverse events in exchange for better glucose control, stated adherence would reduce with increasing risk of weight gain or myocardial infarction. Using a choice-format stated-preference survey, Johnson et al. [12] identified severity of depressive episodes, weight gain and the cognitive effects of treatments for bipolar disorder to affect patients' likelihood to adhere.

The view that non-adherence may be considered a rational behaviour that reveals patient preferences, adds to more established health psychology research studies. Within health and social psychology there exist several theoretical frameworks and models for explaining variation in health-related behaviours, which can be applied to persistence with medications [14]. Sociocognitive theory assumes that persistence is motivated by outcome expectancies and goals (such as improved health), which are determined by individuals' attitudes and beliefs [15-17]. Models within sociocognitive theory that have been applied to persistence with medications include the Health Belief Model [18-19] and The Theory of Planned Behaviour [20]. In this context, the Health Belief Model postulates the likelihood of persistence is increased if the perceived threat of illness from sub-optimal persistence is high, the benefit of medicines-taking is greater than the barriers to medicines-taking, and cues to action (e.g. reminders) are in place. The Theory of Planned Behaviour suggests an individual's intention to persist with medication increases if the perceived consequences are high (attitudes towards behaviour and outcome expectancies are positive), they have strong positive beliefs about what others expect (perceived social norms); and they perceive a high level of personal control / self-efficacy with regards to persisting, even when facing barriers; this will depend on their perception of internal resources (e.g. knowledge) and external resources (e.g. social support).

A more dynamic link between cognitions, motivation and behaviour can be explored using self-regulation theory [21]. Self-regulation theory describes the individual as an active problem solver and describes the cognitive and behavioural process by which individuals monitor and adjust their medication taking as the perceived solution to the problem of illness and its consequences [17]. Illness representations or beliefs, together with treatment beliefs, shape coping responses e.g. persistence with medications. Beliefs about a particular illness and state of ill health are thought to form around five domains: Identity: signs and symptoms; Timeline: ideas about the time-frame of a condition (acute, chronic, cyclical); Cause: perception of cause (internal, external, stable, unstable etc.); Consequences: expected outcomes (physical, psychological and social); and, Control / cure: beliefs about potential cure and (internal/external) control. The contribution of the models described can be measured using self-report questionnaires for each component e.g. Barriers in the Theory of Planned Behaviour, or Illness consequences within Illness Perception Questionnaire.

Concurrent assessment of influences on patients' decisions to persist with a medication in terms of the utility they derive from medication characteristics, and theory driven psychosocial characteristics associated with medication preferences, increases the possibilities for interventions which could be both medicine and person-based. We are unaware of any study in which a range of health psychology theories have been tested simultaneously alongside preference elicitation methods in relation to medication persistence.

This study aims to (i) assess how patients from across Europe value the key attributes of medicines in their stated decision to persist with taking them and to examine the trade-off between potential benefit, harm and convenience; (ii) explore the relationship between these preferences and psychosocial and sociocognitive characteristics.

METHODS

The study involved a multi-national, web-based survey of hypertensive adult patients containing a DCE designed to elicit the preferences of patients for attributes of a hypothetical medication. The survey was piloted and ethically approved for eleven European countries: Austria, Belgium, England, France, Germany, Greece, Hungary, Netherlands, Poland, Portugal, and Wales. Patients were eligible for the study if they self-reported as being 18 years or older, diagnosed by a doctor as having hypertension that lasted at least 3 months, currently prescribed antihypertensive medication, and personally responsible for administering their medication. Respondents were excluded if they were aged less than 18 years, declared a psychiatric disorder, or lived in a nursing home or similar facility where they were not responsible for their own medicines taking. The target sample was for a minimum of 100 respondents per country (consistent with DCE studies [9,10]) up to a maximum of 323 patients per country [22]. Respondents were principally recruited using advertisements in community pharmacies. Additional strategies included advertisements in hypertension clinics (Hungary), GP surgeries (Hungary and Poland) and local press (England and Wales). The survey was anonymous, hosted online and restricted to one respondent per Internet Protocol address.

DCE attributes, levels, and experimental design

We identified a list of potential attributes from 18 DCE studies of medicinal products identified in a systematic review [9]. Attributes identified were categorised as follows: mild adverse drug reactions (n=14 studies), treatment outcome (n=13), severe adverse drug reactions (n=6), dose related (n=5), duration of treatment (n=4), location of treatment (n=3), cost (n=3), route of administration (n=1), quality of life (n=1). The four most commonly used attributes were selected: treatment benefit, risk of common mild adverse drug reactions (ADRs), risk of rare but potentially life-threatening ADRs and dosage frequency (table 1).

We hypothesised that benefits would have a positive influence on patients' stated intention to persist with treatment, while increased risk of harms and dose frequency would be negative.

Insert Table 1 here

Each attribute was set to have three levels, representative of treatments used commonly for the management of chronic diseases. These were set at plausible values with a range sufficient to encourage respondents to trade, and limit potential dominance (Table 1), while allowing for scenarios (e.g. for improved benefit) to be modelled. For the DCE to be broadly generalizable across many common treatments, we used a hypothetical scenario of an unlabelled medicine and respondents were not given information on any specific condition or disease area. The question posed was: Which medicine would you be most likely to continue taking? Figure 1 provides an example of the pairwise choice used in the experiment.

Insert Figure 1 here

The number of possible choice scenarios in a full factorial design was $3^4 = 81$. As this would pose too great a burden on respondents, a fractional factorial design was selected with 9 profiles from a published design catalogue [23]. Binary choices were created using the fold-over method which replaces each attribute level with its opposite [24]. The attribute and question order was randomised to avoid left or right selection bias. Rational trading was tested by examining responses to a dominant profile which had a lower risk of mild ADR, lower dosage frequency, higher treatment benefit and lower risk of severe ADR.

Survey of psychosocial and sociocognitive factors

Validated self-report instruments were used to assess sociocognitive determinants of adherence [22]. Illness representations were measured using the Brief Illness Perception Questionnaire (B-IPQ) [25]. Patient beliefs in the necessity and concerns of medications were measured using the Beliefs about Medicines Questionnaire [26]. Constraints and facilitators of adherence were measured using barrier and social support subscales of the BRIGHT questionnaire [27-28]. Attitudinal and belief components of the Theory of Planned Behaviour (TPB) were scored on a 5-point Likert scale [29-30]. Self-reported adherence was 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 questions posed; and the Medication Adherence Rating Scale (MARS) which results in a continuous score for adherence (range 5-25) [32]. Details of the psychosocial measures used in the exploratory analysis are provided in Appendix 1. The full survey content is detailed elsewhere [22].

Translation

Measures that were not validated and available in the required language were translated into the appropriate languages (and back-translated for checks of compatibility with the English version) using accredited translators who were native speakers of the target languages and fluent in English. Descriptions of ADR prevalence were taken from the European Medicines Agency's standard text for summaries of product characteristics, which is available in all European languages.

Data analysis

Results of the DCE were analysed in STATA (version 10; StataCorp LP, College Station, TX) using a random effects logit model that allowed for repeated observations from the same respondent:

$$U = \beta_0 + \beta_1 SEVERE\_ADR + \beta_2 DOSE + \beta_3 BENEFIT + \beta_4 MILD\_ADR + \varepsilon$$

U = utility derived by individual

β_0 = constant term

198 β_i = estimated coefficient for each attribute (variable)

199 ε = error term

200 Treatment benefit and risk of mild ADR were included in the analysis as linear continuous variables.
201 We explored the assumption of linearity for frequency of dose and risk of severe ADR, using effects
202 coding and plotting the resulting size of the coefficient against the level of each attribute. The level of
203 the base case was calculated using the estimated levels: e.g.

204 $\beta_{\text{very rare SEVERE\_ADR}} = -(\beta_{\text{rare SEVERE\_ADR}} + \beta_{\text{uncommon SEVERE\_ADR}})$

205 The DCE contained two value attributes: treatment benefit and risk of common, mild ADR, that were
206 used to compare the rate at which patients were willing to give up a unit change in benefit or harm in
207 exchange for a unit change in another, whilst maintaining the same utility (marginal rates of
208 substitution, MRS). 95% confidence intervals were calculated by Bootstrapping with 1,000
209 replications. Lexicographic preferences were explored by looking for left or right hand bias, using
210 counts of how many respondents continually selected medicine A or B. The influence of psychosocial
211 and sociocognitive factors on preferences for persistence was assessed using exploratory subgroup
212 analyses. Subgroups were selected for analysis if they: (i) had a statistically significant association
213 with adherence (as defined by Morisky or MARS) [22]; and (ii) were confirmed as significant predictors
214 of persistence in other published studies [14]. Log likelihood ratio tests of the base case regression
215 and the models comprising the two subgroups were performed at a 5% level of significance. If the
216 subgroup model was significantly different, the MRS for harms and benefits were calculated for each
217 category within the subgroup.

218

219

220 RESULTS

221 The analysis was restricted to nine countries that reached the target sample size. There was an
222 inadequate level of available research support in France and Portugal that resulted in low response
223 (n=11, n=33 respectively) thus these were excluded. Eighty-nine percent (n=2,549) of people who
224 started the survey completed at least one DCE question. These were from Austria (n=321), Belgium

(n=175), England (n=315), Germany (n=266), Greece (n=288), Hungary (n=322), Netherlands (n=231), Poland (n=312) and Wales (n=319).

Sample characteristics

Participants' characteristics are presented in Table 2. Respondents were split almost equally according to gender (51% male) and employment status (52% employed), had a median age of 60 years, and were prescribed a median of 3 different medicines per day. The majority of patients (54%) were prescribed medicines that required more than once-daily dosing.

Insert Table 2 here

Magnitude and statistical significance of attributes

Among respondents to the DCE, 91.2% selected the dominant choice while only 2.5% of respondents showed lexicographic preferences, consistently choosing medicine A (1.77%) or B (0.76%).

All four attributes influenced respondents' stated intention to persist with treatment ($p<0.01$) (Table 3). Respondents were most likely to persist with the treatment offering greatest benefit ($\beta=0.031$), least risk of mild but common ADRs ($\beta=-0.023$), or severe but rare ADRs ($\beta=1.553$), and the least frequent dosing regimen ($\beta=0.869$). The signs and direction of the regression coefficients were consistent with expectation.

Insert Table 3 here

All else being equal, the odds of patients stating that they would continue taking their medicines increased by 3% for every 1 percentage point increase in the chance of treatment benefits, and increased 2% for every 1 percentage point decrease in the risk of common mild side-effects. A medicine with the lowest risk of severe ADR (very rare) increased the odds of persistence four-fold, and the lowest dose frequency (once daily) more than two-fold.

Comparing preferences

Marginal rates of substitution, using treatment benefit as the value attribute, suggest that patients were willing to forego improvements in treatment benefits in order to: reduce the risk of severe ADR (forego 50.6 percentage point improvement in treatment benefit for a 'very rare' risk of severe of ADR as opposed to a rare risk); reduce the frequency of dosing (forego 28.3 percentage point improvement in treatment benefit for once-daily dosage frequency as opposed to twice daily); and to reduce the risk of common mild side-effects (forego 7.4 percentage point improvement of treatment benefit for a 10 percentage point reduction in mild ADR) (Table 4). When considering harm as the value attribute, respondents were also willing to accept an increase in risk of mild ADR to avoid severe ADR (68.6 percentage point increase in risk of mild side-effects for a 'very rare' risk of severe ADR as opposed to rare); and to move to a less frequent dosing schedule (38.4 percentage point increase in risk of mild ADR for once daily dose frequency as opposed to twice daily).

Insert Table 4 here

Exploratory analysis

Regressions controlling for psychosocial variables were significantly different from the base-case regression in 10/12 cases (Appendix 2), but in each case, all four attributes were significant and in the expected directions.

Respondents' willingness to trade treatment benefit for once daily dosing, as opposed to twice daily, was significantly higher for respondents who were unlikely to take their medicines regularly. These respondents, who had low intentions, were willing to forgo an additional 29.9 percentage point benefit to take medication once, rather than twice a day (i.e. Appendix 2; MRS of lower intentions 49.97 minus MRS of high intentions 20.06). Individuals with high concerns about medicines were also willing to forgo an additional benefit to take medication once, rather than twice a day (22.2 percentage points); as where those who lacked confidence in their medicines-taking i.e. those with low self-efficacy (16.6 percentage points) and, those with higher illness concern (willing to forgo a 15.5 percentage point improvement in benefit to take medication once, rather than twice a day).

Respondents' willingness to trade treatment benefit for the lowest risk of ADR (very rare) opposed to a rare risk was significantly higher for respondents who were (i) unlikely to take their medicines regularly (people with low intention were willing to forgo a 32.4 percentage point additional benefit for a very rare risk of severe ADR, than those categorised as high TPB intentions); (ii) demonstrated high illness concern (24.5 percentage points); and (iii) had high concerns about medicines (23.8 percentage points).

DISCUSSION

The results of the study suggest that, in addition to treatment benefits, patients place a high value on reduced risk of severe (but relatively rare) ADRs and less frequent dosing when stating that they choose to continue taking a medicine. Stated preference to persist is therefore associated with the willingness to trade potential benefits for reduced harm and increased convenience. The total utility produced by different combinations of these attributes may have value in assessing patients' likelihood of persisting with medicines, in the context of health care provider-patient communications, and the personalisation of medicines, or formulations thereof, to maximise persistence.

This study has shown that the evidence-based medicine model of health maximisation via use of treatments with the highest expected net benefit may not necessarily result in the best outcome for patients if there is misalignment in preferences. Persistence with medications can be considered as an outcome of a decision patients make about whether the continued taking the medication will increase their utility [6]. Maximising utility may therefore increase persistence, which may lead to better health outcomes – even when using a less effective treatment. Our analysis therefore suggests a mechanism via which the prescribing of alternative treatments might improve persistence and hence health outcome. We have also found that patients' trade-offs between benefits, harm and convenience are influenced by psychosocial and sociocognitive factors. Interventions to improve persistence, grounded in theory and targeted towards psychosocial variables (e.g. barriers to medicines, self-efficacy / confidence in medicines taking) may therefore improve the probability of

persistence directly [22], and indirectly through changing patients' preferences for medicines-related attributes. This study illustrates the potential for improvements in sociocognitive factors to increase the utility of routinely prescribed drugs and thus encourage persistence. Further research is necessary to design and provide evidence on the efficacy of potential interventions. Our findings suggest that several factors influence persistence, however a simple intervention, such as a guided conversation or a medicines review, could enable health care professionals to identify barriers to medicines taking and assess how other people influence perceptions of medicines (subjective norms), in order increase an individual's self-efficacy via education or counselling.

Previous DCEs of preferences for medicines reveal that patients are willing to trade benefit for reduced harm [9,10]. In the context of adherence, a DCE by Mohamed et al. [13] showed that lower frequency of administration, shorter administration times, and milder ADR appear to improve stated adherence to antibiotic treatment of CF lung infections. A study of patients with HIV, using a modified adaptive conjoint analysis, identified pill burden, dosing frequency, and adverse events as having the greatest impact on patients' perceived ability to adhere to antiretroviral medication regimens [33].

To our knowledge this is the first study of preferences for persistence with medication to survey a large multi-national sample; and, the first study to measure both stated preferences and a wide range of psychosocial factors concurrently. The DCE was generic, based on previously tested actionable attributes and used European Medicines Agency data and terminology where possible to enable general application. The selection of psychosocial and sociocognitive factors tested alongside the DCE attributes was guided by theory and based on empirical evidence.

There were a number of limitations. Firstly, patients self-selected to participate in the study and we must therefore acknowledge the risk of selection bias which may influence the results insofar as only people who were actively interested in expressing their views on their medicines taking behaviour participated, which may reduce the external validity of our findings. Secondly, our study was restricted to four attributes to cover benefits, harms and convenience; findings from other studies of

preferences for medications (not persistence with) suggest that attributes such as route of administration [34], quality of life, location / provider, duration of treatment, among others, may also have a significant influence on preference. The risk attributes were also presented as probabilities with no indication of frequency or time horizon. It is acknowledged, however, that trading multiple attributes is cognitively challenging [35]. We aimed to minimise this by piloting the DCE extensively and by using two methods of displaying risk. Event frequencies were supplemented by pictograms which were intended to aid interpretation by depicting probabilities graphically and colour-coding positive and negative effects. Respondents find it much easier to understand pictorial representations than presenting probabilities in the form of 1 in X chance [36]. Thirdly, the respondents were diagnosed with hypertension whereas the DCE was aimed to cover a broad spectrum of pharmaceuticals.. The DCE was not amenable to treatments for hypertension as they are mainly once daily. Fourthly, the length of the survey (135 items) represents a further limitation, but completion rates were high as the DCE was purposely put towards the beginning of the survey before participants were asked to complete any items that may have conditioned their choice [22]. Finally, as with any stated preference study, the findings need to be confirmed by studies of revealed preference.

Patients were willing to trade potential benefits, harms, and convenience in responding that they would persist with treatment. Potentially alterable, psychosocial factors influence the extent of the trade-offs between these attributes. Persistence may therefore be enhanced directly, through selection of medicines meeting preferred levels of attributes; or, indirectly through targeting modifiable psychosocial factors that affect trade-off choices. The novel finding of an interaction between patients' stated preferences to persist with medication and their sociocognitive characteristics (i.e. high/low illness concerns, high/low self-efficacy etc.) provides a basis for synergistically effective approaches aimed to change behaviour (e.g. to increase self-efficacy) and treatment selection (e.g. reduced dose frequency).

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Contributions: All authors contributed substantially to the conception and design of the work; and, to the acquisition, analysis, or interpretation of data. EAFH drafted the paper and DH and VM revised it critically for important intellectual content, and gave their final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Figures and Tables

Electronic Supplementary Material

Figure 1. Example of pairwise choice

We would like you to imagine that you have been prescribed a **new** medicine that you should continue taking until your doctor advises otherwise. In the following questions the characteristics of two alternative medicines will be described to you, please indicate which medicine you would be most likely to continue taking, 'Medicine A or Medicine B'.

	Medicine A	Medicine B
Mild side-effects *e.g. feeling sick, diarrhoea*	5 in 10 	1 in 10 
Number of times you need to take the medicine	Once a day	Twice a day
Treatment benefits	4 in 20 	1 in 20 
Potentially life-threatening side-effects	Uncommon: 1 person in 100	Very Rare: 1 person in 10,000
Which medicine would you be most likely to continue taking?	☐	☐

490 **Table 1**. Attributes and Levels

Attribute name	Attribute description	Level description	Rationale for levels
Benefit	Treatment benefits	1 in 20 2 in 20 4 in 20	Based on typical Numbers Needed to Treat for treatment for chronic conditions (e.g. hypertension, diabetes, ulcerative colitis)
Dose	Number of times you need to take the medicine	Once a day Twice a day Four times a day	The majority of chronic disease treatments are in the range of once to four times daily dosing
Mild ADR	Mild side-effects e.g. feeling sick, diarrhoea	1 in 10 3 in 10 5 in 10	Gastrointestinal irritation is a common ADR for many treatments. Frequency based on representative range
Severe ADR	Potentially life-threatening side-effects	Very rare: 1 in 10,000 Rare: 1 in 1,000 Uncommon: 1 in 100	Likelihood of life-threatening ADRs are typically uncommon to very rare

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493 **Table 2**. Values of regression variables used to estimate utility and probability of persistence with 5-
494 ASAs for ulcerative colitis

	Drug name				References
	sulfasalazine	mesalamine	olsalazine	balsalazide	
Probability of remission	0.37	0.42	0.33	0.24	[35]
Probability of ADR	0.34	0.13	0.20	0.10	[35]
Frequency of severe ADR (aplastic anaemia)	Very rare	Rare	Very rare	Very rare	SmPC
Maintenance dose frequency	Four times daily	Once a day	Twice a day	Twice a day	SmPC

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496 SmPC summary of product characteristics

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Table 3. Random effects logit model

Attribute	Coefficient (95%CI)	p-value	Odds Ratio
Severe ADR - Very rare	1.553 (1.469, 1.637)		4.726
Severe ADR - Rare	-0.444 (-0.488, -0.401)	0.0000	0.641
Severe ADR - Uncommon	-1.109 (-1.149, -1.068)	0.0000	0.330
Dose - Once a day	0.869 (0.776, 0.961)		2.383
Dose - Twice a day	-0.296 (-0.341, -0.250)	0.0000	0.744
Dose - Four times a day	-0.573 (-0.620, -0.526)	0.0000	0.564
Treatment benefit	0.031 (0.028, 0.034)	0.0000	1.031
Common mild side-effects	-0.023 (-0.024, -0.022)	0.0000	0.978
Constant	0.452 (0.414, 0.490)	0.0000	1.572
Number of observations	22277		
Number of groups	2549		
Wald chi^2 (6 degrees of freedom)	1465		
Log likelihood	-11952.52		

Table 4. Patients' marginal rates of substitution between treatment benefit or reduction in common mild side-effects and other attributes

Attribute	Marginal rate of substitution (MRS)	
	Treatment benefit	Risk of mild ADRs
	% (95% CI)	% (95% CI)
Severe ADR - Very rare	50.58 (46.07, 57.87)	-68.60 (-72.35, -63.98)
Severe ADR - Rare	-14.48 (-16.99, -12.77)	19.64 (17.49, 21.60)
Severe ADR - Uncommon	-36.10 (-41.24, -32.94)	48.96 (45.90, 51.25)
Dose - Once a day	28.29 (25.18, 33.11)	-38.36 (-42.50, -34.77)
Dose - Twice a day	-9.63 (-11.88, -8.14)	13.05 (11.15, 15.33)
Dose - Four times a day	-18.66 (-21.51, -16.67)	25.31 (22.95, 27.60)
Treatment benefit		-1.36 (-1.49, -1.17)
Common mild side-effects	-0.74 (-0.85, -0.67)	

Appendix 1: Psychosocial measures

Psychological theory, model, variable	Number of items {score}	Item description	Scoring scale
Sociocognitive theory:			
Theory of Planned Behaviour			
Subjective norms	3-items {3-15}	1. My doctor or nurse would approve of me taking my medicines regularly 2. My wife/husband/partner would approve of me taking my medicines regularly 3. Members of my family or close relatives would approve of me taking my medicines regularly	5-point Likert scale: I agree a lot {5} I agree a little I neither agree or disagree I disagree a little I disagree a lot {1}
Barriers	1-items {3-15}	1. Changes to my daily routine would make it more difficult for me to take my medicines regularly	
Intention	2-items {2-10}	1. It is likely that I will take my medicines regularly 2. I intend to take my medicines regularly	
Self-efficacy	2-items {2-10}	1. Overall, how confident are you that you will always take your medications as prescribed? 2. Overall, how confident are you that you will always take your medications at the prescribed times?	5-point Likert scale: Not at all confident {1} Somewhat confident Very confident Extremely confident Completely confident {5}
BRIGHT Environmental Constraints / Facilitators			
Social support	7-items {0-35}	1. Was there someone who reminded you to take your medicines? 2. Was there someone who helped you to prepare the medicines? 3. Was there someone who encouraged you to take your medicines correctly? 4. Was there someone who gave practical tips to make it easier for you to take your medicines? 5. Was there someone who adapted his or her own life habits (waking up, schedule…) to make it easier for you to take your medicines?	5-point Likert scale: In the past 4 weeks … Never {0} Occasionally Sometimes Frequently All the time {4}

Psychological theory, model, variable	Number of items {score}	Item description	Scoring scale
		6. Was there someone who understood the problems or discomfort that resulted from your medicines? 7. Was there someone who reprimanded you because you didn't take your medicines correctly?	
BRIGHT Barriers	15-items {0-75}	1. I ran out of medicines 2. I was confused about which medicines to take 3. I did not want other people to know that I have a health problem 4. Something disrupted my daily medicine routine (e.g., I was on holiday) 5. I was forgetful 6. I could not afford to buy my medicines 7. I felt depressed or overwhelmed 8. I forgot to take my medicines with me when leaving the house 9. I had too many medicines to take 10. I suffered from the side effects of my medicine. 11. I had to take too many different doses during the day 12. I had problems swallowing the large pills of my medicines 13. I did not like the taste of my medicines 14. I had problems removing the medicines from the package 15. I had problems drinking enough water to swallow the medicines	5-point Likert scale: In the past year … Never {0} Occasionally Sometimes Frequently All the time {4}
Self-regulation theory: Illness Representations			
Illness consequences	1-item {0-10}	1. How much does your illness affect your life?	{0} - no affect at all {1 2 3 4 5 6 7 8 9} {10} - severely affects my life
Personal control	1-item {0-10}	1. How much control do you feel you have over your illness?	{0} - absolutely no control {1 2 3 4 5 6 7 8 9} {10} - extreme amount of control

Psychological theory, model, variable	Number of items {score}	Item description	Scoring scale
Treatment control	1-item {0-10}	1. How much do you think your treatment can help your illness?	{0} - not at all {1 2 3 4 5 6 7 8 9} {10} - extremely helpful
Illness concern	1-item {0-10}	1. How concerned are you about your illness?	{0} - not at all concerned {1 2 3 4 5 6 7 8 9} {10} - extremely concerned
Treatment Beliefs			
Necessity of medicine	5-items {5-25}	1. My health, at present, depends on these medicines 2. My life would be impossible without these medicines 3. Without these medicines I would be very ill 4. My health in the future will depend on these medicines 5. These medicines protect me from becoming worse	5-point Likert scale: Strongly Agree {5} Agree Uncertain Disagree Strongly Disagree {1}
Concerns about medicine	6-items {6-30}	1. Having to take these medicines worries me 2. I sometimes worry about long-term effects of these medicines 3. These medicines are a mystery to me 4. These medicines disrupt my life 5. I sometimes worry about becoming too dependent on these medicines 6. These medicines give me unpleasant side effects	5-point Likert scale: Strongly Agree {5} Agree Uncertain Disagree Strongly Disagree {1}

Appendix 2. Results of exploratory subgroup analysis of willingness to trade benefit or mild ADR with other attributes, presented by psychological theory, model, and factor

Psychological theory Model Factor	Trade-off	Subgroup MRS (95% confidence interval)	
Sociocognitive Theory			
Theory of Planned Behaviour			
Subjective norms: *Perception that persistence is influenced by approval of others: doctor, nurse, partner, family.*		Higher influence of others	Lower influence of others
	Mild ADR / Benefit	-0.64 (-0.79, -0.56)	-0.77 (-0.94, -0.68)
	Once daily dose / Benefit	23.25 (19.23, 29.40)	31.77 (27.06, 39.57)
	Twice daily dose / Benefit	-8.39 (-11.58, -6.60)	-9.70 (-13.27, -7.77)
	Four times a day dose / Benefit	-14.86* (-18.26, -12.22)	-22.07* (-26.78, -19.04)
	Very rare severe ADR / Benefit	50.91 (43.99, 60.89)	45.56 (39.24, 54.81)
	Rare severe ADR / Benefit	-14.85 (-18.34, -12.39)	-12.23 (-15.39, -9.77)
	Uncommon severe ADR / Benefit	-36.06 (-43.10, -31.43)	-33.33 (-39.89, -29.10)
	Benefit / Mild ADR	-1.55 (-1.80, -1.27)	-1.29 (-1.48, -1.06)
	Once daily dose / Mild ADR	-36.14 (-42.92, -30.20)	-41.01 (-47.13, -35.56)
	Twice daily dose / Mild ADR	13.04 (10.11, 16.67)	12.52 (10.00, 15.72)
	Four times a day dose / Mild ADR	23.10 (19.24, 26.99)	28.49 (24.98, 32.02)
	Very rare severe ADR / Mild ADR	-79.14* (-86.43, -71.82)	-58.81* (-64.10, -53.07)
	Rare severe ADR / Mild ADR	23.08* (19.59, 26.38)	15.78* (12.99, 18.62)
	Uncommon severe ADR / Mild ADR	56.06* (50.93, 60.76)	43.03* (39.34, 46.50)
Barriers: *Changes to daily routine would make it more difficult to take medicines regularly*		Higher barriers	Lower barriers
	Mild ADR / Benefit	-0.77 (-0.92, -0.67)	-0.59 (-0.74, -0.52)
	Once daily dose / Benefit	30.33 (25.80, 36.85)	22.68 (18.57, 28.91)
	Twice daily dose / Benefit	-9.49 (-12.40, -7.46)	-8.24 (-11.43, -6.24)
	Four times a day dose / Benefit	-20.84* (-24.68, -17.97)	-14.44* (-17.94, -11.98)
	Very rare severe ADR / Benefit	46.27 (40.24, 55.68)	49.72 (43.71, 59.66)
	Rare severe ADR / Benefit	-12.73 (-16.20, -10.49)	-14.27 (-18.07, -11.86)
	Uncommon severe ADR / Benefit	-33.53 (-39.42, -29.24)	-35.45 (-42.26, -31.38)
	Benefit / Mild ADR	-1.30* (-1.49, -1.09)	-1.69* (-1.93, 1.36)
	Once daily dose / Mild ADR	-39.43 (-44.74, -34.36)	-38.23 (-45.75, -31.34)
	Twice daily dose / Mild ADR	12.34 (9.84, 15.07)	13.89 (10.28, 18.00)
	Four times a day dose / Mild ADR	27.09 (23.74, 30.44)	24.35 (19.98, 29.05)
	Very rare severe ADR / Mild ADR	-60.15 (-64.87, -55.26)	-83.81* (-91.51, -75.28)
	Rare severe ADR / Mild ADR	16.55 (14.18, 19.01)	24.06* (20.23, 27.60)
	Uncommon severe ADR / Mild ADR	43.59 (40.27, 46.51)	59.75* (54.13, 64.69)
Intention: *Likely to and/or intend to take medicines*		Higher intentions	Lower intentions
	Mild ADR / Benefit	-0.58* (-0.67, -0.52)	-1.10* (-1.58, -0.86)
	Once daily dose / Benefit	20.06* (17.08, 24.18)	49.97* (38.10, 70.71)
	Twice daily dose / Benefit	-6.67* (-8.77, -5.28)	-16.64* (-24.72, -11.80)
	Four times a day dose / Benefit	-13.39* (-15.72, -11.58)	-33.34* (-46.34, -25.70)
	Very rare severe ADR / Benefit	40.26* (36.21, 45.97)	72.70* (56.78, 101.43)
	Rare severe ADR / Benefit	-11.10* (-13.20, -9.48)	-21.31* (-31.12, -16.06)
	Uncommon severe ADR / Benefit	-29.16* (-33.11, -26.36)	-51.39* (-71.54, -40.64)
	Benefit / Mild ADR	-1.73* (-1.91, -1.50)	-0.91* (-1.16, -0.64)
	Once daily dose / Mild ADR	-34.64 (-40.38, -29.79)	-45.36 (-52.58, -38.07)
	Twice daily dose / Mild ADR	11.51 (9.09, 14.70)	15.10 (11.37, 18.86)
	Four times a day dose / Mild ADR	23.12 (20.00, 26.34)	30.26 (25.79, 34.79)
	Very rare severe ADR / Mild ADR	-69.53 (-74.41, -63.71)	-65.99 (-73.01, -59.12)
	Rare severe ADR / Mild ADR	19.17 (16.56, 21.79)	19.34 (16.13, 22.86)
	Uncommon severe ADR / Mild ADR	50.36 (46.44, 53.33)	46.65 (42.12, 50.80)

Self-efficacy: *Confidence of taking medicines* and*/or at the prescribed times*	Higher confidence	Lower confidence
Mild ADR / Benefit	-0.58* (-0.68, -0.52)	-0.93* (-1.17, -0.78)
Once daily dose / Benefit	21.31* (18.08, 25.71)	37.90* (30.67, 48.12)
Twice daily dose / Benefit	-7.26 (-9.63, -5.80)	-12.34 (-16.92, -9.20)
Four times a day dose / Benefit	-14.06* (-16.46, -12.10)	-25.56* (-32.06, -20.90)
Very rare severe ADR / Benefit	44.11 (39.51, 50.42)	55.71 (47.02, 68.98)
Rare severe ADR / Benefit	-12.25 (-14.64, -10.40)	-15.90 (-20.92, -12.80)
Uncommon severe ADR / Benefit	-31.86 (-36.06, -28.76)	-39.81 (-49.21, -33.43)
Benefit / Mild ADR	-1.71 (-1.91, -1.47)	-1.08* (-1.28, -0.86)
Once daily dose / Mild ADR	-36.50 (-42.82, -31.06)	-40.92 (-46.81, -35.06)
Twice daily dose / Mild ADR	12.43 (10.02, 16.01)	13.33 (10.27, 16.46)
Four times a day dose / Mild ADR	24.07 (20.54, 27.42)	27.59 (23.95, 31.05)
Very rare severe ADR / Mild ADR	-75.55* (-82.07, -68.88)	-60.14* (-66.36, -54.28)
Rare severe ADR / Mild ADR	20.99 (18.03, 24.01)	17.16 (14.27, 20.21)
Uncommon severe ADR / Mild ADR	54.56* (50.02, 58.65)	42.98* (39.13, 46.59)

Sociocognitive Theory

Bright: Environmental Constraints / Facilitators

Social support: *Support from people in personal environment*	Higher social support	Lower social support
Mild ADR / Benefit	-0.64 (0.78, -0.56)	-0.87 (-1.09, -0.74)
Once daily dose / Benefit	25.76 (21.93, 32.10)	30.73 (24.84, 39.28)
Twice daily dose / Benefit	-8.44 (-11.46, -6.69)	-10.67 (-14.99, -7.87)
Four times a day dose / Benefit	-17.32 (-21.13, -14.65)	-20.06 (-25.21, -16.61)
Very rare severe ADR / Benefit	42.01* (36.55, 50.80)	61.01* (51.62, 75.39)
Rare severe ADR / Benefit	-11.52 (-14.65, -9.44)	-17.24 (-22.12, -14.04)
Uncommon severe ADR / Benefit	-30.49* (-36.48, -26.85)	-43.76* (-53.90, -37.17)
Benefit / Mild ADR	-1.55* (-1.78, -1.29)	-1.15 (-1.36, -0.92)
Once daily dose / Mild ADR	-40.02 (-46.49, -34.07)	-35.39 (-41.63, -29.68)
Twice daily dose / Mild ADR	13.11 (10.32, 16.79)	12.29 (9.40, 15.65)
Four times a day dose / Mild ADR	26.91 (23.10, 30.77)	23.10 (19.43, 26.43)
Very rare severe ADR / Mild ADR	-65.25 (-71.52, -58.83)	-70.25 (-76.67, -63.43)
Rare severe ADR / Mild ADR	17.90 (14.93, 21.19)	19.86 (16.75, 23.03)
Uncommon severe ADR / Mild ADR	47.36 (43.06, 51.18)	50.40 (45.86. 54.30)

Self-regulation Theory

Illness Representations

Illness consequences: *How much does your illness affect your life?*	Higher illness consequences	Lower illness consequences
Mild ADR / Benefit	-0.77 (-0.94, -0.65)	-0.64 (-0.76, -0.57)
Once daily dose / Benefit	32.67 (27.43, 40.65)	22.58 (18.88, 28.03)
Twice daily dose / Benefit	-10.18 (-13.80, -7.87)	-8.07 (-10.83, -6.17)
Four times a day dose / Benefit	-22.50* (-27.20, -19.10)	-14.51* (-17.46, -12.22)
Very rare severe ADR / Benefit	53.76 (45.87, 64.60)	43.36 (38.35. 51.07)
Rare severe ADR / Benefit	-15.24 (-19.24, -12.56)	-12.16 (-14.94, -10.17)
Uncommon severe ADR / Benefit	-38.52 (-46.03, -33.07)	-31.20 (-36.62, -27.56)
Benefit / Mild ADR	-1.31* (-1.53, -1.07)	-1.56 (-1.76, -1.32)
Once daily dose / Mild ADR	-42.70 (-49.51, -36.83)	-35.34 (-41.33, -29.57)
Twice daily dose / Mild ADR	13.30 (10.37, 16.80)	12.63 (9.80, 15.77)
Four times a day dose / Mild ADR	29.40 (25.49, 33.59)	22.71 (19.28, 25.93)
Very rare severe ADR / Mild ADR	-70.26 (76.95, -64.03)	-67.84 (-73.64, -61.77)
Rare severe ADR / Mild ADR	19.92 (16.77, 23.28)	19.03 (16.27, 22.06)
Uncommon severe ADR / Mild ADR	50.34 (45.92, 54.69)	48.82 (44.94, 52.40)

Personal control: *How much control do you feel you have over your illness? illness*	Higher personal control	Lower personal control
Mild ADR / Benefit	-0.83 (-1.01, -0.71)	-0.60 (-0.72, -0.53)
Once daily dose / Benefit	30.79 (24.97, 38.61)	24.53 (20.66, 30.01)

Twice daily dose / Benefit	-10.26 (-13.77, -7.52)	-8.25 (-11.03, -6.39)
Four times a day dose / Benefit	-20.53 (-25.22, -17.20)	-16.28 (-19.41, -13.96)
Very rare severe ADR / Benefit	58.86* (50.95, 71.72)	39.59* (34.61, 47.11)
Rare severe ADR / Benefit	-16.64 (-20.96, -13.42)	-11.08 (-14.01, -9.20)
Uncommon severe ADR / Benefit	-42.23* (-51.55, -36.86)	-28.51* (-33.68, -25.19)
Benefit / Mild ADR	-1.21 (-1.41, -0.99)	-1.67 (-1.89, -1.40)
Once daily dose / Mild ADR	-37.28 (-43.27, -31.74)	-40.96 (-47.13, -34.53)
Twice daily dose / Mild ADR	12.42 (9.48, 15.49)	13.78 (10.76, 17.26)
Four times a day dose / Mild ADR	24.85 (21.23, 28.23)	27.18 (23.19, 30.67)
Very rare severe ADR / Mild ADR	-71.27 (-77.02, -65.43)	-66.11 (-72.54, -59.50)
Rare severe ADR / Mild ADR	20.14 (17.28, 23.25)	18.50 (15.62, 21.65)
Uncommon severe ADR / Mild ADR	51.12 (47.16, 54.78)	47.61 (43.33, 51.46)
Treatment control: *How much do you think your treatment can help your illness?*	Higher treatment control	Lower treatment control
Mild ADR / Benefit	-0.67 (-0.80, -0.60)	-0.77 (-0.96, -0.65)
Once daily dose / Benefit	24.35 (20.81, 29.84)	32.92 (27.15, 41.82)
Twice daily dose / Benefit	-8.56 (-11.27, -6.77)	-10.19 (-14.33, -7.46)
Four times a day dose / Benefit	-15.79* (-18.89, -13.57)	-22.74* (-28.29, -19.18)
Very rare severe ADR / Benefit	49.91 (44.64, 58.58)	46.26 (39.16, 57.57)
Rare severe ADR / Benefit	-14.28 (-17.33, -12.30)	-12.60 (-16.86, -9.92)
Uncommon severe ADR / Benefit	-35.64 (-41.91, -31.83)	-33.66 (-41.27, -28.44)
Benefit / Mild ADR	-1.48 (-1.67, -1.25)	-1.30 (-1.54, -1.04)
Once daily dose / Mild ADR	-36.12 (-42.10, -30.87)	-42.90 (-49.92, -36.54)
Twice daily dose / Mild ADR	12.69 (10.16, 15.96)	13.27 (10.07, 16.82)
Four times a day dose / Mild ADR	23.43 (19.95, 26.71)	29.63 (25.71, 33.81)
Very rare severe ADR / Mild ADR	-74.05 (-79.96, -68.30)	-60.27* (-66.63, -53.91)
Rare severe ADR / Mild ADR	21.18 (18.46, 24.12)	16.41 (13.37, 20.09)
Uncommon severe ADR / Mild ADR	52.87 (48.71, 56.44)	43.85* (39.62, 47.88)
Illness concern: *How concerned are you about your illness?*	Higher illness concern	Lower illness concern
Mild ADR / Benefit	-0.90* (-1.10, -0.78)	-0.51* (-0.61, -0.44)
Once daily dose / Benefit	35.45* (29.60, 44.41)	19.98* (16.30, 25.06)
Twice daily dose / Benefit	-11.91 (-16.01, -9.30)	-6.61 (-9.32, -4.77)
Four times a day dose / Benefit	-23.54* (-28.63, -20.11)	-13.37* (-16.22, -11.12)
Very rare severe ADR / Benefit	60.83* (52.54, 73.78)	36.33* (31.85, 43.05)
Rare severe ADR / Benefit	-17.17* (-21.47, -14.36)	-10.07* (-12.86, -8.02)
Uncommon severe ADR / Benefit	-43.66* (-52.71, -37.86)	-26.26* (-30.82, -23.13)
Benefit / Mild ADR	-1.11* (-1.29, -0.91)	-1.98* (-2.25, -1.63)
Once daily dose / Mild ADR	-39.40 (-45.00, -34.82)	-39.55 (-47.39, -32.48)
Twice daily dose / Mild ADR	13.24 (10.82, 16.22)	13.09 (9.39, 17.41)
Four times a day dose / Mild ADR	26.16 (23.07, 29.40)	26.47 (21.82, 30.81)
Very rare severe ADR / Mild ADR	-67.61 (-73.02, -62.02)	-71.91 (-79.68, -63.11)
Rare severe ADR / Mild ADR	19.08 (16.56, 21.61)	19.93 (16.15, 23.72)
Uncommon severe ADR / Mild ADR	48.52 (44.84, 51.78)	51.98 (46.36, 56.85)

Self-regulation Theory

Treatment Beliefs

Concerns about medicine	Higher concerns about medicines	Lower concerns about medicines
Mild ADR / Benefit	-1.01* (-1.33, -0.85	-0.53* (-0.63, -0.47
Once daily dose / Benefit	41.48* (33.90, 54.45)	19.31* (16.38, 23.61)
Twice daily dose / Benefit	-13.34* (18.84, -10.10)	-6.62* (-8.99, -5.13)
Four times a day dose / Benefit	-28.14* (-36.63, -23.24)	-12.70* (-15.11, 10.84)
Very rare severe ADR / Benefit	63.88* (52.54, 82.42)	40.06* (35.95, 46.87)
Rare severe ADR / Benefit	-17.70 (-23.79, -13.92)	-11.31 (-13.94, -9.60)
Uncommon severe ADR / Benefit	-46.17* (-59.47, -38.47)	-28.75* (-33.10, -25.81)
Benefit / Mild ADR	-0.99* (-1.18, -0.75)	-1.90* (-2.12, -1.60)
Once daily dose / Mild ADR	-40.89 (-46.88, -34.80)	-36.77 (-43.18, -30.91)

Twice daily dose / Mild ADR	13.15 (10.18, 16.36)	12.60 (9.62, 16.13)
Four times a day dose / Mild ADR	27.74 (24.20, 31.29)	24.17 (20.44, 27.60)
Very rare severe ADR / Mild ADR	-62.97* (-68.84, -57.12)	-76.27* (-83.20, -69.36)
Rare severe ADR / Mild ADR	17.45 (14.46, 20.80)	21.53 (18.31, 24.93)
Uncommon severe ADR / Mild ADR	45.52* (41.84, 48.88)	54.74* (49.92, 58.89)

Notes. MRS. Marginal Rate of Substitution between attributes. * Indicates statistically significant sub-groups ($p<0.004$, critical p-value for multiple comparison for 12 subgroups). Spilt sample analysis not significantly different to base case for: Sociocognitive theory, BRIGHT Barriers: problems with taking medicines or taking them on time $p=0.0093$; and, Self-regulation Theory, Treatment beliefs: beliefs about the necessity of medicine $p=0.0645$; therefore marginal rates of substitution were not calculated.