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Self-Reported Adherence to Cholesterol-Lowering Medication in Patients with Familial Hypercholesterolaemia: The Role of Illness Perceptions

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Summary. Background: **The objectives of this study are to describe levels of adherence to cholesterol-lowering medication and to identify predictors of adherence in patients with familial hypercholesterolaemia (FH).**

Design: **Descriptive questionnaire study.**

Methods: **336 adults patients with FH attending one of five outpatient lipid clinics in South East England underwent a clinical assessment by a nurse and completed a questionnaire. The questionnaire assessed self-reported adherence to cholesterol-lowering medication, anxiety, depression, and patient perceptions of heart disease**

Results: **Overall, participants reported high levels of medication adherence, although 63% reported some level of non-adherence. Total medication adherence (never deviating from the regimen) was more likely to be reported by older participants, those with no formal educational qualifications, those with a personal history of cardiovascular disease, those with a lower total cholesterol level, and those with a greater difference between untreated cholesterol levels and current cholesterol levels. The illness perceptions associated with reported total adherence were lower perceived risk of raised cholesterol, perceiving greater control over FH, and perceiving genes and cholesterol to be important determinants of a heart attack. Emotional state was not associated with medication adherence. In logistic regression analysis, predictors of total medication adherence were having personal history of cardiovascular disease, having no formal qualifications, and perceiving genes to be important determinants of a heart attack.**

Conclusions: **Both clinical factors and patients' illness perceptions were associated with self-reported cholesterol-lowering medication adherence. The association with illness perceptions was small and many of these associations may be a consequence, rather than a cause, of greater adherence. Given this, intervention strategies aimed at helping patients' to establish routines for medication taking may be more effective in increasing adherence than interventions designed to alter perceptions related to taking statins.**

Key Words. **familial hypercholesterolaemia, patient nonadherence, risk reduction behaviour, self efficacy**

Introduction

Current cholesterol-lowering therapies, particularly statins, are very effective at reducing mortality and morbidity [1,2]. However, non-adherence to cholesterol-lowering medication has been identified as a significant clinical problem [3,4]. In a review of the literature, Insull [3] reports that discontinuation with treatment ranges from 6–30% after five years for clinical trials and from 12–45% over one year for Health Maintenance Organisation (HMO) studies. Although discontinuation with treatment is likely to result in the most adverse health outcomes, deviation from the recommended treatment regimen also presents a problem. Insull [3] estimates that up to 50% of patients receiving cholesterol-lowering medication will take their medication at doses or times that deviate substantially from those recommended. Of these, 30–40% are expected to be partially adherent (defined as 20–79% adherence) and 5–10% are described as non-adherent (defined as <20% adherence). Non-adherence has serious implications both for the individual patient and for healthcare services [5].

Gaining a better understanding of the determinants of adherence to cholesterol-lowering medication is the first step towards implementing effective and efficient interventions to increase adherence. Adherence to cholesterol-lowering medication is increased by having fewer daily doses, fewer different medications, fewer and less severe side effects [3]. Adherence has

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been found to be higher for statins than for cholestyramine [6,7]. Possible explanations are that statins have fewer daily doses, fewer noticeable side effects, and are often more effective at lowering cholesterol.

Insull [3] also states that both patient knowledge of the disease and attitudes towards cholesterol-lowering treatment are determinants of adherence, although little research has quantified the strength of these associations. Research in health psychology has shown that patients' beliefs about their condition often determine their health-related behaviour above and beyond the effects of clinical factors [8]. This is termed an *illness perception* approach to understanding health-related behaviour. For example, perceptions of hypertension are associated with whether or not patients adhere to anti-hypertensive medication [9]. Other research has shown that beliefs about the medication, particularly whether it is considered to be necessary and whether the patient has any concerns about it, are strongly associated with adherence [10].

Few studies appear to have investigated the association between adherence to cholesterol-lowering medication and hypercholesterolaemic patients' perceptions of their raised cholesterol and risk of cardiovascular disease (CVD). In one descriptive study, higher self-report of adherence in 193 hyperlipidaemic patients was reported by those who were older, smoked less, reported fewer side effects, had a routine way of taking medication, were more likely to attend routine appointments, and perceived their treatment as more effective [11]. A number of variables were not associated with adherence, such as perceiving a role for cholesterol in causing CVD, perceiving oneself to be at risk for CVD, mood, and stress. These authors [11] provide little information regarding how perceptions and mood state were assessed. The use of measures that are established to be both reliable and valid may lead to greater statistical prediction of adherence and more generalisable findings.

The first aim of the present study is to describe self-reported adherence to cholesterol-lowering medication in patients with familial hypercholesterolaemia (FH). Given this population's greatly increased risk of developing early CVD, high levels of long-term adherence are extremely important in reducing mortality and morbidity. The second aim of the present study is to assess the extent to which both clinical factors and patient illness perceptions are associated with adherence. If illness perceptions are found to be associated with adherence this offers an opportunity for relatively low-cost interventions to increase adherence through changing illness perceptions.

Methods

Participants

These comprised 340 adults previously diagnosed with definite or possible FH, using criteria specified by the Simon Broome register [12], and attending lipid clinics in one of five hospitals in the South East of England, UK.

Design

The design is cross-sectional, comprising data from the baseline of randomised trial of genetic and non-genetic diagnosis of familial hypercholesterolaemia [13].

Measures

Self-reported medication adherence: was assessed using the five-item Medication Adherence Report Scale (MARS-5) which has been found to have good reliability and validity [10]. Frequency of deviation from the prescribed regimen for cholesterol-lowering medication over the past month was assessed using five response options (always, sometimes, occasionally, rarely, never). The specific items are reported in the Results section.

Demographic characteristics. The questionnaire included items assessing gender, age, ethnicity, and highest level of qualification. The qualification item had the following possible response options: no qualifications, GCSE grades D-G, GCSE grades A-C, foreign/other, higher education to less than degree level, degree or equivalent.

Personal history of CVD.

1. *Length of awareness of raised cholesterol* was assessed using the item "*For how long have you known that you have a high cholesterol level?*"
2. *Length of attendance at the lipid clinic* was assessed using the item "*For how long have you been attending the lipid clinic at the hospital?*"
3. *History of heart disease* was assessed by the research nurse during the clinical assessment when taking a personal and family history. This measure consists of self-perceived history of heart disease and includes perception of previous heart attack, angioplasty, and bypass surgery. *Angina symptoms* were assessed using the Rose questionnaire which categorises symptoms into Grade 1 and Grade 2 angina [14].
4. *Total cholesterol level*: *Current total cholesterol* was assessed using a fasting lipid profile, comprising total cholesterol, triglycerides, HDL, and LDL, was made by standard automated methods. Only the data pertaining to total current cholesterol is reported in the present paper. *Untreated total cholesterol* was assessed from patient self-report and from medical records. The *difference between untreated and current total cholesterol* was calculated as an estimate of the benefit derived from cholesterol-lowering medication.

5. *Presence of physical manifestations of raised cholesterol*: This was assessed by the nurse during the clinical assessment. Knuckles and ankles were examined for presence of *tendons xanthomata*, part of the diagnostic criteria for FH. Eyes were examined for presence of *xanthelasma and corneal arcus*. As the manifestations can recede with treatment, participants' reports of previous manifestations were also included in this measure.

Illness perceptions.

1. *Perceived control*: Three aspects of perceived control were assessed. All three scales had satisfactory internal consistency (alphas >.70). (1) *Perceived control over FH* was assessed using five items from the Revised Illness Perceptions Questionnaire (IPQ-R) [15]. These items concerned the extent to which FH was perceived to be controllable and amenable to treatment. All items were rated on five-point Likert-type scales ranging from "strongly disagree" to "strongly agree". (2) *Perceived control over cholesterol* was assessed by two items on seven-point scales ranging from "not at all" (0) to "completely" (6). The perceived control over cholesterol scale ranged from 0 (low perceived control) to 6 (high perceived control). (3) *Perceived control over heart disease* was assessed by two items on seven-point scales ranging from "not at all" (0) to "completely" (6). The perceived control over heart disease scale ranged from 0 (low perceived control) to 6 (high perceived control).
2. *Causal attributions for a heart attack*: Nine items were rated for their perceived importance in causing a heart attack on seven-point scales ranging from "not at all important" (0) to "extremely important" (6). These nine items formed four scales comprising attributions to *behaviour*, *genes*, *cholesterol*, and *chance*.
3. *Perceptions of risk*. *Perceived risk of raised cholesterol* was assessed with the item "how likely do you think you are to have a raised cholesterol level over the next 10 years" rated on a seven-point scale ranging from "not at all likely" (0) to "extremely likely" (6). A similar item was used to assess *perceived risk of heart attack*.

Emotional state.

1. *State anxiety* was assessed using the short-form of the state scale of the Speilberger State Trait Anxiety Inventory (STAI) [16]. The internal consistency of the scale was satisfactory (alpha = .84). A total of 108 participants (35%) scored above the cut-off of 42 for clinical levels of anxiety.
2. *Depression* was assessed using the depression subscale of the Hospital Anxiety and Depression Scale (HADS) [17]. The internal consistency of the scale was satisfactory (alpha = .84). A total of 58 participants (18%) scored 8 or above indicating possible mild to severe depression.

Ethics

Ethical committee permission to conduct the study was sought and obtained from the South Thames Multicentre Research Ethics Committee (Ref: 99/62) and the five appropriate Local Research Ethics Committees.

Procedure

Lipid clinic patients who met the eligibility criteria were sent information about the study by post. At three hospitals, information was sent two weeks before a routine clinic appointment and patients decided whether to participate at their routine hospital appointments. At two hospitals, information was sent to patients who were then invited to telephone to make a specific appointment for the study. Those who wanted to participate completed the consent form and were randomly-allocated to either a genetic or non-genetic diagnosis of FH. After the research nurse had taken the clinical assessments described above, participants were given a questionnaire to complete at home. The baseline questionnaire was, therefore, completed after the explanation of the study and random allocation but prior to receiving the results of the clinical assessment. A total of three postal reminders at fortnightly intervals were sent to participants who failed to return their questionnaires.

Statistics

Pro-rated mean scale scores were used to replace missing data when less than 20% of the total scale was missing. Seven variables were not normally distributed and were therefore transformed: length of attendance at the lipid clinic; length of awareness of having raised cholesterol; current total cholesterol level; depression; and, attributions for a heart attack to behaviour, genes, and cholesterol. Although transformed variables were used in all analyses, mean scores are presented for the untransformed variables for ease of interpretation.

A description of medication adherence is presented, followed by comparison of clinical and psychological factors between groups differing in their reported level of medication adherence. The statistical analysis consisted of chi-square analysis for categorical variables and t-tests for continuous variables.

Results

Participants and response rate

Overall uptake for the trial was 340 (68.5%), comprising 224 (84% uptake) people invited prior to a routine clinic appointment and 116 (50% uptake) people invited by post to make a specific appointment. A total of 336 individuals returned questionnaires (99.8% response rate).

Table 1. *Characteristics of the study participants*

	Frequency or range	Mean (SD)
Gender	156 men 180 women	
Age	24–79 years	55 years (12.5)
Ethnic group	320 white 15 other	
Educational achievement	119 no qualifications 139 school/higher 66 degree level	
History of CVD	98 history CVD 51 heart attack 57 CABG 14 angioplasty	
Symptoms of angina	53 Grade 1 angina 40 Grade 2 angina	
Awareness of raised cholesterol	2 months–50 years	9.8 years (8.1)
Attendance at lipid clinic	1 month–34 years	6.3 years (6.4)
Tendons xanthomata	153	
Corneal arcus	120	
Xanthelasma	93	
Untreated total cholesterol	6.00–16.10 mmol/l	9.58 (1.86) mmol/l
Current total cholesterol	3.70–14.60 mmol/l	6.50 (1.53) mmol/l

The individual and clinical characteristics of the sample are described in Table 1. There were no differences in any of the baseline measures between the groups allocated to receive a genetic or a non-genetic diagnosis in this trial. The difference between original untreated and current total cholesterol ranged from −2.70 mmol/l to 10.00 mmol/l (Mean = 3.12 mmol/l, SD = 2.17). Seventeen participants (6%) had a current cholesterol level that was the same or higher than their original untreated cholesterol and 288 participants (94%) had a current cholesterol level that was lower.

Self-reported medication adherence

A total of 295 participants (87.8%) stated that they were currently prescribed cholesterol-lowering medication. The mean self-reported adherence score was 4.71 (SD = 0.46) and scores ranged from 1.8 to 5.0 (possible range 1 to 5). Given the high level of reported adherence (indeed no participant reported poor adherence), this variable was not normally distributed and was dichotomised. A total of 104 participants (36.6%) reported total adherence to their cholesterol-lowering medication regimen. That is, they responded "never" to all five items assessing deviation from the regimen. A total of 180 (64.4%) reported some level of non-adherence, that is, responding other than "never" to at least one of the five items. The "total adherence" and "partial adherence" groups are compared in subsequent analysis.

Partial medication adherence consisted of the following: 59% ($n = 172$) who forget to take their medication; 15% ($n = 43$) who stop taking their medication; 14% ($n = 41$) who decide to miss out a dose; 6% ($n = 18$) who take less than instructed; and 5% ($n = 15$) who alter the dose of their medication.

Factors associated with medication adherence

Total cholesterol level. As shown in Table 2, the total adherence and partial adherence groups differed in current total cholesterol level but not in untreated total cholesterol. Current total cholesterol level was significantly lower in the total adherence group compared with the partial adherence group. From untreated to current levels, total cholesterol had decreased by a mean of 3.92 mmol/l (SD = 2.20) in the total adherence group and by a mean of 3.04 mmol/l (SD = 1.96) in the partial adherence group. This is a statistically significant difference, $t(255) = 3.32$, $p < .001$.

Clinical and individual factors. Men and women did not differ in their reported level of adherence, $\chi^2(1) = 1.10$. Nor did participants with and without angina or with and without xanthomata, $\chi^2(1) = 1.33$ and $\chi^2(1) = 2.26$ respectively. Participants with a personal history of heart disease were more likely to report being totally adherent (47%) than were participants with no personal history of heart disease (31%), $\chi^2(1) = 6.88$, $p < .01$.

Participants with no formal educational qualifications were more likely to report total adherence (54%) than those with school-level qualifications (26%) or degree-level qualifications (25%), $\chi^2(2) = 22.87$, $p < .001$. A likely explanation for this finding is that the participants with no qualifications were significantly older (Mean = 61.8 years, SD = 9.0) than those with qualifications (Mean = 50.5 years, SD = 12.1), $t(302.88) = 9.55$, $p < .001$. In addition, the total adherence group were older (Mean = 59.4 years, SD = 10.3 years) than the partial adherence group (Mean = 53.0 years, SD = 12.2 years; $t(244.74) = 4.79$, $p < .001$). The two groups did not differ in the length of their awareness of having a raised cholesterol or length of attendance at the lipid clinic.

Emotional state and illness perceptions. As shown in Table 2, the total adherence group, compared with the partial adherence group, perceive greater control over FH, perceive themselves to be less at risk for a raised cholesterol, and attribute importance to both genes and cholesterol in causing a potential heart attack. The two groups did not differ in terms of their mood state, perceptions of control over cholesterol and over heart disease, perceived risk of a heart attack, or attributing importance to either behaviour or chance in causing a potential heart attack.

Predictors of medication adherence. Hierarchical logistic regression analysis was used to investigate the extent to which illness perceptions predicted

Table 2. *Association of medication adherence with total cholesterol level and psychological factors*

	Partial adherence ($n = 180$)	Total adherence ($n = 104$)	T value
Current total cholesterol mmol/l	6.46 (1.49)	6.03 (1.27)	2.42*
Untreated total cholesterol mmol/l	9.47 (1.68)	9.92 (2.12)	1.77
Emotional state			
Anxiety	37.77 (13.60)	38.16 (13.68)	0.23
Depression	4.08 (3.65)	3.89 (3.51)	0.24
Perceptions of control			
Perceived control over FH	4.01 (0.47)	4.17 (0.50)	2.67**
Perceived control over cholesterol	4.15 (0.96)	4.22 (0.98)	0.55
Perceived control over heart disease	4.00 (1.01)	3.87 (0.94)	1.04
Perceptions of risk			
Perceived risk of high cholesterol	3.38 (1.65)	2.82 (1.61)	2.72**
Perceived risk of heart attack	2.88 (1.42)	3.17 (1.36)	1.69
Causal attributions for heart attack			
Behavioural attribution	4.38 (1.46)	4.68 (1.36)	1.69
Chance attribution	2.24 (1.77)	2.34 (1.96)	0.43
Genetic attribution	4.65 (1.44)	5.10 (1.14)	2.51*
Cholesterol attribution	5.03 (1.13)	5.23 (1.26)	2.00*

$*p < .05$; $**p < .01$; for two-tailed tests of probability.

medication adherence over and above the effect of demographic and clinical variables. Only the illness perceptions associated with medication adherence in univariate analysis were entered into the regression. On the first step, age, gender, qualifications (no qualifications versus any), history heart event, presence xanthomata, angina symptoms, and length of attendance at lipid clinic were entered. On the second step, perceived control over FH, perceived risk of raised cholesterol, attributions to genes, and attributions to cholesterol were entered. In the final model, $\chi^2(11) = 40.70$, $p < .001$ and χ^2 was significant at both the first step, $\chi^2(7) = 28.17$, $p < .001$, and the second step, $\chi^2(4) = 12.58$, $p < .05$. Thus, illness perceptions did make a significant contribution to the prediction of medication adherence over and above the effect of demographic and clinical factors. The individual variables that were significantly associated with medication adherence were personal history of a heart event, B = −0.81, wald = 5.39, $p < .05$, OR = 0.44 (95% CI: 0.22–0.88); having no formal educational qualifications, B = 0.89, wald = 8.03, $p < .01$, OR = 2.45 (95% CI: 1.32–4.55), and attributing greater importance to genes, B = 0.27, wald = 5.18, $p < .05$, OR = 1.31 (95% CI = 1.04–1.64).

Discussion

The aims of the present study were to describe self-reported adherence to cholesterol-lowering medication in a population of patients diagnosed with FH and to assess the extent to which both clinical factors and patients' perceptions of FH are associated with adherence. With respect to the first aim, self-reported medication adherence was high and a substantial proportion of participants, some 36%, reported that they never deviate from their recommended treatment regimen. The remaining 64% of participants reported some level of deviation from the recommended regimen. These figures are comparable with a study of French hyperlipidaemic patients amongst whom 42% reported total adherence and 39% reported missing less than 6% of their prescribed medication [11].

Debate surrounds the validity of self-report measures of adherence with the suggestion that these reports are subject to both self-presentational and recall biases in the direction of over reporting adherence [18]. Although it is likely that patients over-report their level of adherence there is some biochemical evidence for the validity of the measure used in the present study. Despite the fact that none of the participants reported particularly poor adherence (e.g. taking less than 75% of their prescribed medication), those reporting total adherence had lower total cholesterol levels than those reporting partial adherence. This effect cannot be explained by a difference in untreated cholesterol levels between the two groups. Thus, this type of self-report measure appears to be sensitive to potentially clinically significant differences in adherence behaviour. The type of partial adherence most frequently reported was occasionally forgetting medication rather than reporting intentional deviation from the recommended regimen.

The second aim of the study was to investigate whether differences in medication adherence can be explained by either the clinical history of the patient or by patient perceptions of FH and heart disease. Patients with a personal history of heart disease were more likely to be totally adherent than patients with no personal history. History of heart disease was a significant predictor of adherence in logistic regression analysis. It is possible that the threat of heart disease needs to be concrete to motivate long-term adherence to medication. However there were no differences in adherence between patients with and without xanthomata and patients with and without angina. In addition, patients

who were older and who had no formal educational qualifications were more likely to report total adherence. Indeed having no qualifications was a significant predictor of adherence in logistic regression analysis. Unfortunately our measure of educational achievement is flawed in that many participants would have been in education prior to the introduction of GCEs in 1951 (in the present study those with no qualifications had a mean age of 61 years). Also, we did not assess the nature or frequency of the medication regimen, but previous research suggests that these factors would also be associated with adherence [3].

There were a few small differences in patient perceptions between the total adherence and partial adherence groups. The total-adherence group perceived greater control over FH and perceived less risk of having a raised cholesterol in the future than the partial-adherence group. These associations are similar to those reported previously [11]. Patients' perceptions of the likely cause of a heart attack also had small but significant associations with medication adherence. The total-adherence group believed more strongly that a heart attack would be caused by their genes or by their cholesterol level than the partial adherence group. A stronger belief that a heart attack would be caused by genes was the only patient perception variable that predicted adherence over and above the effect of clinical and demographic factors in hierarchical logistic regression analysis. It may be that an understanding of, and belief in, the genetic causes of FH and chronic nature of the condition helps in motivating long-term adherence. The present data are taken from the baseline assessment in a trial of genetic and non-genetic diagnosis of FH [13]. In this trial we found no main effect of having a genetic diagnosis on medication adherence, although the genetic diagnosis did result in greater endorsement of genetic causes of FH and CHD. Alternatively, it may be the experience that drug interventions are effective, whilst dietary interventions are not, reinforces belief in the efficacy of drug-based intervention and in the genetic causes of FH. Thus, this finding may be peculiar to patients with FH and may not generalise to patients diagnosed with non-genetic forms of hyperlipidaemia.

Neither anxiety nor depression was associated with medication adherence in the present study. Although this is comparable to a previous study of hyperlipidaemic patients [11], it is at odds with a recent meta-analysis which found that depressed patients were three times more likely to be non-adherent than non-depressed patients [19]. In this meta-analysis, which used data from patients with a variety of chronic conditions, there was no consistent relationship between anxiety and adherence. In the present study, 18% of participants scored above the cut-off for possible clinical levels of depression. However only a small proportion of these scored towards the more severe end of the depression scale and therefore this lack of effect may be due to the low numbers of depressed patients in this population.

There are a number of limitations to the present study that may compromise the generalisability of these findings. Although the sample size and study uptake rate are reasonable, this sample comprises of a highly motivated and compliant group of patients given that they all attend a lipid clinic on a regular basis and agreed to take part in a trial of genetic testing for FH. This may help to explain the high mean level of reported medication adherence and the fact that there was very little variance in the measure. In addition, we did not systematically record the type and number of different therapies prescribed to our participants. These variables have been shown to be important determinants of adherence in previous research [3]. The cross-sectional nature of the present study precludes any analysis of causal relationships. Thus, patient perceptions of FH and heart disease are as likely to be a consequence, as a cause, of adherence.

These findings suggest that interventions that target patient perceptions in an attempt to increase medication adherence are likely to be unsuccessful, at least in such a compliant population. This is because we found only small associations between perceptions and behaviour. Thus, large changes in illness perceptions would be necessary for small changes in behaviour. As those reporting partial adherence had higher total cholesterol levels, interventions that shift these people towards total adherence could have clinical benefits. These people mostly reported forgetting medication rather then intentional deviation. Thus, interventions that help patients establish a routine of medication taking may be effective. Interventions that establish environmental contingencies for the behaviour, rather than relying purely on patient memory and motivation, have been effective in other domains and could prove equally effective here [20]. These interventions (sometimes termed implementation intention or action plan interventions) typically require the patient to think about and specify "when", "where", and "how" they will perform the desired behaviour. Memory of the action plan is triggered when the specific situation is encountered, thus making performance of the behaviour more likely. This type of intervention has been successful in increasing adherence to taking vitamin C tablets in one study with students [21]. It remains to be determined whether this approach will prove effective in encouraging long-term adherence to cholesterol-lowering medication.

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