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ORIGINAL ARTICLE

Association between non-adherence behaviors, patients' experience with healthcare and beliefs in medications: a survey of patients with different chronic conditions

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ABSTRACT

Objective: The objective of the current work was to assess the frequency of non-adherence behaviors and potential association with patients' experience with healthcare and beliefs in medicines self-reported by patients with four different chronic conditions.

Methods: Patients responded anonymously to a survey comprising five non-adherence behaviors (based on physician and patient input), an assessment of patients' experience with healthcare using the validated Instrument to Evaluate the EXperience of PAtients with Chronic diseases (IEXPAC), and a validated Spanish version of the Beliefs about Medicines Questionnaire (BMQ). Associations of non-adherence behavior were analyzed using logistic regression models.

Results: Of 1530 respondents, 53.1% reported ≥1 non-adherence behavior. Non-adherence rates were 59.8% in diabetes mellitus (DM), 56.0% in rheumatic disease, 55.6% in inflammatory bowel disease, and 42.8% in human immunodeficiency virus (HIV) infection patients ($p < .001$). IEXPAC and BMQ scores were higher in adherent vs. non-adherent patients. In multivariate analysis, non-adherence behavior was strongly associated with lower overall BMQ, lower BMQ Necessity scores and higher BMQ Concerns scores ($p < .001$ for all), and with a lower IEXPAC self-management score ($p = .007$), but not with the overall IEXPAC score. Non-adherence was more frequent in DM patients compared with HIV infection patients ($p < .001$).

Conclusions: Patients' beliefs in medicines-a lower perception for the necessity of medication, and higher concerns in taking medication-and low patient self-management experience score were associated with non-adherence behavior. These are modifiable aspects that need to be addressed to increase medication adherence in chronic disease.

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Chronic disease; medication adherence; surveys and questionnaires; patient preference; patient satisfaction; beliefs about medicines

Introduction

Adherence rates to long-term therapy of chronic diseases are typically lower than those for acute diseases, averaging around 50% in developed countries, with rates showing a dramatic reduction after the first 6 months of treatment, especially in non-symptomatic conditions or in diseases with periods of inactivity[1,2]. Non-adherence to therapy can be unintentional due to unplanned behavior, or intentional reflecting a rational decision-making process in which patient beliefs and the level of cognition are important factors in the process[3,4].

Several factors are related to non-adherence (i.e. patient-, disease-, condition-, social/economic- and health system-related[1,2]). In chronic disease, several studies have shown a relationship between adherence and patients' beliefs in medicines[5–12]. Higher adherence rates in chronic disease have also been equated with better patient experiences with current and past care[13,14]. Both patients' beliefs and patients' experiences are relevant because they have the potential to be modified using a patient-centered approach from the clinical teams.

With the number of patients with chronic conditions increasing dramatically, the real challenge is not only to identify non-adherent patients but to prevent non-adherence behaviors to achieve better outcomes[1,2]. Understanding the impact of patients' experiences and patients' beliefs' on non-adherence behaviors is very relevant because it can guide the implementation of specific preventative actions for patients with chronic conditions. Although studies have demonstrated a link between patients' beliefs in medicines

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and patients' healthcare experience with adherence[5–10], to the best of our knowledge, no studies have been conducted that have included both experience with healthcare and beliefs in medications as covariates for their association with behaviors of medication adherence/non-adherence in patients with different chronic conditions. Moreover, it is also important that this information is self-reported by patients to avoid potential bias imposed by the intervention of the clinical team.

The objective of the current work was to assess the frequency of non-adherence behaviors and their potential association with patients' experience with healthcare and beliefs in medicines, in a large group of patients with chronic diseases who self-reported information on these topics via an anonymous survey.

Methods

A cross-sectional survey was handed to 2474 adult patients with four chronic diseases: diabetes mellitus (DM), human immunodeficiency virus (HIV) infection, inflammatory bowel disease (IBD) or rheumatic diseases, as described previously[15]. The survey content was developed by a group of physicians with experience in the care of the abovementioned patients, with input from members of patients' associations, which reviewed and approved the final content and endorsed the project. The protocol, instructions for patients and survey content were reviewed and approved by the Clinical Research Ethics Committee of the Gregorio Marañón Hospital of Madrid, Spain. Due to the anonymous nature of the survey, and as agreed by the Clinical Investigation Ethics Committee, the voluntary return of completed surveys was taken as patient implied consent to participate in the survey. There was no collection of data from clinical charts.

The survey included multiple-choice questions concerning patient demographics and healthcare-related characteristics, the Instrument to Evaluate the EXperience of PAtients with Chronic diseases (IEXPAC) Questionnaire[16] and the Beliefs About Medicines (BMQ) Questionnaire[17]. Five non-adherence behaviors were agreed by both physicians and patients: (1) forgetfulness in taking medication resulting in skipped doses; (2) taking doses of medication at unscheduled hours; (3) stopping the medication when feeling well; (4) stopping medication if it makes the patient feel unwell; (5) and stopping medication after reading the patients' information leaflet.

The IEXPAC tool, which was developed and validated in Spain[16], was used to evaluate patients' experience with healthcare. IEXPAC is a 12-item instrument involving 11 items which refer to patients' experiences within the previous 6 months, and the 12th item concerning hospitalization, which refers to patient experience within the previous 3 years. Answers are recorded on a 5-point Likert Scale ranging from always (scored as 10) to never (scored as 0). The overall IEXPAC score is the sum of scores from items 1–11 divided by eleven. In addition, three factors are derived from these items: Factor 1 termed "productive interactions" is the average of the scores for items 1, 2, 5, and 9 and refers to the characteristics and content of interactions between patients and professionals; Factor 2, termed the "new relational model" is the average of scores for items 3, 7, and 11 and refers to new forms of patient interaction with the healthcare system, via the internet, or with peers; and Factor 3, termed "patient self-management" is the average of scores for items 4, 6, 8, and 10 and refers to the ability of patients to manage their own care and improve their well-being, following interventions mediated by healthcare professionals[16].

The BMQ assesses patients' beliefs about disease-specific drugs (BMQ-Specific) used to control their illness[17]. The validated Spanish version of BMQ[18] was used in this study. This 10-item questionnaire covers two domains - Necessity and Concerns consisting of five statements per domain. Patient response is indicated on a 5-point Likert Scale, ranging from strongly agree (scored as 5) to strongly disagree (scored as 1). Scores are summed for each individual item, and total scores for the Necessity and Concerns domains (each ranging from 5 to 25) are also calculated. Higher scores in the Necessity Scale indicate stronger beliefs in the necessity of the prescribed medication; in the Concerns Scale, higher scores indicate more concern about taking the medication. The overall BMQ score is calculated as the difference between the Necessity Scale and Concerns Scale scores, with a possible range of -20 to $+20$.

Statistical analysis

The survey was exploratory, and no formal hypothesis or pre-specified sample size was calculated. The sample size was conservatively estimated based on the prevalence of a qualitative variable (50%), confidence intervals (CI; 95%), precision (6%) and incorrectly completed questionnaires (15%), which yielded an initial sample size of 314 patients for each of the four chronic diseases studied. Assuming an expected response rate of 50%, the final sample size was 628 patients for each disease. Thus, we planned to hand the survey to $\sim$2500 patients (625 patients for each chronic disease)[15].

Quantitative variables are described by mean and standard deviation (SD), and qualitative variables using frequencies or percentages. The main variable studied was the presence of at least one non-adherence behavior, dichotomized as a binary variable, and described by percentage. A sensitivity analysis was also performed considering the number of non-adherence behaviors as the main variable instead of treating it as a binary variable.

Differences in the frequency of the main variable (presence of at least one non-adherence behavior) in bivariate analysis were analyzed with χ^2 or Fisher exact tests. The Student *t*-test was used to compare the IEXPAC and BMQ scores in patients with or without non-adherence behaviors. Association between the presence of non-adherence behaviors with demographic, treatment-related variables, and IEXPAC and BMQ scores, were studied with logistic regression models. Odds ratios with 95% CI were calculated.

Results

The survey was handed to 2474 patients and was returned by 1618 patients, giving a response rate of 65.4%. A total of 1530 patients were suitable for study of medication adherence (336 with rheumatic disease [22.0%], 322 with IBD [21.0%], 442 with HIV infection [28.9%], and 430 with DM [28.1%]). The 88 patients excluded from this analysis did not provide reliable information for questions relating to adherence, thus precluding their classification as with/without non-adherence behaviors. The mean age was 56.2 (14.6) years, and 59.2% of patients were male. The demographic characteristics and distribution of the current population were similar to the overall population, as described by Orozco-Beltran et al.[15].

Non-adherence behaviors

Of 1530 patients, 813 (53.1%, 95% CI, 50.6–56.6) reported at least one non-adherence behavior. The proportion of patients reporting non-adherence ranged from 42.8% (189 of 442) for patients with HIV infection to 59.8% (257 of 430) for patients with DM; differences between the four chronic diseases were statistically significant ($p < .001$). Specific non-adherence behaviors, presented in Table 1, showed significant differences between the four diseases for stopping medication "when feeling well", "if it makes the patient feel unwell", and "after reading the patients' information leaflet" ($p < .001$ for all). Compared with DM, IBD and rheumatic disease, patients with HIV infection had the lowest proportion of patients for each of these non-adherence behaviors (Table 1).

The proportion of patients with at least one non-adherence behavior was similar in men and women ($p = .323$), and by age quartiles ($p = .424$), and was slightly higher in patients who declared having no educational level achievement (67.4%, $p = .056$; Supplementary Table 1). Regarding medication, the proportion of patients with non-adherence behavior did not differ by number of medicines taken daily but was higher in patients who took their medications 3 or 4 times per day (58.1%) compared with those taking medication once or twice per day (50.2%, $p = .004$; Supplementary Table 1).

Patients' experience with healthcare, beliefs about medicines and non-adherence behaviors

Table 2 shows the overall IEXPAC score, Factors 1–3 scores and patients' responses to each IEXPAC statement, stratified by adherence/non-adherence. The overall IEXPAC score, and Factor 1 (productive interactions) and Factor 3 (self-management) scores were significantly higher in patients without non-adherence behaviors ($p < .001$ for all). Factor 2 scores (new relational model) were similar in both groups (Table 2).

The proportion of patients who responded always/mostly to Factor 1 and Factor 3 statements were generally high and slightly higher in patients without non-adherence behaviors, except for statement 9 ("They worry about my welfare"), which was high in both groups, and statement 10 ("I have been informed about health and social resources that can help me"), which was low in both groups. The proportions of patients answering always/mostly were similar for Factor 2 statements and did not differ between patients with or without non-adherence behaviors (Table 2).

Figure 1 shows the proportion of patients with at least 1 non-adherence behavior displayed by quartiles of overall IEXPAC and Factor scores, with patients in quartile 1 having the lowest scores (worse experience) and those in quartile 4 having the highest scores (better experience). Significant differences between the quartiles were found for overall IEXPAC scores and for Factor 1 and Factor 3 scores, with higher frequencies of non-adherence in patients with lower experience scores (all p linear-trend values $<.001$), but not for Factor 2 score. This linear relationship was also seen when patients were stratified by number of non-adherence behaviors present in 4 groups ($n = 0$, $n = 1$, $n = 2$, $n = 3$ or more non-adherence behaviors). Higher frequencies of 3 or more non-adherence behaviors were seen in patients in the lowest quartiles of IEXPAC scores, whilst higher frequencies of zero non-adherence behavior were seen in the highest experience quartiles (p linear-trend $<.001$, Supplementary Table 2).

Table 3 shows the overall BMQ score, and Necessity and Concerns Scale scores in patients with or without non-adherence behaviors, and the proportion of patients giving strongly agree/agree responses to individual BMQ items. Patients with non-adherence behaviors had significantly lower overall BMQ and Necessity Scale scores, and significantly higher Concerns Scale compared with patients without non-adherence behavior ($p < .001$ for all).

In general, the proportion of patients who strongly agreed/agreed with the Necessity statements was high (>70%), and all of them were higher in patients without non-adherence behaviors. A meaningful proportion of patients strongly agreed/agreed with the Concerns statements: for example, 44.1 and 61.4% strongly agreed/agreed with the statements "Having to take my medicines worries me" and "I sometimes worry about the long-term effects of

Table 1. Prevalence of non-adherence behaviors in chronic diseases.

	All patients ($n = 1,530$)	Rheumatic disease ($n = 336$)	IBD ($n = 322$)	HIV infection ($n = 442$)	DM ($n = 430$)	p-Value
At least one non-adherence behavior, n (%)	812 (53.1)	188 (56.0)	179 (55.6)	189 (42.8)	257 (59.8)	<.001
Forgetfulness in taking medication (skipping doses), n (%)	496 (32.4)	96 (28.6)	117 (36.2)	140 (31.6)	143 (33.3)	.199
Taking medication at unscheduled hours, n (%)	89 (5.8)	19 (5.6)	18 (5.5)	22 (5.0)	31 (7.1)	.588
Stopping medication when feeling well, n (%)	90 (5.9)	34 (10.1)	21 (6.5)	11 (2.5)	25 (5.7)	<.001
Stopping medication if it makes the patient feel unwell, n (%)	418 (27.3)	111 (33.0)	91 (28.3)	55 (12.5)	160 (37.2)	<.001
Stopping medication after reading the patients' information leaflet, n (%)	179 (11.7)	39 (11.5)	27 (8.4)	30 (6.8)	83 (19.4)	<.001

Abbreviations. DM, Diabetes mellitus; HIV, Human immunodeficiency virus; IBD, Inflammatory bowel disease.

Table 2. Overall IEXPAC and Factor scores in patients with or without non-adherence behaviors, and the proportion of patients giving always/mostly responses to individual IEXPAC items.

	All patients	Patients with ≥1 non-adherence behavior	Patients without non-adherence behavior	*p*-Value
IEXPAC and Factors, mean (SD)				
IEXPAC overall score	6.0 (1.9)	5.8 (1.9)	6.2 (1.9)	< .001
Factor 1: Productive interactions score (items 1, 2, 5, and 9)	8.0 (2.2)	7.8 (2.2)	8.3 (2.2)	< .001
Factor 2: New relational model score (items 3, 7, and 11)	2.0 (2.3)	2.1 (2.2)	2.0 (2.3)	.193
Factor 3: Self-management score (items 4, 6, 8, and 10)	7.1 (2.3)	6.8 (2.3)	7.4 (2.3)	<.001
IEXPAC items		Always/mostly responses (%)		*p*-Value
1. They respect my lifestyle The professionals who care for me listen to me and ask me about my needs, habits and preferences to adapt my treatment and care plan	81.5	78.9	84.3	.007
2. They are coordinated to offer good health care to me Health and social care services are coordinated to improve my wellbeing and quality of life in my environment (family, neighborhood, town).	69.1	66.1	72.5	.008
3. They help me to get information from the internet The professionals who care for me inform me about trustful webpages and internet forums that I can consult to know my disease better, its treatment and the consequences they may have on my life.	15.0	16.0	13.8	.233
4. Now I can take care of myself better I feel that my confidence in my ability to take care of myself, manage my health problems and keep my autonomy has improved.	80.8	76.2	86.1	<.001
5. They ask me and help me to follow my treatment plan I regularly review adherence to my treatment and care plan with the professionals who care for me.	79.5	76.1	83.3	.001
6. We set goals for a healthy life and better control my illness I've been able to agree with the professionals who care for me on specific objectives regarding diet, physical exercise and medication to get better control of my health problems.	69.8	65.8	74.3	<.001
7. I can use the internet and my mobile phone to consult my medical records I can consult my clinical record, tests results, programmed visits and access to other services through the internet or the mobile app of my health service.	7.2	6.4	8.0	.241
8. They make sure that I take medication correctly The professionals who care for me review with me all of the medication I take, how I take it and how it suits me.	75.8	71.8	80.3	<.001
9. They worry about my welfare The professionals who care for me are concerned with my quality of life and I feel they are committed to my wellbeing.	84.1	82.9	85.6	.151
10. I have been informed on health and social resources that can help me The professionals who care for me inform me about health and social resources available in my neighbourhood or town that I can use to improve my health problems and take better care of myself.	41.3	39.1	43.8	.067
11. They encourage me to talk to other patients The professionals who care for me invite me to participate in patients groups to share information and experiences on how to care for ourselves and improve our health. Respond to the following statement only if you have been admitted to the hospital in the last 3 years	14.7	15.2	14.3	.647
12. They care about me when I come home after being in the hospital After hospital discharge, they have called or visited me at home to see how I was and what care I needed.	30.5	31.0	30.1	.783

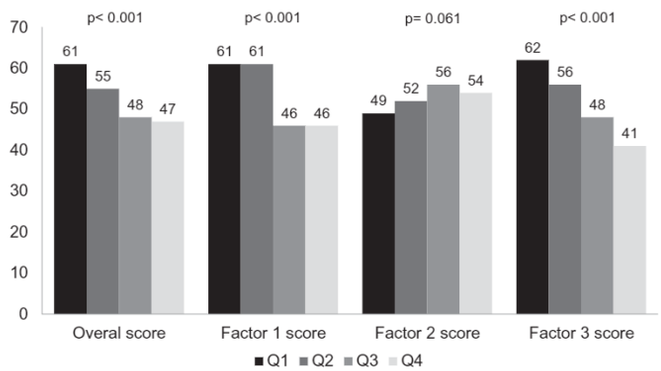

Figure 1. Frequency of at least one non-adherence behavior by quartiles (Q) of IEXPAC experience scores. Quartiles of IEXPAC overall score: Q1: <4.77; Q2: 4.77–6.36; Q3: 6.36–7.27; Q4: >7.27. Quartiles of Factor 1 (productive interactions) score: Q1: <6.87; Q2: 6.87–8.75; Q3: 8.75–10.0; Q4: >10.0. Quartiles of Factor 2 (new relational model) score: Q1: 0; Q2: 0–1.66; Q3: 1.66–3.33; Q4: >3.33. Quartiles of Factor 3 (patient self-management) score: Q1: <5.62; Q2: 5.62–7.50; Q3: 7.50–8.75; Q4: >8.75. *p*-Values denote linear trend.

my medicines". The proportion who strongly agreed/agreed with Concerns statements were even higher in patients with non-adherence behaviors (Table 3).

Figure 2 shows the proportion of patients with ≥1 non-adherence behavior displayed by quartiles of overall BMQ and Necessity and Concerns Scale scores, with patients in quartiles 1 and 4 having the lowest and highest scores, respectively. Significant differences between the quartiles were found for overall BMQ and Necessity Scale scores (*p* linear-trend values < .001), with the highest proportion of non-adherent patients found in quartile 1 (weaker beliefs). There were also significant differences between the quartiles for the Concerns Scale scores (*p* linear-trend <.001), with the highest proportion of non-adherent patients found in quartile 4 (higher concerns). Likewise, there was a linear relationship between beliefs scores and number of non-adherence behaviors, with the highest percentages of

Table 3. Overall Beliefs about Medicines Questionnaire (BMQ), Necessity and Concerns Scale scores in patients with or without non-adherence behaviors, and the proportion of patients giving strongly agree/agree responses to individual BMQ items.

	All	Patients with ≥ 1 non-adherence behavior	Patients without non-adherence behavior	*p*-Value
BMQ and factors, mean (SD)				
BMQ overall score	6.6 (6.3)	5.2 (6.1)	8.2 (6.3)	<.001
Necessity Scale score	21.0 (4.1)	20.4 (4.3)	21.8 (3.8)	<.001
Concerns Scale score	14.4 (4.6)	15.1 (4.3)	13.5 (4.8)	<.001
		Strongly agree/agree (%)		*p*-Value
Necessity Scale				
My health, at present, depends on my medicines	84.8	81.1	88.9	<.001
My life would be impossible without my medicines	75.7	70.7	81.3	<.001
Without my medicines, I would be very ill	78.9	74.6	83.7	<.001
My health, in the future, will depend on my medicines	81.3	77.2	85.9	<.001
My medicines protect me from becoming worse	87.7	86.1	89.6	.037
Concerns Scale				
Having to take my medicines worries me	44.4	51.1	36.8	<.001
I sometimes worry about the long-term effects of my medicines	61.4	65.0	57.4	.003
My medicines are a mystery to me	26.6	27.4	25.6	.446
My medicines disrupt my life	16.2	18.2	13.8	.020
I sometimes worry about becoming too dependent on my medicines	33.7	38.4	28.4	<.001

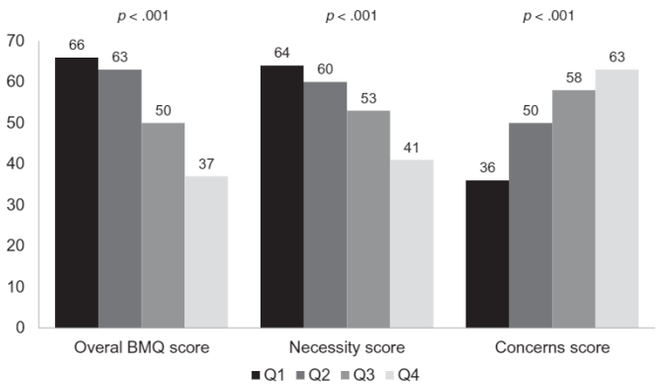

Figure 2. Frequency of at least one non-adherence behavior by quartiles (Q) of BMQ beliefs in medicines scores. Quartiles of BMQ overall score: Q1: <2; Q2: 2–6; Q3: 6–11; Q4: >11. Quartiles of Necessity Scale score: Q1: <19; Q2: 19–21; Q3: 21–25; Q4: >25. Quartiles of Concerns Scale score: Q1: <11; Q2: 11–15; Q3: 15–18; Q4: >18. *p*-Values denote linear trend.

patients with 2 or with 3 or more non-adherence behaviors found in the lowest quartiles of beliefs scores, and the higher frequencies of zero non-adherence behaviors in the highest beliefs quartiles (*p* linear-trend <.001, Supplementary Table 3).

Multivariate analysis

The impact of different variables in the presence of ≥1 non-adherence behavior was studied in two logistic regression models. The first model included age, gender, background disease, number of medicines per day, number of times per day taking medication, overall IEXPAC and BMQ scores (Table 4). Non-adherence was positively associated with DM (Odds Ratio [OR] = 2.17, 95% CI 1.43–3.29, $p < .001$ compared with patients with HIV infection), and negatively associated with Beliefs score (OR per unit of BMQ score increment = 0.93, 95% CI 0.91–0.95, $p < .001$). Associations with the taking of medication 3-4 times per day and the number of medicines per day did not reach statistical significance. Similar results were seen when the study variable was treated as an ordinal variable (number of non-adherence behaviors); the number of non-adherence behaviors was inversely related to BMQ score ($p < .001$) and the association with the taking of medication 3–4 times reached statistical significance ($p = .035$). In the second model, overall scores were substituted by IEXPAC Factor scores (productive interactions, new relational model and self-management) and BMQ Necessity and Concerns Scale scores. Non-adherence was positively associated with DM (OR = 2.29, 95% CI 1.47–3.56, $p < .001$ compared to patients with HIV infection), negatively associated with IEXPAC self-management score (OR per unit of increment = 0.87, 95% CI 0.79–0.96, $p = .007$) and with BMQ Necessity score (OR per unit of increment = 0.93, 95% CI 0.90–0.97, $p < .001$), and positively associated with Concerns score (OR per unit of increment = 1.08, 95% CI 1.04–1.11, $p < .001$) (Table 4). These associations were also found when the number of non-adherence behaviors was studied (*p*-values for self-management, Necessity, and Concerns scores: .003, <.001, and <.001, respectively).

Due to the observed association between background disease and non-adherence behaviors, we performed multivariate analysis for each group of patients to assess whether variables associated with non-adherence differed (Supplementary Tables 4(a–d)). In patients with IBD, non-adherence was inversely associated with IEXPAC experience and BMQ beliefs scores ($p = .025$ and $p = .004$) in model 1 and directly to Concerns score ($p = .006$) in model 2. In rheumatic disease patients, only an inverse association of non-adherence with beliefs score was found in model 1 ($p = .052$). In patients with HIV infection, non-adherence was associated with lower beliefs score ($p = .003$), younger age ($p = .020$) and female sex ($p = .005$) in model 1, and with younger age ($p = .046$), female sex ($p = .005$) and higher Concerns score ($p = .018$) in model 2. Finally, non-adherence in DM patients was inversely associated with beliefs score ($p < .001$) in model 1, whilst in model 2 was associated with higher Concerns score ($p = .001$) and lower Necessity and self-management scores ($p = .028$

Table 4. Multivariate analyses of variables associated with the presence of ≥1 non-adherence behavior.

Variable	Model 1 (IEXPAC and BMQ overall scores)		Model 2 (IEXPAC and BMQ sub-scores)	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Age (1-year increment)	0.99 (0.98–1.00)	.219	0.99 (0.98–1.01)	.476
Gender (female versus male)	1.09 (0.83–1.43)	.558	1.12 (0.84–1.49)	.448
Chronic condition: DM (versus HIV infection)	2.17 (1.43–3.29)	<.001	2.29 (1.47–3.56)	<.001
Chronic condition: IBD (versus HIV infection)	1.26 (0.86–1.85)	.244	1.19 (0.80–1.77)	.398
Chronic condition: rheumatic disease (versus HIV infection)	1.21 (0.81–1.81)	.349	1.16 (0.77–1.76)	.485
Needing to take medication 3–4 times per day (versus 1–2 times per day)	1.34 (0.98–1.83)	.069	1.29 (0.93–1.79)	.135
Number of different medicines (1-unit increment)	0.95 (0.91–1.00)	.071	0.96 (0.91–1.01)	.095
IEXPAC, overall score (1-unit increment)	0.98 (0.91–1.05)	.516		
IEXPAC Factor 1: productive interactions score (1-unit increment)			1.08 (0.98–1.18)	.146
IEXPAC Factor 2: new relational model score (1-unit increment)			1.07 (1.00–1.14)	.064
IEXPAC Factor 3: self-management score (1-unit increment)			0.87 (0.79–0.96)	.007
BMQ, overall score (1-unit increment)	0.93 (0.91–0.95)	<.001		
BMQ Necessity score (1-unit increment)			0.93 (0.90–0.97)	<.001
BMQ Concerns score (1-unit increment)			1.08 (1.04–1.11)	<.001

Abbreviations. BMQ, Beliefs about Medicines Questionnaire; CI, Confidence interval; DM, Diabetes mellitus; HIV, Human immunodeficiency virus; IBD, Inflammatory bowel disease; IEXPAC, Instrument to Evaluate the Experience of Patients with Chronic diseases; OR, Odds ratio.

and $p = .001$). Associations in these cases are limited by the much lower sample sizes of each group.

Discussion

In the current work, we describe associations of non-adherence behaviors with patients' experience with healthcare, and with patients' beliefs in medicines, which were assessed using the validated instruments IEXPAC[16] and BMQ-Specific[17,18], respectively. Patients' responses were obtained through an anonymous and voluntary survey, which should have minimized the potential bias that can be imposed by healthcare professionals when they seek information from patients directly.

In multivariate analysis, we found a strong association of non-adherence with lower scores in the overall BMQ, and also with lower BMQ Necessity and higher BMQ Concerns scores. Thus, patients with strong beliefs in the necessity for their medication and with fewer concerns about taking their medication have a lower frequency of non-adherence behaviors. An association with the overall IEXPAC score was not apparent, although a lower self-management IEXPAC score (Factor 3) was associated with non-adherence behavior. Thus, our study identified several aspects of healthcare and patients' beliefs that have the potential to be addressed in clinical practice with programs that ultimately aim to prevent patients' non-adherence behaviors. Associations of non-adherence with beliefs in medications and IEXPAC self-management scores were also found when the population was stratified by number of non-adherence behaviors, which give strength to the observed results.

Non-adherence behaviors were less frequent in patients with HIV infection compared to patients with other chronic conditions. Moreover, we found a strong association of non-adherence with DM compared with patients with HIV infection in the multivariate analysis. A recent US study that compared adherence rates (assessed by the proportion of days covered) in three chronic conditions found that diabetes had the lowest adherence rate (45.0%) compared with hypertension (56.6%) and hyperlipidemia (52.2%)[19]. A meta-analysis of 17 disease conditions also found that mean adherence was superior in HIV disease (88.3%) compared with diabetes (67.5%)[20]. Non-adherence behavior in the present study was 59.8% for DM (i.e. adherence, 40.2%), 56.0% for rheumatic disease, 55.6% for IBD and 42.8% for HIV infection. A more personalized and comprehensive approach to HIV patients' healthcare, implemented by specialized HIV clinics in Spain during the past decades, and the substantial involvement of these patients in their care, probably account for these differences. Nevertheless, there is still considerable room for improvement for HIV patients, given that more than 40% in this study had non-adherence behaviors, and a recent meta-analysis concluded that only 62% of HIV patients adhered to intake of >90% of their prescribed antiretroviral drugs[21]. The higher frequency of non-adherence in DM patients deserves future research of potential associated factors that may explain this difference. Specific multivariate analysis for each subgroup of patients comprising our sample revealed several differences in the variables associated with non-adherence. Of special interest is the finding, in the group of patients with HIV infection, of a strong association of non-adherence with younger age and female sex, which was not found in patients with other background diseases. Though these multivariate analyses are limited by smaller sample sizes, these associations in the HIV group deserve further investigation of the potential social- or disease-related circumstances with the aim of implementing corrective measures.

To the best of our knowledge, no previous studies have formally assessed the potential impact of two modifiable aspects – the experience of patients with healthcare and their beliefs in medicines – on non-adherence to medication, with all these aspects being self-evaluated by patients without intervention from clinical teams. Previously, the impact of health beliefs and perception of disease control on medication adherence in patients with chronic disease were ascertained in a small patient-focus group study which showed that patient motivation and patient-prescriber relationships were important factors in determining medication adherence[22]. The potential to improve medication adherence by addressing the experience of patients with healthcare and their beliefs in medicines in daily clinical practice highlights the relevance of the current findings. As healthcare is

evolving towards a patient-centered model, in which better outcomes are expected to come from interactions between proactive, well-prepared clinical teams and active, well-informed patients[23], there are a number of practical aspects that healthcare providers can implement which should have a positive impact on improving adherence and patients' outcomes. A recent, small qualitative study which evaluated barriers to medication adherence in patients with chronic illnesses, highlighted the potential of counseling to increase patient knowledge about medication use and active collaboration between pharmacists and physicians to improve medication adherence[4]. Based on the findings from our study, actions could include targeting information to patients (to increase patients' self-care abilities and/or reduce patients' concerns about taking medication), setting clear health/lifestyle objectives which are agreed jointly by patients and physicians (to increase patient confidence about the level of control they have regarding their chronic illness and to reinforce the necessity for diet, physical activity and medication to get better control of health problems [e.g. diabetes]), close follow-up of how patients are taking their medication (to nurture closer physician-patient relationships and ensure that patients are taking their medication correctly, and to increase patients' understanding of the need for, often, long-term medication), and making use of health and social resources that are close-at-hand to patients and that can help them in their everyday life (e.g. encouraging patients to engage in local activities which can help them to improve their health problems and/or reducing their concerns about medication/chronic illness). Moreover, reinforcing positive patient beliefs in the need for medication is particularly important for "silent" chronic conditions, such as diabetes and HIV infection[24,25]. The use of good, targeted information to reduce patients' concerns about medications, and close supervision from the clinical team to promote patient self-management, may be particularly beneficial in such conditions. Thus, while the requirement for addressing modifiable risk factors for non-adherence in clinical practice is well recognized[26], the current study emphasizes the importance of reducing patients' concerns about medication whilst also reinforcing the need for patients to continue with their medication.

As there is no optimal method to measure non-adherence in routine clinical practice, we defined five non-adherence behaviors based on physician and patient input. However, we recognize that results might have varied if other behaviors had been included or an alternative method of adherence/non-adherence had been used. Indeed, a recent systematic literature review that compared different approaches to estimating persistence and adherence in chronic diseases with polypharmacy of oral and subcutaneous treatments concluded that considerations about the route of medication administration, available resources, setting and aim of the assessment should guide decisions about which method to use[27]. Additional limitations of the current study are those previously recognized in surveying patients with chronic diseases[15]. These include possible selection bias of patients with more severe chronic conditions, which was negated to some extent by the selection of consecutive patients attending clinics. As the survey was anonymous, the characteristics of patients who did not return the survey are unknown. It is possible that those patients with more motivation were more likely to complete the survey. In addition, study outcomes refer to the profiles of specific patient groups (i.e. the four chronic diseases studied) which are not representative of all chronic disease patients. On the other hand, the anonymous survey format of the current study minimizes the potential response bias imposed by the clinical team when they collect information directly from patients.

Conclusions

This study allowed us to identify potentially modifiable variables associated with non-adherence behaviors. Behaviors leading to non-adherence to prescribed therapy were frequent in this cohort of patients with chronic conditions and were associated with patient experience with healthcare: specifically, patient self-management (IEXPAC Factor 3) and, more significantly, with patients' beliefs in medicines (a lower perception for the necessity of medication, and higher concerns in taking the medication). These factors are potentially modifiable and need to be addressed by clinical teams to increase medication adherence in chronic disease. In addition, we identified a strong association of non-adherence behaviors with DM patients and with female sex in HIV patients that deserve further evaluation.

Transparency

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Declaration of financial/other relationships

Luis Cea-Calvo: Full-time employee at Merck Sharp & Dohme, Spain.

Ignacio Marín-Jiménez: Board membership or consultancy for AbbVie, Chiesi, FAES Farma, Falk-Pharma, Ferring, Gebro Pharma, Hospira, Janssen, MSD, Otsuka Pharmaceutical, Pfizer, Shire, Takeda, Tillots, and UCB Pharma, payments for lectures from AbbVie, Chiesi, FAES Farma, Falk-Pharma, Ferring, Gebro Pharma, Hospira, Janssen, MSD, Otsuka Pharmaceutical, Pfizer, Shire, Takeda, Tillots, and UCB Pharma.

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References

[1] World Health Organization. Adherence to long-term therapies: evidence for action [Internet]. Geneva (Switzerland): WHO; 2003 [cited 2019 March 18]. Available from: https://apps.who.int/iris/bitstream/handle/10665/42682/9241545992.pdf;jsessionid=B236F008ABD194E73BD9FD586C666EAB?sequence=1

[2] Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353(5):487–497.

[3] Hugtenburg JG, Timmers L, Elders PJM, et al. Definitions, variants, and causes of nonadherence with medication: a challenge for tailored interventions. Patient Prefer Adher. 2013;7:675–682.

[4] Naqvi AA, Hassali MA, Aftab MT, et al. A qualitative study investigating perceived barriers to medication adherence in chronic illness patients of Karachi, Pakistan. J Pak Med Assoc. 2019;69(2):216–223.

[5] Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. J Psychosom Res. 1999;47(6):555–567.

[6] Horne R, Parham R, Driscoll R, et al. Patients' attitudes to medicines and adherence to maintenance treatment in inflammatory bowel disease. Inflamm Bowel Dis. 2009;15(6):837–844.

[7] Horne R, Chapman SC, Parham R, et al. Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-Concerns Framework. PLoS One. 2013;8(12):e80633.

[8] Krauskopf K, Federman AD, Kale MS, et al. Chronic obstructive pulmonary disease illness and medication beliefs are associated with medication adherence. COPD. 2015;12(2):151–164.

[9] Brandstetter S, Finger T, Fischer W, et al. Differences in medication adherence are associated with beliefs about medicines in asthma and COPD. Clin Transl Allergy. 2017;7(1):39.

[10] Park HY, Seo SA, Yoo H, et al. Medication adherence and beliefs about medication in elderly patients living alone with chronic diseases. Patient Pref Adher. 2018;12:175–181.

[11] Naqvi AA, Hassali MA, Rizvi M, et al. Development and validation of a novel General Medication Adherence Scale (GMAS) for chronic illness patients in Pakistan. Front Pharmacol. 2018;9(9):1124.

[12] Naqvi AA, Hassali MA, Jahangir A, et al. Translation and validation of the English version of the general medication adherence scale (GMAS) in patients with chronic illnesses. J Drug Assess. 2019;8(1):36–42.

[13] Borgsteede SD, Westerman MJ, Kok IL, et al. Factors related to high and low levels of drug adherence according to patients with type 2 diabetes. Int J Clin Pharm. 2011;33(5):779–787.

[14] Fortuna RJ, Nagel AK, Rocco TA, et al. Patient experience with care and its association with adherence to hypertension medications. Am J Hypertens. 2018;31(3):340–345.

[15] Orozco-Beltrán D, de Toro J, Galindo MJ, et al. Healthcare experience and their relationship with demographic, disease and healthcare-related variables: a cross-sectional survey of patients with chronic diseases using the IEXPAC Scale. Patient. 2019;12(3):307–317.

[16] Mira JJ, Nuño-Solinís R, Guilabert-Mora M, et al. Development and validation of an instrument for assessing patient experience of chronic illness care. Int J Integr Care. 2016;16(3):13.

[17] Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health. 1999;14(1):1–24.

[18] Beléndez-Vázquez M, Hernández-Mijares A, Horne R, et al. Evaluación de las creencias sobre el tratamiento: Validez y fiabilidad de la versión Española del Beliefs about Medicines Questionnaire [Factor structure and reliability of the Spanish version of the Beliefs about Medicines Questionnaire]. Int J Clin Health Psychol. 2007;7:767–779.

[19] Oung AB, Kosirog E, Chavez B, et al. Evaluation of medication adherence in chronic disease at a federally qualified health center. Ther Adv Chronic Dis. 2017;8(8–9):113–120.

[20] DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Med Care. 2004;42(3):200–209.

[21] Ortego C, Huedo-Medina TB, Llorca J, et al. Adherence to highly active antiretroviral therapy (HAART): a meta-analysis. AIDS Behav. 2011;15(7):1381–1396.

[22] Pagès-Puigdemont N, Mangues M, Masip M, et al. Patients' perspective of medication adherence in chronic conditions: a qualitative study. Adv Ther. 2016;33(10):1740–1754.

[23] The Chronic Care Model [Internet]. The MacColl Institute. ACP-ASIM Journals and Books. 2019 [cited 2019 May 10]. Available from http://www.improvingchroniccare.org/index.php?p=The_Chronic_Care_Model&s=2

[24] von Birgelen C, Kok MM, Sattar N, et al. "Silent" diabetes and clinical outcome after treatment with contemporary drug-eluting stents: the BIO-RESORT Silent Diabetes Study. JACC Cardiovasc Interv. 2018;11(5):448–459.

[25] Aiuti F, Ensoli F, Fiorelli V, et al. Silent HIV infection. Vaccine. 1993;11(5):538–541.

[26] Allemann S, Nieuwlaat R, van den Bemt B, et al. Matching adherence interventions to patient determinants using the Theoretical Domains Framework. Front Pharmacol. 2016;7:429.

[27] Forbes CA, Deshpande S, Sorio-Vilela F, et al. A systematic literature review comparing methods for the measurement of patient persistence and adherence. Curr Med Res Opin. 2018;34(9):1613–1625.