



# Implication Of Character Traits In Adherence To Treatment In People With Gout: A Reason For Considering Nonadherence As A Syndrome

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**Objective:** Various aspects of nonadherence to therapy (including medication and lifestyle nonadherence) often appear together. Here we report the association between treatment adherence in gout and the two character traits of patience and obedience, which may explain this observation.

**Methods:** Data were collected from a cross-sectional study conducted in a French cohort of 1441 adult patients. Patience was assessed using the choice between receiving €1500 in 1 year or €500 immediately. Obedience was evaluated with a single question assessing the use of the seatbelt in the rear seat of a car. Adherence to recommendations for medication, beverage, food and physical activity and smoking status was assessed using self-report questionnaires.

**Results:** Patience and obedience were strong determinants of adherence to medication in multivariate analysis (OR 2.056, 95% CI [1.414–2.989],  $P < 0.001$ ; OR 1.844, 95% CI [1.273–2.671],  $P = 0.001$ ). In univariate analysis, adherence to medication was also associated with compliance with dietary directives ( $P < 0.001$ ), lower alcohol consumption on an ordinary day ( $P < 0.001$ ), never consuming soda ( $P < 0.001$ ) or beer ( $P < 0.001$ ), practice of physical activity ( $P = 0.002$ ), being a nonsmoker ( $P < 0.001$ ) and monitoring serum levels of uric acid regularly ( $P = 0.011$ ). Multiple-correspondence analysis illustrated the associations of these different aspects of adherence (medication, diet and exercise, smoking status and monitoring of disease control) with patience and obedience. Finally, we observed a link between patience and obedience ( $P < 0.001$ ).

**Conclusion:** Character traits, which shape preferences, may cause the clustering of different aspects of nonadherence in the form of a syndrome, elucidating the still enigmatic link between nonadherence to placebo and mortality in randomised clinical trials. This concept may also explain, at least in part, the difficulty of improving adherence to long-term therapies and may lead to ethical issues.

**Keywords:** adherence, patience, obedience, nonadherence syndrome, character traits, gout

## Introduction

Nonadherence, defined as a lack of concordance between patients' behaviours and medical prescriptions, is a major issue in the care of chronic diseases.<sup>1</sup> This concerns not only medication but also lifestyle changes. Different aspects of treatment adherence often appear together: for example, people adherent to statin therapy were found to be more likely to engage in a broad spectrum of unrelated behaviours that are consistent with a generally healthy lifestyle (e.g., vaccination),<sup>2</sup> and in women treated with bisphosphonate, high adherence was associated to bone

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mineral density testing and different types of preventive testing (e.g., colonoscopy).<sup>3</sup>

In previous studies, one author of this study demonstrated a link in the context of type 2 diabetes between adherence to medication and some character traits such as patience and obedience.<sup>4-8</sup> Specifically, adherence was found to be more frequent in people who declared that they would prefer to receive €1500 in 1 year than €500 today (patience) and that they used to fasten their seatbelts when seated in the back of a car (obedience).

Gout is a chronic disorder, and its treatment is designed to maintain a serum uric acid level below 360  $\mu\text{mol/L}$  (60 mg/L). The treatment requires not only medications (urate-lowering therapy) but also lifestyle changes and weight loss in obese or overweight patients.<sup>9,10</sup> The importance of non-pharmacological therapy in people with gout is justified by a number of arguments: (i) the prevalence of gout is associated to obesity, waist-to-hip ratio and weight gain;<sup>11</sup> (ii) the prevalence of metabolic syndrome is increased in the presence of gout;<sup>12</sup> (iii) in healthy individuals without a history of gout, the magnitude of insulin resistance is associated to serum uric acid concentration and inversely related to urinary uric acid clearance; urinary uric acid clearance is inversely related to serum uric acid concentration;<sup>13</sup> these observations are therefore consistent with a hyperuricemic effect of insulin resistance, and losing weight and exercise fight against insulin resistance; (iv) hyperuricemia is associated with cardiovascular mortality.<sup>14</sup> Therefore, lifestyle changes in gout are recommended in current guidelines, and lifestyle advice belongs to the indicators of quality of care in gout.<sup>15</sup> Unfortunately, not all people with gout receive lifestyle change advice from their doctor,<sup>16</sup> and there is some lack of interest for lifestyle changes from investigators.<sup>17</sup> On the patient's side, it is well known that nonadherence to diet and exercise recommendations is in general even worse than nonadherence to medication.<sup>18</sup>

Published reviews and meta-analyses have indicated a high prevalence of nonadherence to drug therapy in people with gout, which has several consequences in relation to outcomes.<sup>19-22</sup> It decreases the percentage of patients with controlled serum uric acid level,<sup>22</sup> which increases the risk of gouty attacks<sup>23,24</sup> and reduces the decrease in tophus size during treatment.<sup>25</sup>

In this context, this study investigated in people with gout the effects of patience and obedience on adherence to medication. Furthermore, if character traits do have a causal effect on adherence, it could be expected that different aspects of adherence (medication, dietary recommendations, exercise, smoking status and serum uric acid

level monitoring) are linked.<sup>26</sup> We therefore investigated whether they are associated in people with gout.

## Research Design And Methods

### Data Collection

Data were obtained from a cross-sectional study performed in France between November 2014 and June 2015 that involved 630 general practitioners (GPs). The patients included were adults with gout who had been under long-term treatment for over 3 months. Medical data were collected by the GPs during a single visit, conducted under the usual conditions of medical practice. Patients completed during the appointment a self-report questionnaire, investigating general adherence to medication with five questions<sup>4</sup> derived from the Girerd questionnaire<sup>27</sup> and to alcohol and soda restrictions ([Appendix](#)). Patience was assessed using the patient's choice between two fictive monetary proposals: receiving €1500 in 1 year or €500 immediately.<sup>4</sup> Obedience was evaluated with a single question assessing the use of the seatbelt in the rear seat of a car.<sup>6</sup> Visual analogue scales and Likert scales were used to estimate adherence to advice relating to diet and physical activity, importance attributed to long-term treatment of gout, impact of gout on quality of life and life expectancy and satisfaction with the current treatment of gout. The perception of gout and its treatment were also evaluated using the Brief Illness Perception Questionnaire (B-IPQ).<sup>28</sup>

### Statistical Analysis

SAS 9.4 software (SAS Institute Inc., Cary, NC) was used for the statistical analysis. For continuous data, the means and standard deviations were calculated. For categorical data, the frequency and percentage of the class level were calculated. Predictive factors for adherence to treatment and control serum uric acid level were evaluated with a  $\chi^2$  test to compare ratios, a Student's *t* test to compare continuous variables with a normal distribution, and nonparametric tests to compare continuous variables without a normal distribution. Multivariate analyses were performed using multivariate logistic regression. All the prognosis factors that were selected in the first step (univariate analyses with an alpha level of 25% so as not to miss any confounding or predictive factors) were included. If groups of selected factors are highly correlated, the most clinically relevant factors in each group of factors were selected to avoid collinearity problems. A backward elimination procedure was used. Verification of the confounding factor at each step

was performed by calculating the percentage of variation in the estimated parameters with and without the removed candidate factor. If removing a nonsignificant factor changed by more than 20% of the estimated parameters, then it was kept in the model. The selection ceased when all the variables reached a significance level of 5% ( $P \leq 0.05$ ) or were assigned confounding-factor status.

Multiple-correspondence analysis of the data was also performed using the following factors: adherence to medication, adherence to advice relating to practice of physical activity and to diet, regular measurement of serum uric acid, achievement of serum uric acid goal (latest available measurement), obedience (seatbelt fasteners vs nonfasteners), patience (€1500 vs €500), lifestyle changes, amount of alcohol drunk on an ordinary day, use of soda and beer, smoking status and whether a physician had given advice on lifestyle changes.

## Ethical Approval And Consent To Participate

Before patient inclusion, the purpose and objectives of the study were explained orally and in writing to potential subjects, filling the self-questionnaire representing a written consent to participate. The written information given to the patients was included in the protocol submitted to the Advisory Committee on Information Processing in Material Research in the Field of Health (CCTIRS) and to the French Commission Nationale Informatique et Libertés, who gave their approval on 18 June 2014 and 29 October 2014, respectively.

## Role Of The Funding Source And Of The Corresponding Author

The study was sponsored by Menarini. Euraxi Pharma was the contract research organisation appointed by the sponsor to conduct this study together with the academic authors GR, LM and RMF: from the design of the study and recruitment of the investigators to the initial data analysis. Statistical analyses were performed by GC at Capionis, a statistical consulting company whose data analyses are independent of the sponsor. No marketing or commercial representatives of the sponsor were involved in the recruitment of investigators. The sponsor gave its approval for submission of the article but was not involved in writing the report, which was performed by GR, the corresponding author. GR confirms that he had access to

all the data for the study and was given final responsibility for the decision to submit for publication.

## Results

### Characteristics Of Patients Included

In total, 1875 patients were interviewed and the responses of 1441 were analysed; 434 (23.1%) being excluded from the analysis due to absence of long-term treatment or missing data on adherence. As shown in Table 1, 84.6% of the analysable patients were men, the mean age was 64.4 years, 85.1% of the patients were overweight, 38.4% were obese, and a high prevalence of hypertension, dyslipidaemia and type 2 diabetes was observed, with 17.0% of the patients combining the three. The on-going long-term treatment on the day of visit was febuxostat (50.9%) or allopurinol (49.7%). The regular measurement of serum uric acid was performed by 80.3% of the patients, and 41.9% of them were at the recommended goal ( $\leq 360 \mu\text{mol/L}$ ) according to their last measurement.

The analysis of patients' self-questionnaires showed that 79.5% were adherent to medication, 62.2% stated that they complied with dietary advice and 45.2% followed directives on the practice of regular physical activity. Finally, 21.9% of the patients were smokers, 48.4% preferred to receive €1500 in 1 year in the fictive monetary scenario and 75.4% stated that they fastened their seatbelts when seated in the back seat of a car.

### Adherence To Medication: Association With Serum Uric Acid Outcome

In univariate analysis, shown in Table 2, adherence to medication was associated with the regular measurement of serum uric acid (OR 1.486, 95% CI [1.094–2.019],  $P=0.011$ ) and with achieving the goal for serum uric acid level (latest available measurement  $\leq 360 \mu\text{mol/L}$  vs  $>360 \mu\text{mol/L}$ , OR 2.283, 95% CI [1.641–3.178],  $P<0.001$ ).

### Adherence To Medication, Patience And Obedience

More adherent patients preferred to receive €1500 in 1 year (52.7%) than nonadherent patients (31.8%,  $P<0.001$ ), and the percentage of patients who declared that they fastened their seatbelts when in the back of a car was also higher in adherent than in nonadherent patients (78.8% vs 62.2%, respectively,  $P<0.001$ ). These differences resulted in a univariate analysis with ORs of 2.383, 95% CI [1.815–3.129],  $P<0.001$  and 2.259, 95% CI [1.713–2.978],  $P<0.001$  for the relationship between adherence and patience and obedience, respectively.

**Table 1** Characteristics Of Patients

Characteristics Of Patients	Population Of Analysis (n = 1441)	Missing Data
<b>Gender</b>		8
Male, n (%)	1213 (84.6%)	
Female, n (%)	221 (15.4%)	
<b>Age (mean ± SD), years</b>	64.4 ± 11.4	25
<60 years, n (%)	446 (31.5%)	
[60–70] years, n (%)	573 (40.5%)	
>70 years, n (%)	397 (28.0%)	
<b>Body mass index (mean ± SD), kg/m<sup>2</sup></b>	29.4 ± 4.7	13
Overweight (BMI > 25 kg/m <sup>2</sup> ), n (%)	1216 (85.1%)	
Obesity (BMI > 30 kg/m <sup>2</sup> )	549 (38.4%)	
<b>Family history of gout, n (%)</b>	594 (41.7%)	18
<b>Smokers, n (%)</b>	313 (21.9%)	9
<b>Comorbidities</b>		
High blood pressure (HBP), n (%)	1005 (70.1%)	7
Dyslipidaemia (DL), n (%)	881 (61.8%)	16
Type 2 diabetes (T2D), n (%)	3.5%	10
Renal impairment and/or lithiasis, n (%)	195 (13.5%)	0
Concomitant HBP, DL, T2D, n (%)	245 (17.0%)	0
Congestive heart failure, n (%)	76 (5.3%)	0
History of myocardial infarction, n (%)	51 (3.5%)	0
History of stroke, n (%)	33 (2.3%)	0
<b>Number of acute attacks during the last 12 months (mean ± SD), n</b>	1.4 ± 1.4	121
0–2 attacks, n (%)	1116 (84.5%)	
3–5 attacks, n (%)	189 (14.3%)	
>5 attacks	16 (1.2%)	
<b>Symptoms<sup>a</sup> n (%)</b>		17
Pain and swelling	1216 (85.4%)	
Podagra	856 (60.1%)	
Erythema	702 (49.3%)	
Tophus	126 (8.8%)	
Existence of sodium urate crystals	66 (4.6%)	
Renal lithiasis	58 (4.1%)	
<b>Serum level of uric acid at time of diagnosis (mean ± SD), µmol/L</b>	511 ± 76	128
<b>Last measurement of serum level of uric acid (mean ± SD), µmol/L</b>	380 ± 98	331
≤360 µmol/L, n (%)	465 (41.9%)	
>360 µmol/L, n (%)	645 (58.1%)	
<b>Regular measurement of serum level uric acid</b>		23
No, n (%)	280 (19.7%)	
Yes, n (%)	1138 (80.3%)	
<b>Ongoing long-term treatment on day of visit<sup>a</sup></b>		3
Febuxostat, n (%)	732 (50.9%)	
Allopurinol, n (%)	715 (49.7%)	

(Continued)

**Table 1** (Continued).

Characteristics Of Patients	Population Of Analysis (n = 1441)	Missing Data
<b>Treatments prescribed at time of last acute attack<sup>a</sup></b>		28
Colchicine, n (%)	1,299 (91.9%)	
Analgesics, n (%)	666 (47.1%)	
Nonsteroidal anti-inflammatory drugs, n (%)	480 (34.0%)	
<b>Daily number of tablets (mean ± SD), n</b>	4.9 ± 3.5	11
<5, n (%)	776 (54.3%)	
5–9, n (%)	498 (34.8%)	
≥10, n (%)	156 (10.9%)	
<b>Lifestyle changes advised on day of visit<sup>a</sup> n (%)</b>		3
Avoiding animal products high in purine	1017 (70.7%)	
Performing physical activity	984 (68.4%)	
Losing weight	944 (65.6%)	
Avoiding beer and alcoholic drinks	914 (63.6%)	
Avoiding drinks with high-fructose corn syrup	607 (42.2%)	
Stopping smoking	251 (17.5%)	
None	139 (9.7%)	
<b>Adherence</b>		
Medication	1145 (79.5%)	0
Diet	891 (62.2%)	10
Exercise	648 (45.2%)	9
<b>Patience: preferring waiting for 1 year for €1500 vs receiving €500 today, n (%)</b>	690 (48.4%)	14
<b>Obedience: being used to fasten seatbelt when seated in a rear seat, n (%)</b>	1072 (75.4%)	19

**Note:** <sup>a</sup>Several possible responses.**Abbreviation:** SD, standard deviation.

### Adherence To Medication And Other Lifestyle Behaviours (Diet, Exercise And Smoking)

We observed that more patients who were adherent to medication regimens complied with advice relating to diet (65.9% vs 46.9%,  $P < 0.001$ ) and the practice of physical activity (47.2% vs 37.0%,  $P = 0.002$ ) than nonadherent patients. This resulted in a univariate analysis that produced ORs of 2.190, 95% CI [1.688–2.841],  $P < 0.001$ , and 1.522, 95% CI [1.169–1.983],  $P = 0.002$  for the relationship between adherence and compliance with diet and exercise, respectively. Furthermore, the number of glasses of alcoholic drinks on an ordinary day was lower in adherent patients (1 or 2 vs >2, OR 2.092, 95% CI [1.610–2.718],  $P < 0.001$ ), and an association with adherence to medication was also observed for the never vs regular consumption of soda (OR 2.516, 95% CI [1.657–3.819],  $P < 0.001$ ) or of

**Table 2** Factors Associated With Adherence To Medication (Univariate Tests)

Factor	Modalities	OR [95% CI]	P	Global P
Age (years)	[60–70] vs. <60	1.190 [0.883; 1.603]	0.253	0.111
	>70 vs. <60	1.434 [1.022; 2.011]	<b>0.037</b>	
Gender	Female vs. male	1.039 [0.726; 1.486]	0.835	
BMI (kg/m <sup>2</sup> )	≤25 vs. >30	1.511 [0.995; 2.296]	<b>0.053</b>	0.145
	[25–30] vs. >30	1.148 [0.872; 1.513]	0.325	
Tophus	Yes vs. No	1.230 [0.799; 1.894]	0.348	
Renal disorder	Yes vs. No	1.321 [0.927; 1.882]	0.124	
HBP + T2D + DL	Yes vs. No	1.363 [0.987; 1.883]	0.060	
History of myocardial infarction	Yes vs. No	1.204 [0.622; 2.329]	0.582	
Existence of comorbidities	Yes vs. No	1.142 [0.883; 1.478]	0.311	
Regular measurement of SUA level	Yes vs. No	1.486 [1.094; 2.019]	<b>0.011</b>	
Number of acute attacks of gout during the last 12 months	>5 vs. ≤2	0.377 [0.136; 1.050]	0.062	<b>&lt;0.001</b>
	[2–5] vs. ≤2	0.538 [0.380; 0.761]	<b>&lt;0.001</b>	
Information on lifestyle changes	Yes vs. No	1.814 [1.086; 3.028]	<b>0.023</b>	
Daily number of tablets	Unit= 1	0.950 [0.917; 0.983]	<b>0.004</b>	
Total B-IPQ score	Unit=1	0.929 [0.914; 0.945]	<b>&lt;0.001</b>	
Overall satisfaction with respect to long-term treatment for gout	Unit=1	1.296 [1.218; 1.378]	<b>&lt;0.001</b>	
Frequency of alcohol use	Never vs. Regularly	1.731 [1.010; 2.966]	<b>0.046</b>	<b>0.026</b>
	Occasionally vs. Regularly	1.365 [1.025; 1.817]	<b>0.033</b>	
Number of glasses of alcoholic drink taken during an ordinary day	1 or 2 vs. >2	2.092 [1.610; 2.718]	<b>&lt;0.001</b>	
Frequency of use of 6 or more standard glasses of alcoholic drink	Never or < once/month vs. Regularly	2.489 [1.906; 3.249]	<b>&lt;0.001</b>	
Use of soda	Never vs. Regularly	2.516 [1.657; 3.819]	<b>&lt;0.001</b>	<b>&lt;0.001</b>
	Occasionally vs. Regularly	1.597 [1.081; 2.358]	<b>0.019</b>	
Use of beer	Never vs. Regularly	2.617 [1.808; 3.787]	<b>&lt;0.001</b>	<b>&lt;0.001</b>
	Occasionally vs. Regularly	1.769 [1.297; 2.412]	<b>&lt;0.001</b>	
Smoking	No vs. Yes	1.804 [1.351; 2.408]	<b>&lt;0.001</b>	
Achievement of serum uric acid goal (latest available measurement)	≤360 μmol/L vs. >360 μmol/L	2.283 [1.641; 3.178]	<b>&lt;0.001</b>	<b>&lt;0.001</b>
	>360 μmol/L vs. Missing SUA data	1.032 [0.759; 1.404]	0.840	
	≤360 μmol/L vs. Missing SUA data	2.357 [1.623; 3.423]	<b>&lt;0.001</b>	
Long-term treatment with Febuxostat at time of inclusion	Yes vs. No	1.462 [1.130; 1.892]	<b>0.004</b>	
Patience	Preferring €1500 in one year	2.383 [1.815; 3.129]	<b>&lt;0.001</b>	
Obedience	Declaring fasting seatbelt	2.259 [1.713; 2.978]	<b>&lt;0.001</b>	
Compliance to diet advice	Yes vs. No	2.190 [1.688; 2.841]	<b>&lt;0.001</b>	
Compliance to exercise advice	Yes vs. No	1.522 [1.169; 1.983]	<b>0.002</b>	

**Notes:** Model of probability is “Adherence to long-term treatment = Yes”. Bold data indicates significant data.

**Abbreviations:** OR, odds ratio comparing relative risk of being adherent based on modalities of the risk factors studied; 95% CI, 95% confidence interval of the OR; P, probability that the OR is not different from 1 for the two modalities of risk factors tested (risk factors with more than two modalities); global P, probability that OR is not globally different from 1 for modalities of risk factors; B-IPQ, Brief Illness Perception Questionnaire; HBP, high blood pressure; T2D, Type 2 diabetes; DL, dyslipidaemia; SUA, serum uric acid.



beer (OR 2.617, 95% CI [1.808–3.787],  $P < 0.001$ ). Finally, patients adherent to their medication regimen were more often nonsmokers (OR 1.804, 95% CI [1.351–2.408],  $P < 0.001$ ) and monitored their serum uric acid level more frequently (OR 1.486, 95% CI [1.094–2.019],  $P = 0.011$ ).

### Analysis Of People With Missing Data For Recent Serum Uric Acid Level

As shown in Table 1, there were in general little missing data, except for the last available serum uric acid level ( $n = 331$ , i.e., 23% of the patients). In univariate analysis (Table 2), patients with these missing data were found to have the same risk of being adherent to medication than those with uncontrolled ( $>360 \mu\text{mol/L}$ ) serum uric acid levels (OR 1.032, 95% CI [0.759–1.404],  $P = 0.840$ ) and they had a half as low risk of being adherent to medication than those with controlled ( $\leq 360 \mu\text{mol/L}$ ) serum uric acid levels (OR 2.357, 95% CI [1.623–3.423],  $P < 0.001$ ).

In univariate analysis, the patients with missing data were found different from those for whom serum uric acid was available (Table 3) Their disease appeared less severe: absence of tophus ( $P = 0.009$ ), of comorbidities ( $P = 0.002$ ), lower daily tablet number ( $P < 0.001$ ). They were less likely to adhere to medications ( $P = 0.028$ ) and to advice on diet ( $P = 0.005$ ), alcohol and sodas ( $P = 0.005$  and  $P = 0.005$ , respectively) and were more likely to smoke ( $P = 0.013$ ).

### Factors Associated With Adherence To Medication (Multivariate Logistic Model)

Eight factors were significantly associated with adherence to medication (Table 4): patience and obedience were among the determinants that were most strongly associated with adherence to medication regimen, with ORs of 2.056, 95% CI [1.414–2.989],  $P < 0.001$ , and 1.844, 95% CI [1.273–2.671],  $P = 0.001$ , respectively. The other determinants were compliance with diet advice and never vs regular consumption of soda (OR 1.706, 95% CI [1.197–2.429],  $P = 0.003$ , and OR 1.899, 95% CI [1.058–3.407],  $P = 0.032$ , respectively), having a good perception of one's illness (B-IPQ score,  $P < 0.001$ ), being satisfied with one's long-term treatment of gout ( $P = 0.0016$ ), age ( $>70$  vs  $<60$ ,  $P = 0.014$ ), and a lower daily number of pills ( $P = 0.039$ ). The area under the receiver operating characteristic curve (AUC) was 0.767.

Table 5 shows data from the multivariate analyses when the 331 patients with unknown uric acid levels were included in the analysis. The results were essentially similar, except that not drinking soda regularly was not retained by the model. Here again, patience and obedience

were found to be determinants of adherence to medication, with ORs of 1.894, 95% CI [1.377–2.605],  $P < 0.001$ , and 1.806, 95% CI [1.310–2.490],  $P < 0.001$ , respectively. The AUC was 0.756.

### Obedience, Patience And Control Of Serum Levels Of Uric Acid

In univariate analysis, obedience, but not patience, was found to be a determinant for achieving control of serum uric acid levels ( $P < 0.001$ , Table 6) together with adherence to medication, diet and exercise recommendations ( $P < 0.001$ ). In multivariate analysis, obedience ( $P = 0.020$ ), but not patience, was a determinant of this parameter together with compliance with diet advice ( $P = 0.007$ ), compliance with exercise directives ( $P = 0.035$ ), overall satisfaction with respect to long-term treatment of gout ( $P < 0.001$ ), treatment with febuxostat at inclusion ( $P < 0.001$ ), presence of tophus ( $P = 0.004$ ) and the total B-IPQ score ( $P = 0.009$ ) (Table 7, AUC 0.828).

### Clustering Between Different Aspects Of Adherence, Patience And Obedience

The results of multiple-correspondence analyses, shown in Figure 1, illustrate the association between different aspects of adherence (medication, diet and exercise, smoking status and regular measurement of serum levels of uric acid), obedience and patience, and control of serum levels of uric acid, forming two separated clusters defining adherent and nonadherent patients.

Finally, a  $\chi^2$  test demonstrated the existence of a link between patience and obedience ( $P < 0.001$ , Table 8).

## Discussion

### Main Findings

First, we observed that people with gout who were adherent to their medication regimens gave a patient answer more frequently to a fictive monetary choice, and they more frequently declared their habit to fasten their seatbelts while in the back of a car than nonadherent patients.

The meaning of these answers needs to be clarified. The implication of patience in the adherence to long-term therapies is consistent with the fact that the respective benefits of adherence and nonadherence in chronic diseases are often remote (preserving health, avoiding complications of the disease) and immediate (e.g., avoiding drug side effects), respectively.<sup>29,30</sup> Thus, a fictive monetary choice (e.g., €1500 in 1 year vs €500 today) is an attempt to allow patients

**Table 3** Factors Associated With Missing Data Concerning Serum Uric Acid Measurement (Univariate Tests)

Factor	Modalities	OR [95% CI]	P	Global P
Age (years)	[60–70] vs. <60	0.776 [0.580; 1.038]	0.087	0.165
	>70 vs. <60	0.778 [0.565; 1.071]	0.123	
Gender	Female vs. male	1.076 [0.768; 1.507]	0.670	
BMI (kg/m <sup>2</sup> )	≤25 vs. >30	0.966 [0.660; 1.414]	0.859	0.945
	[25–30] vs. >30	1.027 [0.785; 1.343]	0.846	
Tophus	No vs. Yes	2.012 [1.188; 3.407]	<b>0.009</b>	
Renal disorder	No vs. Yes	1.678 [1.119; 2.516]	<b>0.012</b>	
HBP + T2D + DL	No vs. Yes	1.593 [1.111; 2.284]	<b>0.011</b>	
History of myocardial infarction	No vs. Yes	1.088 [0.552; 2.144]	0.809	
Existence of comorbidities	No vs. Yes	1.479 [1.148; 1.906]	<b>0.002</b>	
Regular measurement of SUA level	No vs. Yes	147.12 [93.043; 232.64]	<b>&lt;0.001</b>	
Number of acute attacks of gout during the last 12 months	≤2 vs >5	0.818 [0.261; 2.558]	0.729	0.295
	[2–5] vs. ≤2	1.079 [0.333; 3.501]	0.899	
Information on lifestyle changes	Yes vs. No	1.046 [0.693; 1.579]	0.830	
Daily number of tablets	Unit= 1	0.932 [0.896; 0.970]	<b>&lt;0.001</b>	
Total B-IPQ score	Unit=1	1.005 [0.990; 1.019]	0.524	
Overall satisfaction with respect to long-term treatment for gout	Unit=1	0.952 [0.899; 1.009]	0.096	
Frequency of alcohol use	Occasionally vs. Never	1.024 [0.634; 1.656]	0.922	0.916
	Regularly vs. Never	0.968 [0.611; 1.532]	0.888	
Number of glasses of alcoholic drink taken during an ordinary day	>2 vs 1 or 2	1.427 [1.115; 1.828]	<b>0.005</b>	
Frequency of use of 6 or more standard glasses of alcoholic drink	Regularly vs. Never or < once/month	1.645 [1.267; 2.135]	<b>&lt;0.001</b>	
Use of soda	Occasionally vs. Never	1.474 [1.125; 1.931]	<b>0.005</b>	<b>0.011</b>
	Regularly vs. Never	1.568 [1.027; 2.394]	<b>0.037</b>	
Use of beer	Occasionally vs. Never	1.282 [0.955; 1.722]	0.099	0.141
	Regularly vs. Never	1.393 [0.974; 1.993]	0.069	
Smoking	Yes vs. Never	1.433 [1.078; 1.905]	<b>0.013</b>	
Adherence to medication	No vs. yes	1.387 [1.037; 1.855]	<b>0.028</b>	
Long-term treatment with Febuxostat at time of inclusion	No vs. Yes	1.246 [0.974; 1.594]	0.080	
Patience	Preferring €500 now vs €1500 in one year	1.134 [0.885; 1.452]	0.322	
Obedience Declaring fasting seatbelt	No vs. Yes	0.965 [0.723; 1.287]	0.808	
Compliance to diet advice	No vs. Yes	1.427 [1.111; 1.832]	<b>0.005</b>	
Compliance to exercise advice	No vs. Yes	0.901 [0.704; 1.153]	0.406	

**Notes:** Model of probability is "Missing data concerning serum uric acid = Yes". Bold data indicates significant data.

**Table 4** Factors Associated With Adherence To Medication (Multivariate Logistic Model)

Factor	Modalities	OR [95% CI]	P	Global P
Age (years)	[60–70] vs <60	1.444 [0.954–2.184]	0.082	<b>0.042</b>
	>70 vs <60	1.881 [1.137–3.111]	<b>0.014</b>	
Daily number of tablets	Unit = 1	0.950 [0.904–0.997]	<b>0.039</b>	
Total B-IPQ score	Unit = 1	0.947 [0.925–0.969]	<b>&lt;0.001</b>	
Overall satisfaction with respect to long-term treatment of gout	Unit = 1	1.197 [1.099–1.303]	<b>&lt;0.001</b>	
Use of soda	Never vs regularly	1.899 [1.058–3.407]	<b>0.032</b>	<b>0.035</b>
	Occasionally vs regularly	1.182 [0.697–2.004]	<b>0.535</b>	
Patience	Preferring €1500 in 1 year	2.056 [1.414–2.989]	<b>&lt;0.001</b>	
Obedience	Declaration of preference for fastening seatbelt	1.844 [1.273–2.671]	<b>0.001</b>	
Compliance with diet advice		1.706 [1.197–2.429]	<b>&lt;0.001</b>	

**Notes:** This table shows data based on patients without missing data (n= 952). Bold data indicates significant data.

**Table 5** Factors Associated With Adherence To Medication (Multivariate Logistic Model)

Factor	Modalities	OR [95% CI]	P	Global P
Age (years)	[60–70] vs <60	1.292 [0.908–1.839]	0.154	<b>0.004</b>
	>70 vs <60	2.077 [1.350–3.195]	<b>&lt;0.001</b>	
Daily number of pills	Unit = 1	0.948 [0.908–0.990]	<b>0.016</b>	
Total B-IPQ score	Unit = 1	0.946 [0.928–0.964]	<b>&lt;0.001</b>	
Overall satisfaction with long-term treatment of gout	Unit = 1	1.205 [1.120–1.297]	<b>&lt;0.001</b>	
Patience	Preferring €1500 in 1 year	1.894 [1.377–2.605]	<b>&lt;0.001</b>	
Obedience	Declaration of preference for fastening seatbelt	1.806 [1.310–2.490]	<b>&lt;0.001</b>	
Compliance with diet advice	Yes	1.868 [1.378–2.533]	<b>&lt;0.001</b>	

**Notes:** This table shows data where patients with missing data on the most recent measured serum levels of uric acid level were included in the analysed population (n 1204). Bold data indicates significant data.

to represent this “intertemporal choice”, assuming that there is a correlation between preferences in financial and health domains.<sup>31</sup> The seatbelt behaviour question centres on another health behaviour intended to indirectly protect the respondent, and, indeed, fastening seatbelt behaviour was found in this study to be associated with health preventive practices.<sup>32</sup> However, concerning more specifically the rear seat, the intention to be obedient to the law may also cause this behaviour;<sup>33</sup> in fact, some may refuse to fasten their seatbelts, manifesting reactance, i.e., a resistance that arouses in people when they consider that their freedom is threatened.<sup>34</sup> In a previous study of people with type 2

diabetes, we observed a link between reactance and nonadherence to medication.<sup>7</sup>

A link between patience and adherence to medication was observed in patients with type 2 diabetes<sup>4–8</sup> and asthma,<sup>35</sup> whereas impatience was found to be associated with obesity,<sup>36</sup> overweight<sup>37</sup> and various addictions.<sup>38</sup> A link between obedience, assessed by this seatbelt question, and adherence to medication was also observed in people with type 2 diabetes in two independent studies.<sup>6,7</sup> Here, the two traits of character patience and obedience were investigated simultaneously in a single study for the first time, and both were found to be strong determinants of



**Table 6** Factors Associated With Controlled Serum Uric Acid Levels (Univariate Tests)

Factor	Modalities	OR [95% CI]	P	Global P
Age (years)	[60–70] vs <60	1.198 [0.896–1.603]	0.223	0.068
	>70 vs <60	1.451 [1.059–1.989]	<b>0.021</b>	
Gender	Female vs male	0.878 [0.626–1.228]	0.447	
BMI (kg/m <sup>2</sup> )	≤25 vs >30	1.438 [0.999–2.069]	0.051	0.046
	[25–30] vs >30	1.341 [1.031–1.744]	<b>0.029</b>	
Tophus	Yes vs no	2.028 [1.308–3.145]	<b>0.002</b>	
Renal disorder	Yes vs no	1.083 [0.772–1.518]	0.645	
HBP + T2D + DL	Yes vs no	0.987 [0.725–1.342]	0.932	
History of myocardial infarction	Yes vs no	0.877 [0.465–1.654]	0.685	
Existence of comorbidities	Yes vs no	0.914 [0.720–1.162]	0.464	
Regular measurement of serum uric acid	Yes vs no	4.825 [1.673–13.916]	<b>0.004</b>	
Number of acute attacks of gout	>5 vs ≤2	0.254 [0.055–1.168]	0.078	<b>&lt;0.001</b>
	During the last 12 months	[2–5] vs ≤2	0.428 [0.285–0.642]	
Information on lifestyle changes	Yes vs no	2.091 [1.393–3.139]	<b>&lt;0.001</b>	
Daily number of tablets	Unit = 1	1.002 [0.968–1.037]	0.915	
Total B-IPQ score	Unit = 1	0.944 [0.930–0.959]	<b>&lt;0.001</b>	
Overall satisfaction with respect to long-term treatment of gout	Unit = 1	1.416 [1.324–1.515]	<b>&lt;0.001</b>	
Frequency of alcohol use	Occasionally vs regularly	1.697 [1.090–2.641]	<b>0.019</b>	<b>&lt;0.001</b>
	Never vs regularly	1.605 [1.236–2.082]	<b>&lt;0.001</b>	
Number of glasses of alcohol taken during an ordinary day	1 or 2 vs >2	1.852 [1.449–2.368]	<b>&lt;0.001</b>	
Frequency of drinking six or more standard glasses of alcohol	Never or < once/month vs regularly	1.705 [1.287–2.259]	<b>&lt;0.001</b>	
Consumption of soda	Never vs regularly	2.028 [1.286–3.199]	<b>0.002</b>	<b>0.010</b>
	Occasionally vs regularly	1.799 [1.147–2.823]	<b>0.011</b>	
Consumption of beer	Never vs regularly	2.241 [1.553–3.233]	<b>&lt;0.001</b>	<b>&lt;0.001</b>
	Occasionally vs regularly	2.045 [1.452–2.880]	<b>&lt;0.001</b>	
Smoking	No vs yes	1.566 [1.151–2.130]	<b>0.004</b>	
Long-term treatment with febuxostat at time of inclusion	Yes vs no	7.922 [5.996–10.467]	<b>&lt;0.001</b>	
Patience	Preferring €1500 in 1 year	1.214 [0.955–1.543]	0.113	
Obedience	Declaration of preference for fastening seatbelt	1.827 [1.366–2.444]	<b>&lt;0.001</b>	
Adherence to medication prescription Adherent vs nonadherent		2.283 [1.641–3.178]	<b>&lt;0.001</b>	
Compliance with dietary advice	Yes vs. No	2.246 [1.730–2.916]	<b>&lt;0.001</b>	
Compliance with exercise advice	Yes vs. No	1.666 [1.308–2.122]	<b>&lt;0.001</b>	

**Notes:** Model of probability is "last serum uric acid level is ≤360 μmol/L = Yes". Bold data indicates significant data.

**Table 7** Factors Associated With Controlled Uric Acid Levels (Multivariate Logistic Model)

Factor	Modalities	OR [95% CI]	P
Presence of tophus	No vs yes	2.321 [1.307–4.122]	<b>0.004</b>
Total B-IPQ score	Unit = 1	0.975 [0.957–0.994]	<b>0.009</b>
Overall satisfaction with respect to long-term treatment of gout	Unit = 1	1.258 [1.156–1.368]	<b>&lt;0.001</b>
Treatment by febuxostat at inclusion	Yes vs no	8.019 [5.742–11.200]	<b>&lt;0.001</b>
Obedience (seatbelt)	Yes vs no	1.583 [1.076–2.330]	<b>0.020</b>
Compliance with diet	Yes vs no	1.614 [1.141–2.284]	<b>0.007</b>
Compliance with advice for physical activity	Yes vs no	1.434 [1.025–2.007]	<b>0.035</b>

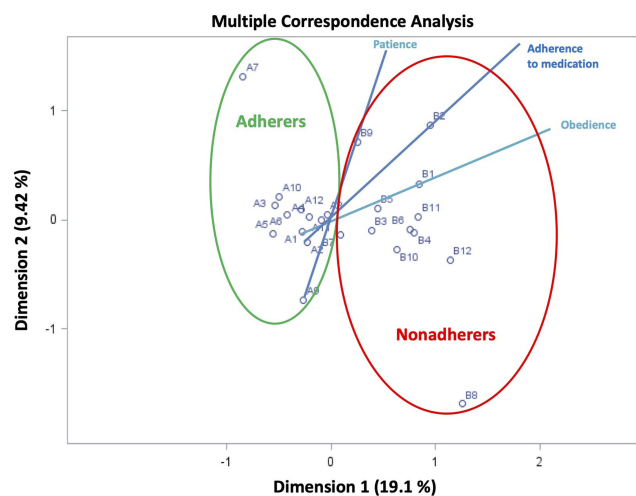
**Notes:** This table shows data based on patients without missing data (n= 936). Bold data indicates significant data.

adherence to medication in multivariate analyses (Tables 4 and 5). Obedience was found to be an independent determinant of achievement for the control of serum levels of uric acid in multivariate analyses (Table 7). In the same vein, we observed in another study in people with diabetes a link between obedience, as determined by the seatbelt question, and HbA1c.<sup>6</sup>

Secondly, this study also provided strong evidence that different aspects of adherence (medication, compliance with dietary, alcohol, soda and beer recommendations, exercise practices, smoking status and regular screening of serum uric acid levels) were linked; this was shown both in the univariate analyses of adherence to medication (Table 2) and in multiple-correspondence analyses

(Figure 1). This clustering was expected if character traits do have real causal effects on adherence.

Finally, this study, which investigated the effects of patience and obedience simultaneously for the first time, provided evidence that these traits, as defined in this study, are linked (Table 8). This link may be caused by the fact that the seatbelt question is not specific for obedience and may also be influenced by the patient's relationship to temporality. However, it is tempting to speculate that patience and obedience represent the manifestations of two related brain executive functions that are by and large located in the prefrontal cortex. This speculation is consistent with the hypothesis that the lack of maturation of these two functions in adolescents<sup>39,40</sup> explains the frequent nonadherence and risk-taking observed at this age.



**Figure 1** Nonadherence as a syndrome. A1: obedience (fastening seatbelt): yes; B1: no. A2: adherence to medication: yes; B2: no. A3: achieving goal for serum uric acid (latest available measurement,  $\leq 360$   $\mu\text{mol/L}$  vs  $>360$   $\mu\text{mol/L}$ ): yes; B3: no. A4: nonsmoker; B4: smoker. A5: compliance with directives on exercise: yes; B5: no. A6: compliance with diet recommendations: yes; B6: no. A7: lifestyle instructions given by the doctor: yes; B7: no. A8: regular measurements of serum uric acid level: yes; B8: no. A9: patience (preferring to receive €1500 in 1 year): yes; B9: impatience (preferring to receive €500 today). A10: 1 or 2 glasses of alcohol on an ordinary day; B10:  $>2$  glasses of alcohol. A11: consumption of soda only occasionally or never; B11: regular consumption of soda. A12: consumption of beer only occasionally or never; B12: regular consumption of beer.

## Strengths And Limitations Of The Study

One of the strengths of this study is the consistency exhibited between the data presented here and those previously observed in different patient populations and in different settings,<sup>4–8</sup> which is reassuring regarding their respective validities and generalisability. In addition, this study's originality lay in its simultaneous testing of the involvement of the two traits of character. Moreover, it provided a detailed analysis of adherence to diet prescriptions, allowing a link to be demonstrated between adherence to medication and lifestyle changes.

In general, there were little missing data, except for the last measurement of serum uric acid level (n = 331). Interestingly, the data shown in Table 2 indicate that people with missing data had a half as low risk of being adherent to medication than controlled patients. Actually, data presented in Table 3 indicate that they had fewer gout complications and comorbidities than people in whom serum uric acid data were available. This disease characteristics may explain the lack of serum uric acid measurement since data

**Table 8** Patience And Obedience Relationship

		Obedience		
		Yes (N = 1073)	No (N = 350)	P value Yes Vs No
Patience	Yes	553 (51.8%)	134 (38.5%)	<b>&lt;0.001</b>
	No	514 (48.2%)	214 (61.5%)	
	Missing data	6	2	

**Notes:** Patience: answer of €1500 to the question: "Imagine that one day you were offered €500 now or €1500 in 1 year: which would you choose?" Obedience: answer Yes to "do you fasten your seatbelt when seated in the back seat of a car?" Bold data indicates significant data.

missing was not associated with patience or obedience. Importantly, we checked that including these patients with missing data in the multivariate analyses had essentially no effect on the demonstration of the determining effects of patience and obedience on adherence to medication (Table 5).

The main limitation of this study is the relative value of the data, which relied on self-report questionnaires and not on the direct observation of patients' behaviours. Thus, the associations found for different aspects of nonadherence (i.e., to medication and to lifestyle change) may be simply due to the fact that patients gave similar answers to similar questions. In addition, patients were interviewed at the doctor's appointment. Thus, although their names were not mentioned in the questionnaire, they may have given socially desirable answers.

More specifically, the assessment of adherence through questionnaires and interviews is in general less robust than direct measurements (pharmacy records or pill counts). This cohort presented a higher adherence to medical therapy (almost 80%) than other representative data available in the literature: gout is the chronic illness for which adherence to treatment is the lowest.<sup>19</sup> However, a recent meta-analysis found a mean rate of adherence of 63%, as assessed in interviews, with a 95% CI of 42%–83%.<sup>20</sup> These assessments have therefore only a relative value. Finally, the evaluation of patient adherence in this study relied on a five-item questionnaire that was not formally validated. Nevertheless, the fact that adherence to medication was found to be significantly associated with age,<sup>3,19</sup> and with controlled serum levels of uric acid suggests that this questionnaire may have at least some value as a marker of adherence. Incidentally, the same questionnaire utilised here was also used in our study of people with type 2 diabetes, in which adherence was found to be associated with achievement of control of HbA1c level.<sup>4</sup>

Finally, the percentage of patients under febuxostat therapy in this study was rather high and may not reflect

general gout treatment. No marketing or commercial representatives of the sponsor, who commercialises this new drug, were involved in the recruitment of investigators, which was organised by Euraxi Pharma, the contract research organisation appointed by the sponsor. However, this does not rule out a recruitment bias, linked to the fact that the GPs who participated in the study had a large active file of patients with gout and may have received Menarini reps recently, explaining a high rate of febuxostat prescription.<sup>41</sup> Nevertheless, we do not think that this possible bias changes the main conclusions of this study, the aim of which was to investigate the reasons of adherence to drugs in general. Incidentally, we observed that febuxostat led to better adherence than allopurinol (Table 2, OR 1.462 [1.130; 1.892],  $P=0.004$ ) and seemed to have a better efficacy in achieving serum uric acid control (Table 6, OR 7.922 [5.996–10.467],  $P<0.001$ ). This superiority of febuxostat in achieving serum uric acid control is consistent with other data from the literature. For instance, Cutolo et al observed in a randomised study that febuxostat showed a higher probability to achieve the recommended target serum uric acid concentration than allopurinol (odds ratio: 2.43 [95% CI: 2.119–2.789] and 4.05 [95% CI: 3.41–4.82] for serum uric acid levels  $<6$  mg/dL and  $\leq 5$  mg/dL, respectively.<sup>42</sup>

### Conclusion: Character Traits, Patients' Preferences And Nonadherence As A Syndrome

The determinants of nonadherence to medication are complex, involving factors linked to the nature of the disease, nature of treatment, social context and the psychology of the patient.<sup>1</sup> For people with gout, a study showed the provocative fact that using non-steroidal anti-inflammatory drugs within the year before treatment initiation was predictive of nonadherence to urate-lowering therapy (OR, 1.15; 95% CI, 1.00–1.31), refuting the intuitive hypothesis that active gout responsible for severe pain would improve adherence,<sup>43</sup> in accordance with the idea that nonadherence is more frequent

in silent diseases. Evidently, nonadherence is a complex issue, since we observed in this study that people with less severe gout are also nonadherent to medication (Table 3).

The first main conclusion of this study is that it extends to gout the consideration that among other psychological factors, character traits, specifically patience and obedience, are associated with adherence to long-term therapies, suggesting that this link between character traits and adherence is not specific to a given disease. Second, we propose that the involvement of character traits explains, at least in part, that the different aspects of adherence, medication and lifestyle (diet, exercise, alcohol and smoking status) are often linked together,<sup>2,3,44,45</sup> as illustrated in multiple-correspondence analyses (Figure 1).

Therefore, these observations suggest that nonadherence to treatment is a syndrome. This study provides empirical verification of a hypothesis suggesting, on the basis of essentially philosophical arguments, that different aspects of adherence or nonadherence are interconnected by common causal mechanisms.<sup>26,30</sup> This phenomenology of adherence is especially visible in a disease such as gout, the treatment of which requires, as with diabetes, both a medication regimen and lifestyle changes.<sup>10–18</sup> Incidentally, since the lack of data on serum uric acid was found linked to nonadherence to medication prescriptions and to advice on diet, alcohol and soda, and to smoking, we propose that lack of disease monitoring be included in the nonadherence syndrome. This is consistent with the general observation that patients who are nonadherent to their medication regimens are less likely to perform lab analyses.<sup>2,3</sup>

This interpretation clarifies also the enigmatic fact that, in randomised clinical trials, patients allocated to placebo consistently exhibit a higher survival rate when they are adherent,<sup>46,47</sup> leading to explanations using the “healthy adherer” concept for this fascinating observation.<sup>46</sup> The data reported herein support this explanation by demonstrating a strong link between adherence to medication and dietary and exercise recommendations and other protective behaviours. We suggest that character traits such as patience and obedience and, possibly, others such as fidelity to habits, optimism, joy and caution<sup>29</sup> have a real causal effect, leading, when they are present, to a “healthy adherer” phenotype. By “real causal effect”, we mean that it is not only a statistical link between observations but a mechanism, in the same sense that insulin *causes* a decrease in blood glucose concentration.<sup>26,30</sup> The absence of these positive character traits leads to conditions of what we propose to dub a “nonadherence syndrome”:

patience and obedience may be encompassed in the more general concept of cautious behaviour (avoidance of risks), which has been found by us<sup>7</sup> and others<sup>48</sup> to be linked to adherence in people with diabetes.

Finally, recognising the causal effects of character traits on the occurrence of nonadherence may in part explain the relative failure of interventions intended to improve adherence.<sup>49</sup> Moreover, this new concept may have important ethical implications because character traits shape patients’ preferences, which are a central part of shared decision-making.<sup>50</sup>

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## Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work. More specifically, GR, LM, RMF, PM and IEB were involved in designing the study protocol, coordinating the study, and analysing the results. GC performed the statistical analysis. GR designed and supervised the specific analysis of the implication of character traits in adherence presented in this report and wrote the manuscript.

## Disclosure

GR, LM and RMF received fees from Menarini to design the study and to analyse the results. IEB and PM are Menarini employees. GC is an employee of Capionis. The authors report no other conflicts of interest in this work.

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