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Perceived control as a predictor of medication adherence in people with Parkinson's: a large-scale cross-sectional study

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ABSTRACT

Purpose: Medication adherence is a multi-faceted construct associated with several positive consequences in people with chronic conditions. However, non-adherence currently represents a major issue in Parkinson's, potentially due to low perceptions of control. This study investigated the predictive ability of several aspects of perceived control on adherence in people with Parkinson's, while accounting for previously established predictors such as depression and medication variables.

Materials and Methods: An online cross-sectional survey was carried out with 1210 adults with Parkinson's from 15 English-speaking countries. Demographic and clinical questions, as well as measures of depression, aspects of perceived control, and medication adherence were included. Pearson's correlations and a 4-block hierarchical regression analysis were performed to assess the relationship between the variables.

Results: Perceived control explained a slightly higher amount of variance in medication adherence compared to medication variables when entered in the last block. Unexpectedly, depression was not significantly related with adherence. Internal locus of control was an independent negative predictor of adherence, while external dimensions of locus of control emerged as independent positive predictors.

Conclusions: In people with Parkinson's, perceptions of control may have a larger impact on adherence compared to medication variables. Implications for clinical practice and future research are discussed.

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Parkinson's disease; perceived control; depression; medication adherence; mastery; locus of control; self-efficacy; symptom control; adaptive control

➤ IMPLICATIONS FOR REHABILITATION

- Perceived control and depression are considered important constructs for medication adherence in Parkinson's, which in turn is often problematic for affected individuals.
- The specific predictive value of different aspects of perceived control on medication adherence in Parkinson's is currently unclear.
- This large-scale study found that perceptions of control may have a larger impact on adherence compared to medication variables, while depression was unrelated to it.
- A need for psychologically-informed interventions, person-centred approaches to medication management, and Parkinson-specific measures of adherence are highlighted.

Introduction

Parkinson's[1] is the second most common neurodegenerative disease in older people [1]. It is associated with movement disorders, including bradykinesia, muscular rigidity, resting tremor, and postural and gait impairment, as well as cognitive difficulties leading to dementia [2]. In addition, a range of psychological difficulties can be experienced by people with Parkinson's (PwP). These often include low mood, anxiety, uncertainty, and reduced impulse control [3–5], while hallucinations are observed more rarely [6]. Apathy is also frequently reported, although the validity of current conceptualisations in PwP has been critically examined [7].

Since there is currently no cure for Parkinson's, symptomatic treatments represent the cornerstone of its clinical management [2]. Many PwP take a number of different medications, especially at later stages [8], and are 40% more likely to be on five to nine repeated prescriptions compared to the general population [9]. These medications often include neurological (e.g., levodopa) and psychiatric (e.g., antidepressants, anxiolytics) treatments, need to be taken a very specific times, and have potentially serious side effects that require close monitoring and multiple daily doses [10]. As a consequence, it is perhaps not surprising that up to 70% of PwP do not adhere partially or completely to the prescribed medication regime [10], making medication adherence a major issue in Parkinson's, arguably more than in other complex conditions [9,11].

Medication adherence can be defined as the extent to which patients' medication behaviour is consistent with the medical

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guidance provided [12]. It is associated with a wide range of positive consequences, including better clinical outcomes, fewer remissions, and increased quality of life [13]. As a result, non-adherence represents a major issue in modern healthcare, and is believed to be influenced by multiple components, such as healthcare settings, socio-economic variables, therapy regimes, health conditions, and patients' behaviour [14]. Accordingly, factors such as comorbid health problems, side effects, and the frequency and complexity of treatments have all been traditionally proposed to explain non-adherence in individuals with Parkinson's [15,16]. Psychological factors also play a pivotal role [17], as psychological difficulties have been shown to influence medication adherence in PwP [18,19]. In particular, higher levels of depression have consistently proved to predict lower adherence [20–23], mirroring a finding which has been historically reported with older people in general [24,25]. As depression is estimated to affect up to 50% of PwP [26], it could be hypothesised that its successful management would be a viable route to tackle non-adherence in this population. However, this is currently unclear, as suggested by a systematic review which found that, while the association of depression with suboptimal adherence was evident, no indication could be provided on whether managing depression would improve adherence [18].

Perceived control, defined as beliefs about the extent of one's influence over internal states, behaviours, environments, and outcomes [27], may also affect medication adherence in PwP [28]. These beliefs are often conceptualised as a number of distinct sub-constructs [29,30], which may include: a) mastery (feeling in control of health and social aspects of life; [31]); b) locus of control (or 'LOC', attributing outcomes to own's effort rather than external forces or circumstances; [32]); symptom control (feeling in control over symptoms and treatment; [33]); c) adaptive control (feeling capable of adapting to events in life; [29]); and d) self-efficacy (control over the execution of actions required by an outcome; [34]). Along with its sub-constructs, perceived control is thought to play a pivotal role in the successful adjustment not only to chronic illness in general [35], but also to neurodegenerative diseases specifically [36–39], including Parkinson's [40]. Moreover, it has been consistently associated with medication adherence in people with chronic conditions, with internal locus of control, increased feelings of personal and symptom control, and higher self-efficacy found to predict higher levels of adherence in several clinical populations [41,42] – again including Parkinson's [43,44].

A number of studies have tested the extent to which depression and specific sub-constructs of perceived control predict medication adherence in PwP (e.g., [43–45]). However, to our knowledge no study to date has investigated the role of these constructs as predictors of adherence in Parkinson's within the same multifactorial model, nor which aspect of perceived control most strongly predicts adherence. This represents a considerable limitation in the current literature, since evidence has shown that behavioural interventions can successfully improve perceptions of control in individuals with Parkinson's [46–48] as well as other chronic conditions [49,50].

As a consequence, the aim of the present study was to test whether different sub-constructs of perceived control predict medication adherence in PwP after taking into account demographics as well as medication and clinical variables, including depression. More specifically, it was hypothesised that perceived control would explain a higher amount of variance in adherence after controlling for the predictive value of other variables.

Methods

Design

The present study adopted an online cross-sectional survey design, consisting of demographic and clinical questions, as well as measures of depression, different aspects of perceived control (mastery, adaptive control, symptom control, self-efficacy, locus of control), and medication adherence.

Participants

Convenience sampling methods were used. Eligible and potentially interested PwP were offered the opportunity to participate by voluntary sector organisations (e.g., Parkinson's organisations) and through social media channels (Facebook and Twitter). To be eligible for the study, participants had to meet all the following criteria: a) be aged 18 or older; b) be living in a country where English was one of the official languages; c) be diagnosed with idiopathic Parkinson's; d) be currently taking any medications for Parkinson's. Informed consent was obtained from all participants *via* an electronic form presented on a webpage at the beginning of the survey.

An *a priori* power calculation based on the overall R^2 significance for a multiple regression analysis – assuming a medium effect size ($f^2 = 0.15$) with a projected inclusion of 10 to 20 predictors and an α level of $p = 0.05$ – indicated that between 118 and 157 participants were required to achieve a 0.80 level of power.

Measures

Predictors

Demographic and clinical information. Participants responded to questions about demographic variables (e.g., age, gender, country, and ethnicity) and their condition and its treatment (e.g., time since diagnosis, disease severity, comorbidities, complexity of medication regime, access to medication).

Parkinson's Disease Questionnaire - 8 (PDQ-8). The PDQ-8 measures perceived disease severity over eight dimensions: mobility, activities of daily life, emotional well-being, social support, cognition, communication, bodily discomfort, and stigma [51]. It yields a standardised score (0 – 100), with higher scores indicating higher disease impact, and has consistently demonstrated good validity and reliability (Cronbach's $\alpha = 0.73 - 0.88$ [52]).

Geriatric Depression Scale – Short Form (GDS-15). The GDS-15 is a 15-item self-report questionnaire which measures depression in older adults. The items are based on yes/no questions, yielding a total score ranging between zero and 15, with higher scores indicating higher levels of depression [53]. It is among the most frequently adopted measures for depression in PwP due to its excellent psychometric properties (e.g., high discriminant validity and Cronbach's α of 0.92; [54]) as well as low overlap with symptoms of potential physical comorbidities [55]. A score higher than four is suggested as optimal to distinguish clinical levels of depression [56].

Pearlin Mastery Scale (PMS). The PMS is a self-report measure of perceived mastery, consisting of seven items rated on a 4-point rating scale [31]. It yields a total score ranging from seven to 28, with higher scores representing higher perceived mastery.

The scale has been previously used with PwP [57], showing good validity and reliability (Cronbach's $\alpha = 0.70$).

Multidimensional Health Locus of Control – Form C (MHLC-C). The MHLC-C is an 18-item self-report measure assessing LOC in people with an existing health condition on a 6-point rating scale [58]. It examines four main LOC dimensions, each yielding an independent score: Internal (i.e., attributing control of outcomes to oneself; range: 6 – 36), Chance (i.e., attributing control of outcomes to chance; range: 6 – 36), Doctors (i.e., attributing control of outcomes to doctors or other clinicians; range: 3 – 18), and Other People (i.e., attributing control of outcomes to significant others; range: 3 – 18). Higher scores indicate the higher prominence of each attributional style. The MHLC-C has been used with PwP before, showing good validity as well as acceptable to good reliability across its dimensions (e.g., Cronbach's α ranging from 0.60 to 0.80; [59,60].

Symptom Control Scale (SCS). The SCS consists of six items rated on a 6-point rating scale, yielding a score ranging between six and 36, with higher scores indicating higher levels of perceived symptom control in people with an existing health condition [33]. Although it has not been used with PwP before, it has consistently shown good to excellent psychometric properties when used with people with other chronic diseases (Cronbach's $\alpha = 0.80 - 0.89$; [61]).

Parkinson's UK Scale of Perceived Control (PUKSoPC). The PUKSoPC is a self-report 15-item questionnaire evaluating adaptive control in PwP. It consists of a 5-point rating scale yielding a total out of 75, with higher scores indicating higher levels of adaptive control [62]. The PUKSoPC has been extensively validated with a sample of over 200 PwP, showing good face, concurrent and convergent validity, as well as good test-retest reliability and internal consistency (Cronbach's α ranging from 0.77 to 0.92; [62]).

General Self-Efficacy Scale (GSE). The GSE is a 10-item self-report measure of self-efficacy beliefs about difficult demands in life [63]. It is rated on a 4-point rating scale, yielding a total score ranging between 10 of 40, with higher scores representing higher levels of perceived self-efficacy. The GSE has been previously validated with a sample of PwP, showing excellent psychometric properties (Cronbach's $\alpha = 0.95$; [64]).

Outcome variable

Medication Adherence Report Scale (MARS-5; [65]*).* The MARS-5 is a 5-item self-report measure of medication adherence based on a 5-point rating scale. It is worded neutrally to be applicable to any disease and yields a total score out of 25, with higher scores indicating higher levels of adherence. Currently, no self-report adherence scale has been validated for Parkinson's specifically, and none of the scales used previously with PwP fully capture all its components [66]. Therefore, the MARS-5 was chosen in light of its good validity and reliability (Cronbach's α ranging from 0.67 to 0.89; [65]), its recognised usefulness in populations with psychological difficulties [67], as well as its previous use with PwP [68]. A score below 23 has been suggested as a highly sensitive cut-off for non-adherence (i.e., 89.5%; [69]).

Patient and Public Involvement

Prior to beginning data collection, Patient and Public Involvement was sought with 10 volunteers with Parkinson's *via* local Parkinson's organisations (e.g., Parkinson's UK), five of whom eventually accepted to assess the acceptability and feasibility of the full draft of the survey and advertising materials (with the remaining five having to withdraw due to personal commitments). While demographic data were not collected systematically, these PPI experts fell within the range of the typical age of onset for Parkinson's (i.e., 60+), were currently retired, and reported having average digital literacy for their age cohort (e.g., being able to handle emails, web browsing and other basic internet-related tasks). Thus, they were believed to represent the target PwP population for the survey.

In response to the feedback received by the PPI experts, the following changes were made: a) to reduce burden on participants, the chosen measures were reviewed to ensure that the shortest versions of the most appropriate tools were adopted, which were later confirmed to be accessible and feasible by PPI experts; b) the text of the advertising material was reviewed and shortened to improve flow and readability, and an approximate indication of the duration of the survey was added; c) questions exploring Parkinson's medications were made more specific to avoid confusion between daily timing and doses; d) a progress bar was added to allow participants to monitor their progress throughout the survey; e) additional instructions were added to the MHLC-C in order to make its items more compatible with the progressive nature of Parkinson's (e.g., beliefs around improving the management of Parkinson's rather than the condition itself), as also recommended by the measure's author for such specific cases [58].

Procedure

The survey was hosted on the Qualtrics survey platform. Participants were approached *via* collaborating associations and social media with a weblink to an information sheet outlining the details of the project. If interested, they were asked to fill in a written consent form and answer a number of questions to check whether they met all the inclusion criteria[2]. Following positive confirmation, the survey was opened, with the order of the standardised questionnaires randomised to prevent any order effects [70]. On average, the survey took 20 to 25 min to complete. Survey fatigue was managed by allowing participants to save their progress on the survey and resume it within two weeks.

Missing data were avoided by requiring responses to all of the online questions and recording responses only when participants submitted the complete survey. The potential risk for fraudulent responses and bots was managed *via* Qualtrics' built-in fraud and bot detection feature. The data collection was carried out between January and June 2021.

Data analysis

Data were analysed using IBM SPSS Statistics 28. Descriptive statistics were collated and the absence of concerning numbers of outliers was confirmed [71]. While all outcome variables were analysed as continuous, available established cut-offs were utilised for sample descriptive purposes. Two-tailed Pearson's correlations were used to investigate the degree of relationship between variables. Following this, a hierarchical regression analysis was conducted to investigate the differences in predictive values between

demographic, clinical, and medication variables, and different aspects of perceived control.

Predictors were entered into the regression model if they correlated significantly with the outcome variable ($p < 0.05$; [72]). Based on previous similar research [73,74], a 4-block structure theoretically relevant for the hypothesis was planned: 1) Demographics (age, gender); 2) Clinical Variables (time since diagnosis, impact of Parkinson's, comorbidities, depression; 3) Medication Variables (e.g., number of daily doses, paying for medications); 4) Perceived Control Variables (adaptive control, symptom control, mastery, self-efficacy, Internal LOC, Doctors LOC, Other People LOC). This enabled us to test the extent to which variation in medication adherence in PwP could be explained by perceived control after controlling for demographic, clinical, and medication variables, and if so, which aspect of perceived control best predicted adherence.

Ethical approval

This study was reviewed and approved by the Faculty of Medicine and Health Sciences Research Ethics Committee at the University of East Anglia (ref: 2020/21-045).

Results

Characteristics of the sample

In total, 1210 individuals with Parkinson's from 15 English-speaking countries participated. The majority were female (60.5%, $n = 732$), white ($n = 1143$; 94.5%), native English speakers (96.2%, $n = 1164$), and 65 years old on average ($SD = 9.08$, range: 26 – 89). Most participants came from the United Kingdom (65.3%, $n = 790$), with the second largest group residing in the United States (17.9%, $n = 217$) and the third in Canada (4.2%, $n = 51$). The mean time since diagnosis was 6.58 years ($SD = 5.30$, range: 0.08 – 30 years), while the mean perceived impact of Parkinson's was 32.93/100 with a SD of 18.96 – i.e., consistent with the mean impact reported by PwP across stages I-III of the Hoehn and Yahr Scale of Parkinson's severity [51]. Just over half of participants reported clinical levels of depression (i.e., GDS-15 > 4; 52.2%, $n = 632$), with a mean score of 5.72 (SD = 4.10, range: 0 – 15), corresponding to mild depression. Similarly, the majority reported sub-optimal medication adherence (i.e., MARS-5 < 23; 54.3%, $n = 657$), with a mean score of 21.47 (SD = 2.99, range: 9 - 25).

The average number of medication doses per day was 4.36 (SD = 1.94, range: 1 – 18). Medications were taken alone (i.e., without the support of a carer) by the majority of PwP (96%; $n = 1162$), typically without having to pay for medication (67.7%, $n = 819$), experiencing physical issues accessing medication (85%, $n = 1028$), and without varying the dosage or the number of doses with their clinical team's approval (76%, $n = 919$). On average, the participants rated their knowledge of the purpose of their Parkinson's medication as moderately high (mean = 7.23/10; 0 = low, 10 = high), albeit with considerable variability among them (SD = 4.40). Slightly less than half of PwP had comorbid physical issues (47.4%, $n = 573$), but the majority took other types of medication besides those for Parkinson's (77.8%, $n = 941$). These included psychiatric medication for around one third of participants (36.2%, $n = 438$). When asked whether they received any form of psychological support for mental health difficulties, only 8.5% of participants ($n = 103$) answered positively. The analysis of reliability showed internal consistencies ranging from acceptable to excellent for all measures (Cronbach's $\alpha = 0.60 - 0.92$; [75]), except for the Other People subscale of the MHLC-C (Cronbach's $\alpha = 0.56$), potentially due to its 3-item structure [76]. Table 1 summarises demographic information and Table 2 summarises the participants' scores on standardised measures and the reliability figures.

Table 1. Demographic characteristics.

Variable	N	%	Mean	SD
Age (yrs.)			65.05	9.08
Gender				
Female	732	60.5		
Male	478	39.5		
Language (English)				
Native	1164	96.2		
Non-native	46	3.8		
Country				
Anguilla	1	0.1		
Australia	40	3.3		
Barbados	1	0.1		
Canada	51	4.2		
Guernsey	1	0.1		
Hong Kong	1	0.1		
India	5	0.4		
Ireland	26	2.1		
Malta	1	0.1		
New Zealand	42	3.5		
Nigeria	1	0.1		
Philippines	3	0.2		
South Africa	30	2.5		
United Kingdom	790	65.3		
United States	217	17.9		
Ethnicity				
White (any white background)	1143	94.5		
Asian (any Asian background)	18	1.5		
Prefer not to say	12	1.0		
Mixed/multiple ethic groups	12	1.0		
Other	8	0.7		
Hispanic or Latino/a	7	0.6		
Aboriginal (Australia & New Zealand)	5	0.4		
Black, African, or Caribbean	3	0.2		
Arab	1	0.1		
Native American	1	0.1		
Time since diagnosis (yrs.)			6.58	5.30
Physical comorbidity				
Yes	573	47.4		
No	637	52.6		
Taking medication alone				
Yes	1162	96.0		
No	48	4.0		
Doses per day			4.36	1.94
Varying doses (with clinical team approval)				
Yes	291	24.0		
No	919	76.0		
Paying for medication				
Yes	391	32.3		
No	819	67.7		
Medication knowledge (0 = low, 10 = high)			7.23	4.40
Physical problems accessing medication				
Yes	182	15.0		
No	1028	85.0		
Other medication				
Yes	941	77.8		
No	269	22.2		
Psychiatric medication				
Yes	438	36.2		
No	772	63.8		
Psychological support				
Yes	103	8.5		
No	1107	91.5		
Depression (GDS-15 > 4)				
Depressed	632	52.2		
Not depressed	578	47.8		
Adherence (MARS-5 < 23)				
Adherent	553	45.7		
Not adherent	657	54.3		

GDS-15: Geriatric Depression Scale-15; MARS-5: Medication Adherence Report Scale; SD: standard deviation; yrs: years.

Table 2. Descriptive statistics for standardised measures.

Variable	Mean	SD	α
PDQ-8	32.93	18.96	0.84
PUKSoPC	51.91	10.08	0.89
PMS	19.08	3.73	0.81
GDS-15	5.7174	4.10	0.87
SCS	26.61	5.18	0.86
GSE	29.22	5.39	0.92
MHLC-C Internal	21.54	5.88	0.73
MHLC-C Chance	16.84	5.63	0.73
MHLC-C Doctors	12.79	3.13	0.60
MHLC-C Other People	9.98	3.18	0.56
MARS-5	21.47	2.99	0.72

α: Cronbach's alpha; GDS-15: Geriatric Depression Scale-15; GSE: General Self-Efficacy Scale; MARS-5: Medication Adherence Report Scale; MHLC-C: Multidimensional Health Locus of Control – Form C; PDQ-8: Parkinson's Disease Questionnaire-8; PMS: Pearlin Mastery Scale; PUKSoPC: Parkinson's UK Scale of Perceived Control; SCS: Symptom Control Scale; SD: standard deviation; yrs: years.

Correlations

The correlation matrix is illustrated in Table 3. This indicated that only age could be entered in the Demographics block, showing a significant negative relationship with adherence ($r = -0.059$, $p < 0.040$). In the Clinical Variables block, time since diagnosis ($r = -0.231$, $p < 0.001$), number of daily doses ($r = -0.131$, $p < 0.001$), and perceived impact of Parkinson's ($r = -0.160$, $p < 0.001$) were significantly correlated with medication adherence. However, this was not the case with depression, for which no significant relationship was found with the outcome variable ($r = -0.030$, $p = 0.294$).

With regards to the Medication Variables, the following emerged as significant correlates of adherence and were entered in block 3: number of doses per day ($r = -0.131$, $p < 0.001$), varying doses with the clinical team's approval ($r = -0.435$, p = <0.001), paying for medications ($r = -0.099$, $p < 0.001$), knowledge about medication ($r = 0.067$, $p = 0.020$), physical issues accessing medications ($r = -0.165$, $p < 0.001$), and taking medications other than Parkinson's ($r = -0.074$, $p = 0.010$).

Finally, the fourth block (Perceived Control Variables) consisted of all tested aspects of perceived control, except for symptom control ($r = 0.054$, $p = 0.059$) and the Chance dimension of LOC ($r = 0.050$, $p = 0.083$): mastery ($r = 0.058$, $p = 0.045$), self-efficacy ($r = 0.068$, $p = 0.019$), adaptive control ($r = 0.058$, $p = 0.043$), and Internal ($r = -0.066$, $p = 0.022$), Doctors ($r = -0.235$, $p < 0.001$) and Other People ($r = -0.124$, $p < 0.001$) LOC.

Hierarchical regression

The hierarchical regression model used is summarised in Table 4. As depression did not corelate significantly with medication adherence, it was not included among the clinical variables in Block 2[3]. All the data were checked to ensure that the assumptions of multiple regression were met. The scatterplots of predictor and outcome variables showed these were linearly related and that the residuals were uncorrelated (Durbin - Watson = 2.062; [77]). Variance inflation factors (VIF) and tolerance were below 10 and above 0.2 respectively, indicating no significant multicollinearity, while any issues with heteroscedasticity and non-normality of residuals were resolved *via* bootstrapping based on 1000 samples [75].

The final regression model was significant ($F_{(15,\ 1194)}$, $p < 0.001$) and explained 15.3% of variance in medication adherence ($R^2_{adj} = 0.153$). Age alone (Demographics) explained 0.4% of the variance ($p = 0{\cdot}004$), while the Clinical Variables contributed a further significant 6.6% of variance ($\Delta R^2 = 0.066$, $p < 0.001$). The addition of the Medication Variables block accounted for a further significant 4.2% of variance in medication adherence ($\Delta R^2 = 0.042$, $p < 0.001$). Finally, the Perceived Control Variables block accounted for an additional significant 5.2% of variance in medication adherence ($\Delta R^2 = 0.052$, $p < 0.001$).

In the final model, time since diagnosis ($\beta = -0.154$ $p < 0.001$) and perceived impact of Parkinson's ($\beta = -0.101$, $p = 0.005$) emerged as significant negative predictors in the Clinical Variables block. Almost all Medication Variables were significant predictors – taking other medications: $\beta = 0.075$, $p = 0.006$; knowledge of medication: $\beta = 0.073$, $p = 0.009$; having problems physically accessing medication: $\beta = -0.093$, $p = 0.001$; paying for medication: $\beta = -0.066$, $p = 0.021$; varying doses with the clinical team's approval: $\beta = -0.122$, $p < 0.001$.

In the Perceived Control Variables block, the degree to which PwP viewed themselves as having control over outcomes emerged as a negative predictor of medication adherence (Internal LOC; $\beta = -0.095$, $p < 0.001$), whereas attributing more control to doctors ($\beta = 0.177$, $p < 0.001$) and other people ($\beta = 0.086$, $p = 0.004$) both predicted higher levels of adherence.

Discussion

To our knowledge, this is the largest cross-sectional survey to date investigating medication adherence in people with Parkinson's (PwP), with most previous studies recruiting fewer than 500 participants (for the latest reviews see [19,78]) – i.e., less than half the sample in the present study.

The results showed that longer disease duration, higher disease impact, physical issues accessing medications, varying doses with the clinical team's approval, and paying for medication significantly predicted lower levels of adherence, while having more knowledge of the condition predicted more adherence. All these findings are consistent with previous evidence [18,19,45,79]. However, more unexpectedly, taking medications for conditions other than Parkinson's was a significant predictor of higher medication adherence. While this result appears to contradict the traditional link between polypharmacy and low adherence [15], it may also be seen as a form of adaptive behaviour, whereby PwP who need to take multiple medications become better at managing them over time.

All aspects of perceived control investigated, with the exception of having a sense of control over symptoms or attributing control to chance, were significantly associated with medication adherence. Perceived control explained a slightly higher portion of variance ($\Delta R^2 = 0.052$) than medication variables ($\Delta R^2 = 0.042$), even after controlling for all other types of variables, confirming our hypothesis. Internal LOC emerged as a weakly negative predictor of adherence (i.e., if PwP attributed more control over outcomes to themselves, they were slightly less likely to adhere to medication as prescribed). In contrast, Doctors LOC was a stronger positive predictor of adherence (i.e., if PwP attributed more control over outcomes to doctors or other clinicians, they were more likely to adhere to medication as prescribed) and the same was true for those who believed 'Other People' to have control, but to a lesser extent. This suggests that individuals with Parkinson's who attribute more control to themselves are more likely to be non-adherent, whereas those attributing more control to their doctors or significant others show higher levels of adherence.

Table 3. Correlation coefficients for all variables.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1 GENDER																								
2 AGE	−0.091**																							
3 TIME DIAG	.001	0.101**																						
4 COMOR	−0.019	0.154**	−0.049																					
5 MEDS ALONE	.104**	−0.042	−0.123**	−0.019																				
6 DAILY DOSES	0.002	0.023	0.405**	−0.003	−0.104**																			
7 VARY DOSES	0.063*	−0.033	0.179**	0.005	0.035	0.213**																		
8 PAY MEDS	0.045	−0.300**	−0.046	−0.093**	0.068*	−0.089**	0.049																	
9 KNOW MEDS	0.039	−0.004	0.009	−0.022	0.042	0.026	0.058*	0.018																
10 PP MEDS ACCESS	0.042	−0.081**	0.152**	.05	−0.104**	0.167**	0.066*	0.006	−0.013															
11 OTHER MEDS	−0.001	0.140**	−0.001	0.316**	0.014	0.033	0.008	−0.009	−0.045	0.03														
12 PSY MEDS	0.109**	−0.041	0.065*	0.085**	−0.067*	0.047	0.067*	0.127**	−0.039	0.111**	0.337**													
13 PSY SUPPORT	.089**	−0.131**	−0.056	0.132**	−0.059*	0.008	0.05	0.106**	−0.041	0.079**	0.070*	0.245**												
14 PUKSoPC	0.076**	0.105**	0.034	−0.027	0.150**	0	0.077**	−0.013	0.298**	−0.100**	−0.102**	−0.166**	−0.086**											
15 PDQ-8	0.035	−0.106**	0.242**	0.099**	−0.228**	0.259**	0.037	0.016	−0.151**	0.345**	0.151**	0.284**	0.181**	−0.425**										
16 PMS	−0.027	−0.005	−0.102**	−0.079**	0.162**	−0.137**	0.004	0.018	0.147**	−0.155**	−0.086**	−0.142**	−0.096**	0.526**	−0.545**									
17 GDS-15	−0.015	−0.029	0.038	−0.001	−0.103**	0.086**	0.02	0.01	−0.081**	0.107**	0.051	0.140**	0.072*	−0.352**	0.364**	−0.353**								
18 SCS	0.054	−0.090**	−0.099**	−0.049	0.203**	−0.149**	0.025	0.061*	0.173**	−0.125**	−0.092**	−0.111**	−0.053	0.526**	−0.395**	0.520**	−0.296**							
19 GSE	−0.003	−0.006	−0.176**	−0.048	0.191**	−0.153**	−0.002	0.059*	0.141**	−0.130**	−0.106**	−0.181**	−0.082**	0.519**	−0.478**	0.569**	−0.286**	0.471**						
20 MHLC-C_IN	−0.061*	−0.032	−0.021	−0.05	0.095**	−0.069*	0	0.118**	0.049	−0.042	−0.046	−0.075**	−0.039	0.233**	−0.139**	0.291**	−0.086**	0.475**	0.285**					
21 MHLC-C_CH	−0.054	0.012	−0.036	0.031	−0.036	−0.055	−0.053	−0.006	−0.159**	−0.007	0.008	0.014	−0.029	−0.232**	0.130**	−0.305**	0.115**	−0.167**	−0.106**	0.009				
22 MHLC-C_DR	−0.031	0.069*	−0.124**	0.027	−0.009	−0.086**	−0.015	−0.034	0.014	−0.089**	0.076**	−0.002	0.015	0.145**	−0.075**	0.113**	−0.086**	0.166**	0.155**	0.147**	0.048			
23 MHLC-C_OP	−0.049	0.008	−0.002	0.083**	−0.100**	0.043	0.024	−0.155**	−0.112**	0.074*	0.017	−0.004	0.002	−0.065*	0.184**	−0.214**	0.110**	−0.092**	−0.141**	−0.106**	0.223**	0.288**		
24 MARS-5	−0.002	0.059*	−0.231**	0.024	0.033	−0.131**	−0.159**	−0.099**	0.067*	−0.165**	0.074*	−0.054	−0.043	0.058*	−0.160**	0.058*	−0.03	0.054	0.068*	−0.066*	0.05	0.235**	0.124**	

*$p < 0.05$; **$p < 0.01$; COMOR: physical comorbidity; DAILY DOSES: number of daily doses; GDS-15 = Geriatric Depression Scale-15; GSE: General Self-Efficacy Scale; KNOW MEDS: knowledge on medication; MARS-5 = Medication Adherence Report Scale; MEDS ALONE: taking medication alone; MHLC-C_CH: Multidimensional Health Locus of Control – Form C, Chance dimension; MHLC-C_DR: Multidimensional Health Locus of Control – Form C, Doctors dimension; MHLC-C_IN: Multidimensional Health Locus of Control – Form C, Internal dimension; MHLC-C_OP: Multidimensional Health Locus of Control – Form C, Other People scale; OTHER MEDS: taking other medication; PAY MEDS = paying for medication; PDQ-8 = Parkinson's Disease Questionnaire-8; PMS: Pearlin Mastery Scale; PP MEDS ACCESS: physical problems accessing medication; PSY MEDS: psychiatric medication; PSY SUPPORT: psychological support; PUKSoPC: Parkinson's UK Scale of Perceived Control; SCS: Symptom Control Scale; TIME DIAG: time since diagnosis.

These findings appear to contradict the traditional view that higher internal LOC is more adaptive from a general psychological perspective [80], and potentially for medication adherence [81]. However, alternative explanations could be hypothesised. First, due to the high heterogeneity and complex medication profile of Parkinson's [82], some PwP may feel an increased need for external advice compared to people with other chronic conditions. This would explain a higher impact of external attributions of control on adherence in our study, and would be consistent with evidence that external LOC may be more advantageous for specific populations (e.g., [83,84]). In addition, the way medication adherence is measured by most standardised scales may not fully capture some of the dynamics underlying its relationship with different types of LOC. In particular, patient empowerment, which plays a pivotal role in medication adherence [85], may be overlooked by measures which do not explore intentional deviations from medication regimes agreed with the clinical team. This may be especially relevant for Parkinson's, as most adherence scales for PwP focus on non-intentional factors according to a recent systematic review [66]. Thus, high levels of adherence on such measures may fail to account for patients' empowerment and agreed shared responsibility over time (Internal LOC), and only reflect the value of medical advice (Doctors LOC; [41]). In turn, this may lead to a systematic misrepresentation of adherence in this population, which limits the amount of variation in adherence that can be captured by current measures. This could mean that, when adherence is measured on a more person-centred level, which accounts for autonomy, empowerment, and shared control between patients and clinicians, Internal LOC positively predicts adherence in Parkinson's [41] – and particularly a form of 'critical adherence' which reflects increased autonomous and empowered decision-making [86]. This would be consistent with a survey study in people who underwent renal transplantation which also found that Internal LOC predicted lower levels of adherence and highlighted how "a balance of locus of control that optimizes patients' feelings of empowerment but reinforces respect for and faith in their physician is critical" [84, p. 54].

This may be the case of our results as well, since a relatively low standard deviation was found with the MARS-5 (i.e., 2.99) and a quarter of participants in the current study reported varying their doses with the approval of their clinical team – a factor which emerged as a significant negative predictor of adherence in the final regression model. Accordingly, the reduced variation in adherence captured by current measures may also at least partially account for the low amount of variance explained by our model. More specifically, higher levels of Internal LOC predicting lower adherence may also suggest that patient empowerment may be captured as a non-adherent behaviour by current measures. As Chance LOC was also found to have no significant relationship with adherence, the present study ultimately appears to support the need, previously highlighted with PwP, "for looking into the interaction effects between Internal LOC and External LOC as well as External LOC subdimensions on medical regimen adherence" [41, p. 10].

Finally, contrary to what had been consistently reported in previous studies [18–20,22,23,78], depression was not significantly associated with medication adherence in the present study. This constitutes an unexpected yet major finding in itself, as it was true not only with the full sample, but also when only people in the UK ($N = 790$) and the US ($N = 217$) were considered separately. While a potential impact of the abovementioned small variation in adherence may not be excluded, similar results were also observed when suggested cut-offs were used to explore

Table 4. Hierarchical regression model predicting medication adherence with confidence intervals and standard errors based on 1000 bootstrap samples.

	B	95% CI	SE	β	R	R^2	ΔR^2	*p*
Step 1					0.059	0.004	0.004	0.040
CONSTANT	20.203	18.960, 21.321	0.607					<0.001
AGE	0.019	0.003, 0.038	0.009	0.059				0.040
Step 2					0.264	0.070	0.066	<0.001
CONSTANT	21.288	20.105, 22.482	0.605					<0.001
AGE	0.023	0.005, 0.041	0.009	0.070				0.013
TIME DIAG	−0.010	−0.013, −0.007	0.001	−0.213				<0.001
PDQ-8	−0.050	−0.081, −0.022	0.015	−0.101				<0.001
Step 3					0.334	0.111	0.042	<0.001
CONSTANT	21.656	20.143, 23.133	0.755					<0.001
AGE	0.005	−0.012, 0.024	0.009	0.017				0.573
TIME DIAG	−0.008	−0.012, −0.005	0.002	−0.179				<0.001
PDQ-8	−0.037	−0.068, −0.006	0.016	−0.074				0.017
DAILY DOSES	−0.019	−0.118, 0.080	0.050	−0.012				0.694
OTHER MEDS	0.640	0.203, 1.080	0.222	0.089				0.001
KNOW MEDS	0.085	0.008, 0.163	0.038	0.069				0.013
PP MEDS ACCESS	−0.854	−1.405, −0.332	0.270	−0.102				<0.001
PAY MEDS	−0.614	−1.012, −0.241	0.188	−0.096				<0.001
VARY DOSES	−0.801	−1.197, −0.393	0.204	−0.114				<0.001
Step 4					0.404	0.163	0.052	<0.001
CONSTANT	20.044	17.817, 22.126	1.099					<0.001
AGE	0.002	−0.016, 0.020	0.009	0.005				0.867
TIME DIAG	−0.007	−0.010, −0.004	0.002	−0.154				<0.001
PDQ-8	−0.050	−0.084, −0.015	0.018	−0.101				0.005
DAILY DOSES	−0.015	−0.115, 0.081	0.049	−0.010				0.745
OTHER MEDS	0.541	0.125, 0.970	0.211	0.075				0.006
KNOW MEDS	0.090	0.015, 0.164	0.038	0.073				0.009
PP MEDS ACCESS	−0.776	−1.293, −0.272	0.261	−0.093				0.001
PAY MEDS	−0.421	−0.812, −0.042	0.192	−0.066				0.021
VARY DOSES	−0.852	−1.242, −0.465	0.197	−0.122				<0.001
PUKSoPC_SUM	0.005	−0.015, 0.026	0.011	0.018				0.616
PMS	−0.006	−0.070, 0.061	0.032	−0.007				0.849
GSE	−0.007	−0.048, 0.034	0.021	−0.013				0.704
MHLC-C_IN	−0.048	−0.078, −0.017	0.016	−0.095				<0.001
MHLC-C_DR	0.169	0.106, 0.233	0.033	0.177				<0.001
MHLC-C_OP	0.081	0.023, 0.141	0.030	0.086				0.004

CI: confidence interval; COMOR: physical comorbidity; DAILY DOSES: number of daily doses; GSE: General Self-Efficacy Scale; KNOW MEDS: knowledge on medication; MHLC-C_DR: Multidimensional Health Locus of Control – Form C, Doctors dimension; MHLC-C_IN: Multidimensional Health Locus of Control – Form C, Internal scale; MHLC-C_OP: Multidimensional Health Locus of Control – Form C, Other People dimension; OTHER MEDS: taking other medication; PAY MEDS = paying for medication; PDQ-8 = Parkinson's Disease Questionnaire-8; PMS: Pearlin Mastery Scale; PP MEDS ACCESS: physical problems accessing medication; PUKSoPC: Parkinson's UK Scale of Perceived Control; SE: standard error; TIME DIAG: time since diagnosis.

depression and medication adherence as potential dichotomous variables.

The lack of such relationship may lead to an inference that addressing depression does not improve adherence in PwP [18]. In this regard, many of the theoretical explanations for this relationship in Parkinson's appear to have revolved around the long-known significant impact of depression on medication adherence in older people in general [24,25], which in some cases has been shown to be linked to a threefold increase in non-adherence rates [87]. However, while Parkinson's is traditionally considered a condition associated with old age, it is also arguably characterised by higher levels of clinical complexity and heterogeneity compared to other chronic illnesses of the elderly [88,89].

Moreover, a substantial heterogeneity could be observed in previous studies reporting a significant relationship, which are characterised by inconsistent measurement of adherence [19], including Electronic Medication Packaging (i.e., recording each times a medication bottle is opened; [43,90]), older self-report measures based on a small number of dichotomous yes/no questions (e.g., Morisky-Green Test; [45,74,91]), non-quantitative reports (e.g., in case studies; [23]), and different ways to conceptualise sub-optimal adherence (e.g., medication abuse; [92]). These differences in adherence measurement not only highlight a considerable lack of consistency but also demonstrate how aspects of medication adherence such as patients' empowerment, motivation, and agreed deviations from regimens have previously been overlooked [66].

In addition, some previous studies also show a number of methodological limitations. For instance, Vallderiola and colleagues [45] found that depression significantly predicted adherence in PwP based on a logistic regression analysis. However, to perform this, continuous data on depression and adherence were dichotomised, increasing the risk of obtaining spurious positive results [93]. Another investigation instead found a significant positive association between depression and adherence as a univariate correlation [74], but this association did not remain significant when depression was entered in a multiple regression model with other variables.

In conclusion, the high heterogeneity and limitations which characterise the previous evidence, combined with the results from our large-scale study and the limitations of current measures of adherence, appear to suggest a strong need to rethink the

relationship between depression and medication adherence in individuals with Parkinson's.

Clinical implications

Our results have implications for clinical practice. First, the lack of a significant relationship between depression and medication adherence adds further ambiguity to the issue of whether addressing depression will improve medication adherence in this population [18]. Secondly, since different types of perceived control can be targeted selectively by interventions [49,94], psychologically-informed interventions addressing LOC (e.g., cognitive training, empowerment programmes; [41,95]) may have the potential to affect medication adherence in PwP. In addition, only 8.5% of participants reported receiving any psychological support in this survey, suggesting that the provision of psychological services represents a major issue for PwP and should receive further attention from commissioners and healthcare providers.

Finally, considering the high levels of heterogeneity and complexity which characterise the everyday clinical management of Parkinson's, the development of person-centred approaches to medication management revolving around a shared sense of control between patients and clinicians should be considered in everyday clinical practice. More specifically, by recognising the role of PwP as experts in their own condition, a balance between the need for internal and external attributions of control might prove easier to achieve and ultimately beneficial for overall medication adherence [41].

Limitations and future directions

A number of limitations should be considered when interpreting these findings. First, cross-sectional online surveys have the inherent limitation of relying on self-report data collected at a single point in time, thus not affording definitive conclusions on either the direction of any associations or causality. Potential sampling biases (e.g., receiving more responses from more digitally literate, less depressed, more adherent participants [96]) may also affect this design. In the specific case of the present survey, the sample was predominantly characterised by participants who reported stages I, II, and III of the Hoehn and Yahr Scale, thus limiting its representiveness with regards to more severe presentations.

While a large sample size can increase confidence in the generalisability of the findings and the stability of the regression models, it also means that relatively small effects can be statistically significant. The unexpectedly high recruitment for this study does mean that the study is over-powered based on the initial *a priori* power calculation. Consequently, although consistent with a number of theoretical and clinical implications discussed above, some of the statistically significant relationships (such as Other People LOC) which have particularly small effect sizes (e.g., <0.1) would possibly not be replicated in studies with a smaller N.

In addition, while preventive measures were adopted to limit the impact of survey fatigue following the advice of PPI experts – such as the option to save one's progress and resume within two weeks – the high number of items included may still have prevented PwP with higher levels of fatigue from completing the survey. The risk of exacerbating survey fatigue also prevented the inclusion of a wider range of medication-related variables which may have an impact on adherence (e.g., side effects, as seen in cancer populations [97]). Therefore, further research is needed adopting a more comprehensive set of both self-report and objective measures, longitudinal designs, and more representative samples which include participants whose characteristics may lead them to be excluded from online studies (e.g., low digital literacy, reduced access to the internet, higher levels of fatigue).

The Other People sub-scale of the MHLC-C was the only measure to show a low level of internal consistency (Cronbach's $\alpha = 0.56$). While this should be considered when interpreting the current results, it should also be noted that levels of internal consistency as low as 0.50 have been deemed acceptable with subscales characterised by a small number of items [76]. In addition, since no medication adherence scale has been validated for Parkinson's to date [66], the development of a new measure of adherence specifically for PwP is strongly recommended.

Finally, as medication adherence in PwP appears an extremely complex construct unlikely to be explained by a few factors within a single model or perspective, multiple approaches are needed in order to tackle this degree of complexity from a wider range of perspectives. In particular, integrating quantitative and qualitative evidence may help shed light into subjective factors and issues associated with adherence [98].

Conclusions

To our knowledge, this is the largest cross-sectional study to explore the predictors of medication adherence in people with Parkinson's. The results showed that perceived control, a construct which can be addressed and changed by interventions, explained a slightly higher amount of variance in adherence compared to medication variables. Only the Internal, Doctors, and Other People dimensions of LOC emerged as significant independent predictors of medication adherence, while depression showed no significant relationship with the outcome variable. These findings highlight a number of potential clinical implications in individuals with Parkinson's, such as the need for targeted psychologically-informed interventions, person-centred approaches to medication management, and standardised measures of adherence specifically validated for this population.

Notes

1. The term 'Parkinson's' has been adopted in this paper as Parkinson's UK's preferred way to address this population in order to reduce the stigma associated with the term 'disease'.
2. Those responding negatively were redirected to another page which politely explained why they were not eligible for the study.
3. Due to the theoretical importance of depression in medication adherence, we also ran our models with the depression variable included and results remained unchanged.

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