Use of the Pill Questionnaire to detect cognitive deficits and assess their impact on daily life in patients with Parkinson's disease

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Abstract

The Pill Questionnaire (PillQ) has been proposed as a simple way to evaluate cognitive deficits and their impact on the daily lives of those with Parkinson's disease (PD) by asking patients or caregivers about whether patients can independently manage their pills. We used the PillQ to investigate the association of ability to manage medication with cognition and activities of daily living (ADLs) in patients with PD. Patients were divided into two groups based on PillQ scores. The no-impact group was able to take their antiparkinsonian medication independently, and the impact group exhibited problems describing their treatment or taking their drugs independently. A total of 208 participants (93 men) were included. 111 patients (53.4%) were included in the no-impact group, and 97 (46.6%) were included in the impact group. The impact group showed significantly lower cognitive functioning, difficulties with the performance of ADLs, and severe motor dysfunction. PillQ scores were significantly correlated with Mini-Mental State Examination and the Montreal Cognitive Assessment, and Clinical Dementia Rating scores. Management of medication by PD patients is associated with cognitive function, and the PillQ is an easy and useful test for detecting cognitive impairment and its impact on daily life.

INTRODUCTION

Parkinson's disease (PD) is among the most common neurodegenerative disorders affecting elderly individuals. PD is characterized by various motor symptoms including bradykinesia, rigidity, and rest tremors, and treatment is primarily aimed at improving motor function. Although medical treatment can greatly improve overall functioning in early PD, pharmacological treatment encounters difficulties in the advanced stage such as drug complications and low compliance, which may be related to motor disability, depression, or dementia.

According to previous reports, 20–80% of patients with PD will develop dementia over time.[1-3] In patients with PD, dementia affects quality of life, contributes to caregiver distress, limits pharmacotherapy and surgery, and is associated with shorter life expectancy.[4-6] Deficits in verbal memory and executive or visuospatial function have been consistently observed, even in the subclinical stages of Parkinson's disease dementia (PDD), and may be the most important

predictors of subsequent decline.[7,8] Additionally, decline in cognitive functioning is central to the diagnosis of PDD and must be severe enough to impair the ability to negotiate daily life.[9]

Activities of daily living (ADLs) are divided into basic and instrumental. Basic ADLs are related to personal care and include toileting, bathing, eating, and dressing. Instrumental ADLs (IADLs) are more complex activities related to independent living and include preparing meals and managing medications or handling money. Because IADLs are complicated and demanding in terms of cognitive control, they are more vulnerable to cognitive decline. PD is manifested in various combinations of motor symptoms that are associated with impairments in basic ADLs.[10] IADL scores have been shown to be significantly correlated with PD duration and symptom severity among those with PDD.[11]

The Pill Questionnaire (PillQ) has been proposed as a useful instrument for assessing decline in cognitive functioning and its impact on ADLs in patients with PD.[9] The key issue

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is whether the patient is able to reliably take prescribed antiparkinsonian medications. This issue can be assessed by asking the patient or caregiver whether the former can manage his/her pills. Although the PillQ is very simple and easy to administer, little evidence on its correlation with other screening instruments exists.

In this study, we evaluated the correlation between ability to manage medication and cognitive functioning in patients with PD. Two brief cognitive tests, the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), were used to evaluate cognitive functions and determine cognitive profiles, and the PillQ was administered to assess the impact of these variables on daily functioning.

METHODS

Participants

The sample consisted of consecutive patients who visited the Movement Disorders Center of Seoul National University Hospital during a 12-month period and who 1) were older than 40 years of age, and 2) fulfilled the criteria for PD issued by the UK Parkinson's Disease Society Brain Bank for PD. Subjects with signs or symptoms of atypical Parkinsonism, psychological problems such as depression or psychosis, or reversible causes of cognitive impairment or dementia and those who had undergone surgical treatment for PD were excluded.

Clinical evaluation and neuropsychological testing

All patients were assessed during the "on" state.

Patients were initially interviewed about their general history and condition and evaluated for disease severity with the Hoehn and Yahr scale (H&Y) and the Unified Parkinson's Disease Rating Scale (UPDRS). The patients' cognitive state and ability to perform ADLs were evaluated with the MMSE, MoCA, Clinical Dementia Rating (CDR) scale, Schwab and England ADL scale, and PillQ.

The MoCA and MMSE were used to assess a range of cognitive skills on a scale from 0 to 30 points, with higher scores indicating better performance. The MMSE is divided into subscales measuring orientation, recognition, attention, language function, naming, and visuospatial skills. The MoCA is divided into subscales for visuospatial and executive functions, naming, attention, language, abstraction, delayed recall, and orientation. To adjust for the effect of education, one point was added to total MMSE and MoCA scores when patients had completed 6 years or fewer of formal education. The CDR was used to measure seven performance areas: memory, orientation, judgment, problem solving, community affairs, home and hobbies, and personal care. Each area was rated on a 5-point scale on which 0 represented the absence of dementia, 0.5 represented questionable dementia, 1 represented mild dementia, 2 represented moderate dementia, and 3 represented severe dementia.[12-14] Each item on the PillQ, which measures the impact of cognitive impairment on daily life, was rated on scale from 0 to 3: scores of 0 and 1 were taken to indicate no impact of cognitive impairment (no-impact group), and scores of 2 and 3 to indicate some impact of cognitive impairment (impact group). Table 1 presents the PillQ items.

Table 1: The Pill Questionnaire and scoring system[9]

Pill Questionnaire	Score
No impact of cognitive deficits on daily living (no-impact group)	
The patient is able to spontaneously and clearly describe medications including doses (mg. or color of tablet) and medication schedule.	0
The caregiver certifies that the patient can (or could) safely and reliably take medications on a daily basis without supervision.	1
Impact of cognitive deficits on daily living (impact group)	
The caregiver certifies that the patient can (or could) no longer safely and reliably take medications on a daily basis without supervision.	2
The patient is not able to describe the schedule and nature (drugs and doses) of his/her treatment, even with the help of the examiner.	3

Statistical analysis

The statistical analysis was performed with the SPSS software version 19.0 package using independent two-tailed *t*-tests for comparisons of the means for the two groups. Correlates of cognitive-impairment variables, PillQ scores, ADL scores, and ratings of disease severity were determined using logistic regression models. Values are expressed as means and standard deviations. Statistical significance was set at $p < 0.05$.

RESULTS

Baseline characteristics and cognitive profiles

A total of 208 participants (93 men) were included. The mean age and formal educational level of the cohort were 66.4 ± 7.1 and 9.0 ± 4.8 years, respectively. Of the participants, 86 (41.3%) had 6 or fewer years of education, 82 (39.5%) had 7–12 years of education, and 40 (19.2%) had more than 12 years. Seventeen (8.2%) did not have any formal education. The average score on the MoCA was 22.4 ± 5.1, and that on the MMSE was 26.6 ± 3.0. Sixty-seven (27.4%) patients scored <26 on the MMSE, compared with 161 (70.2%) who did so on the MoCA. Despite normal MMSE scores for intact global cognition (≥26), 90 patients (59.6%) scored in the impaired range (<26) on the MoCA. These 90 patients committed more errors than did those who obtained normal MMSE and MoCA (>26) scores on various subscales including delayed recall, attention, executive function, visuospatial, naming, and repetition.

We determined that 111 of the 208 patients (53.4%) manifested no cognitive deficits that affected their daily lives in that they were able to take their antiparkinsonian medications independently without any problems. Of these, four patients could describe the drugs, correct doses, shapes, and treatment schedules (score 0), and 107 patients needed some help from the examiner to describe these factors (score 1). Of the remaining participants, 97 (46.6%) had problems describing or taking the drugs by themselves (scores 2 and 3), and these individuals were identified as experiencing cognitive deficits that affected their daily lives. Higher PillQ scores were associated with more impaired cognition, less ability to perform ADLs, and more severe motor dysfunction (Figure 1). The no-impact group (scores 0 and 1) did not significantly differ

Figure 1. Neuropsychological test and Schwab and England ADL scores by PillQ scores.
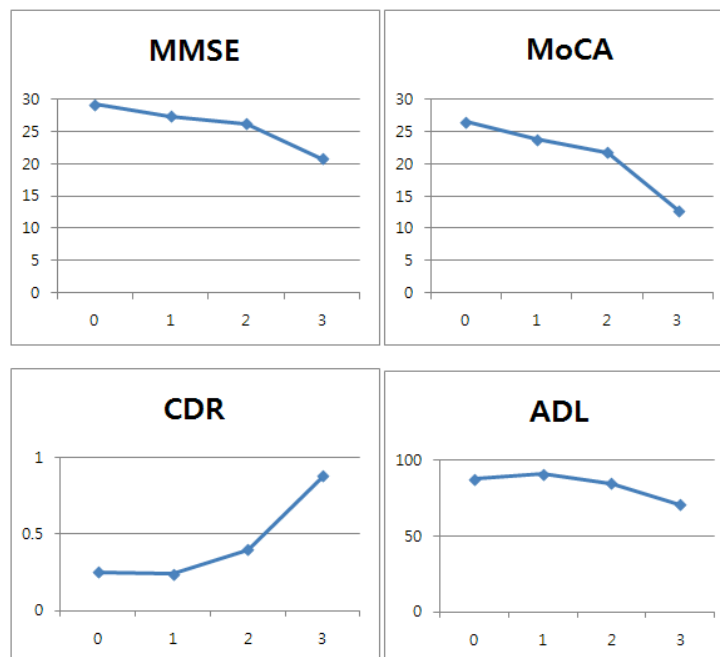
Higher PillQ scores were associated with more impaired cognition and less ability to perform ADL. X-axes show PillQ scores; Y-axes show mean scores, MMSE, MoCA, CDR, and Schwab and England ADL. (ADL, activities of daily living; PillQ, Pill Questionnaire; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; CDR, Clinical dementia rating)

Table 2: Comparison among groups on baseline characteristics and study measures

		No impact group No = 111		Impact group No = 97		T*	P†
PillQ score	**Total**	**0**	**1**	**2**	**3**		
No of cases	208	4	107	85	12		
Age, years	66.4±7.1	67±4.3	65.7±6.7	66.0±7.2	74.0±6.2	-1.3	0.301
Education, years	9.0±4.8	11.8±3.7	9.7±5.0	8.3±4.5	7.0±5.0	-3.0	0.003
Disease duration, months	76.4±58.1	60.0±44.4	64.9±45.4	87.4±68.7	109.5±62.9	-3.4	0.001
Levodopa duration, months	60.8±58.7	57.0±48.7	47.0±43.7	75.5±70.7	92.5±64.8	2.5	0.290
MMSE	26.6±3.0	29.2±1.0	27.4±2.3	26.2±2.6	20.8±4.8	4.7	<0.001
MoCA	22.4±5.1	26.5±3.3	23.8±4.1	21.7±4.4	12.8±6.1	4.8	<0.001
CDR	0.4±0.4	0.3±0.3	0.2±0.3	0.4±0.4	0.9±0.6	-4.7	<0.001
ADL	87.0±10.0	87.5±5.0	90.7±7.9	84.5±9.5	70.8±1.1	5.9	<0.001
UPDRS 1	1.7±2.1	4.0±0.0	1.5±1.9	1.6±2.0	3.8±3.4	-0.8	0.411
UPDRS 2	9.0±6.5	6.8±6.2	7.2±5.3	10.4±6.0	16.9±1.1	-4.7	<0.001
UPDRS 3	20.8±1.1	14.5±5.0	17.1±9.1	23.9±1.0	33.1±1.0	-5.9	<0.001
H&Y	2.3±0.7	2.3±2.9	2.0±0.6	2.5±0.6	3.0±0.6	-5.7	<0.001

Values expressed as mean ± Standard deviation. * T: (degree of freedom) score and †*P* values refer to paired comparisons of two groups, no impact group and impact group.
No, Number of cases; PillQ, Pill Questionnaire; PD, Parkinson's disease; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; CDR, Clinical dementia rating; ADL, Schwab and England activities of daily living; UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr scale.

from the impact group (scores 2 and 3) with respect to age or educational level. However, the impact group reported longer duration of PD and took higher doses of levodopa. Total scores on the MMSE, MoCA, and CDR were significantly lower in the impact than in the no-impact group (Table 2).

Relationship among PillQ scores, scores for cognitive functioning, and scores for motor functioning

Independence in managing antiparkinsonian medication was correlated with scores on neuropsychological screening tests. Table 3 shows the Pearson's correlation coefficients for relationships among PillQ scores and study variables, including demographic characteristics, cognitive functioning, and severity of motor impairment. Correlations between PillQ scores

and scores on the MMSE and MoCA approached moderate strength. Scores on measures of motor functioning, including the UPDRS-III and H&Y, were significantly correlated with PillQ scores. To examine the effect of the relationship between scores on the cognitive subscales of the MMSE and those on the performance subscales of the MoCA on the ability to manage medication, we analyzed the association between these scores and scores on the PillQ. Among the MMSE subscales, orientation and memory registration were most strongly related to scores on the PillQ. The orientation and visuospatial subscales of the MoCA were strongly correlated with PillQ scores (Table 4).

DISCUSSION

This study analyzes the correlation between PillQ scores and cognition in PD. We found that PillQ

Table 3: Pearson's correlation coefficients for relationships among scores for cognitive functions, Schwab and England ADL, motor symptoms, and medication management (PillQ)

	Pill Questionnaire	
	Correlation coefficient	Significance (2-tailed)
Age	0.167	0.016
Disease duration	0.231	0.001
Levodopa duration	0.249	0.001
Education	-0.190	0.006
MMSE	-0.450	<0.001
MoCA	-0.452	<0.001
CDR	0.373	<0.001
ADL	-0.452	<0.001
UPDRS 1	0.101	0.147
UPDRS 2	0.367	<0.001
UPDRS 3	0.425	<0.001
Hoehn and Yahr	0.386	<0.001

PillQ, Pill Questionnaire; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; CDR, Clinical dementia rating; ADL, Schwab and England activities of daily living; UPDRS, Unified Parkinson's Disease Rating Scale;

Table 4: Correlations between PillQ and subscales of the MMSE and MoCA (control variables: age and education)

	Correlation coefficient	Significance (2-tailed)
MMSE	-0.399	<0.001
Orientation	-0.403	<0.001
Language	-0.223	0.001
Registration	-0.314	<0.001
Attention	-0.220	0.001
Recall memory	-0.190	0.006
Interlocking pentagon	-0.147	0.035

Control variable: age and education

MoCA Subscores	Correlation coefficient	Significance (2-tailed)
MoCA score	-0.393	<0.001
Orientation	-0.363	<0.001
Visuospatial	-0.375	<0.001
Executive	-0.274	<0.001
Language	-0.243	<0.001
Delayed recall	-0.185	0.008
Attention	-0.163	0.020

Control variables: age and education
PillQ, Pill Questionnaire; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment

scores were related to patients' cognitive functions and ability to perform ADLs. PillQ scores were significantly correlated with MMSE, MoCA, CDR, and Schwab and England ADL scores.

Traditionally, PD had been regarded as a "motor disease." Recently, however, the non-motor symptoms of PD, including cognitive deficits, have been highlighted.[15-17] Detection of cognitive impairment in PD is important as it predicts the development of dementia and may eventually be a target for pharmacological intervention. The MMSE remains the gold standard among screening instruments for global cognition, and it is used extensively in PD. However, the MMSE may not be sensitive enough to detect mild cognitive deficits and is limited in its ability to assess visuospatial skills and executive function, which are typically impaired in PD. To compensate for the weaknesses in the MMSE, brief screening test tools have been designed and validated for PD.[18-21] The MoCA has been shown to be more sensitive than the MMSE for detecting mild cognitive impairment or dementia in PD.[22-24] Despite normal MMSE scores, approximately 60% of the patients in this study met predefined criteria for cognitive impairment based on their MoCA scores. Impairments were seen in various cognitive domains, including memory, attention, executive and visuospatial abilities, and language. This study demonstrated a clear advantage of the MoCA over the MMSE for the detection of a broad range of cognitive deficits in the early stage of illness.

It is also crucial to note that cognitive deficits had an impact on the ability to perform ADLs, which is critical for a diagnosis of dementia. Indeed, cognitive deficits in patients with dementia would be expected to result in impaired ability to perform ADLs. The PillQ may be an excellent method for monitoring the ability to perform ADLs, especially in those with PD. The majority of patients with PD should receive antiparkinsonian drugs to control motor symptoms, and poor compliance with medication regimens is reflected in motor dysfunction. Therefore, it is clinically necessary to ascertain whether patients can appropriately manage their medications by themselves or whether a caregiver is needed to help them. Loss of personal ability to manage treatment can be considered a sign of dementia.[25] This study showed that higher scores on the PillQ were correlated with loss of the ability to describe and manage drugs, which is correlated with cognitive deficits. Our statistical analysis supports the usefulness of the PillQ. However, the

neuropsychological testing, including the PillQ, was not performed separately and could represent a limitation of this study.

Taking medications as prescribed is among the IADLs, which are more complex activities related to independent living. Shulman and coworkers found that in 80% of PD patients, their self-reported ability to manage medications was better than their performance on an objective test.[26] Concordance between subjective and objective ratings of disability was high for walking and dressing, whereas the most notable discordance was found for medication management, which is an especially cognitively demanding IADL. The PillQ, which asks respondents to verbally describe drug(s), dose(s), and medication schedules, can objectively assess cognitive status and the ability to perform IADLs. Thus, the PillQ may be helpful for monitoring the medication compliance of patients and decrease medication errors caused by inaccurate self-reports.

We found a significant association between PillQ scores and scores on the orientation (Pearson correlation coefficient (r) = -0.403, $P < 0.01$) and registration ($r = -0.314$, $p < 0.01$) subscales of the MMSE and those on the orientation ($r = -0.363$, $p < 0.01$) and visuospatial ($r = -0.375$, $p < 0.01$) subscales of the MoCA. Patients must have a general understanding of their medication regimens and the ability to follow a medication schedule and distinguish among pills based on shape if they are to manage their medications appropriately. Disruptions in orientation and visuospatial functioning may be related to loss of ability to manage medication personally.

The PillQ is limited in its ability to test the impact of "pure" cognition on daily life. Motor disability is a confounding factor, and it is difficult to evaluate personal autonomy owing to the interference of cognitive/behavioral problems. Scores for IADLs have been shown to be significantly correlated with PD duration and H&Y scores in patients with PDD.[11] The univariate analysis in this study found that longer disease duration and greater motor impairment were associated with high PillQ scores. Thus, when patients can no longer manage their medications independently, clinicians should consider possible physical as well as cognitive causes. Indeed, impairment in the ability to live independently may be attributable to various extrapyramidal symptoms or autonomic dysfunctions.

This study demonstrates that the PillQ is strongly correlated with measures of cognitive functioning including the MMSE and MoCA

and ADL scales. Patients who did not manage their medications independently demonstrated greater cognitive impairment and more severe motor symptoms. Because clinical assessment of daily functioning and cognition is integral to clinical decision-making, the easy and simple PillQ is a useful screening instrument that can be administered in both inpatient and outpatient settings.

ACKNOWLEDGEMENT

DISCLOSURE

Conflicts of interest: None

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