The Pill Questionnaire in a Nondemented Parkinson's Disease Population

William Reginold,[1,2] Melissa J. Armstrong, MD,[1,2] Sarah Duff-Canning, PhD, CPsych,[3] Anthony Lang, MD,[1,2] David Tang-Wai, MD,[1,2] Susan Fox, MD, PhD,[1,2] Brandon Rothberg, HBA,[1] Cindy Zadikoff, MD,[4] Nancy Kennedy, PhD,[5] David Gill, MD,[6] Paul Eslinger, PhD,[6] Mark Mapstone, PhD,[7] Kelvin Chou, MD,[8] Carol Persad, PhD,[9] Irene Litvan, MD, FAAN,[10] Benjamin Mast, PhD,[11] and Connie Marras, MD, PhD[1,2]*

[1]Toronto Western Hospital Movement Disorders Centre, and the Edmond J. Safra Program in Parkinson's Disease, Toronto, Ontario, Canada; [2]Department of Medicine (Neurology), University of Toronto, Toronto, Ontario, Canada; [3]Department of Neuropsychology, Toronto Western Hospital, Toronto, Ontario, Canada; [4]Department of Neurology, Northwestern University, Chicago, Illinois, USA; [5]Department of Psychiatry and Behavioral Science, Northwestern University, Chicago, Illinois, USA; [6]Department of Neurology, PennState Hershey, Hershey, Pennsylvania, USA; [7]Department of Neurology, University of Rochester, Rochester, New York, USA; [8]Department of Neurology, University of Michigan, Ann Arbor, Michigan, USA; [9]Department of Psychiatry, University of Michigan, Ann Arbor, Michigan, USA; [10]Department of Neurology, University of Louisville, Louisville, Kentucky, USA; [11]Psychological & Brain Sciences, University of Louisville, Louisville, Kentucky, USA

ABSTRACT

We assessed the Pill Questionnaire as a screen for mild cognitive impairment in nondemented Parkinson's disease patients.

The relationship between ability to remember medications for Parkinson's disease in the Pill Questionnaire, mild cognitive impairment, and deficits on neuropsychological tests performed 2–3 weeks later blind to Pill Questionnaire results was assessed in movement disorders clinic patients.

In 109 subjects, inaccurate medication reporting on the Pill Questionnaire was associated with lower scores on the Montreal Cognitive Assessment, Scales for Outcomes in Parkinson's Disease–Cognition and with deficits in memory, attention, executive function-inhibitory control, processing speed, visuospatial function, and language. Inaccurate medication reporting was also associated with an adjusted odds ratio of 2.4 (95% CI, 0.91–5.88; $P = .06$) for mild cognitive impairment, with a specificity of 80% and sensitivity of 41%.

The Pill Questionnaire is neither sensitive nor specific enough to be used as the sole screening or diagnostic tool for mild cognitive impairment. However, inaccurate medication reporting is associated with deficits spanning many cognitive domains and should alert a clinician to a higher likelihood of cognitive impairment.

Key Words: Pill Questionnaire; MCI; Parkinson's disease; cognitive impairment; screening

Cognitive impairment is common in Parkinson's disease (PD). PD–mild cognitive impairment (PD-MCI), characterized by impaired cognition without significant functional impairment, has a cross-sectional prevalence of 19%–38%.[1] Clinical recognition of PD-MCI is important, as these patients appear to have an increased risk of developing dementia (PDD).[2] A rapid screen for PD-MCI that is possible to implement in a busy clinical practice setting would be useful. The Montreal Cognitive Assessment (MoCA) is a candidate tool for screening for PD-MCI.[3,4] However, it is difficult to allocate 10–15 minutes of every patient encounter to conduct the test.

The Pill Questionnaire asks patients to describe their PD medications, the doses, and their intake times.[5] If there is inaccurate reporting of the treatment regimen, a caregiver is asked to verify whether the patient can take their medications safely and reliably on their own. Difficulty describing their treatment regimen and problems taking their PD medications independently, as reported by their caregiver, have both been associated with dementia in PD patients.[6] We tested the hypothesis that patients with PD-MCI would also have difficulty with this cognitively demanding task. Given that the review of patient PD medications is already a routine part of taking a patient history, the Pill Questionnaire could be a practical screening tool.

Patients and Methods

Consecutive nondemented PD patients were enrolled at 6 North American movement disorders centers. Inclusion criteria were the diagnosis of PD according to United Kingdom PD Society Brain Bank criteria, age greater than 60 years, no impairment in function related to cognition according to the modified Disability Assessment for Dementia (DAD), no depressive

Additional Supporting Information may be found in the online version of this article.

***Correspondence to:** Dr. Connie Marras, Movement Disorders Centre, McL 7-421, Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario M5T 2S8, Canada; cmarras@uhnresearch.ca

Funding agencies: This study was funded by the Michael J. Fox Foundation for Parkinson's Research.

Relevant conflicts of interest/financial disclosures: Connie Marras is supported by a New Investigator Award from the Canadian Institutes for Health Research.

Full financial disclosures and author roles may be found in the online version of this article.

Received: 17 January 2012; **Revised:** 13 June 2012; **Accepted:** 28 June 2012

Published online 1 August 2012 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.25124

disorder (Geriatric Depression Scale $\leq$ 5), caregiver available for collateral history, minimum of a grade 8 education, English as a first language, and a minimum standard score of 80 on the Wechsler Test of Adult Reading. A clinical evaluation was followed 2–3 weeks later by neuropsychological testing performed blinded as to the results of the Pill Questionnaire. The clinical evaluation included the Pill Questionnaire, the MoCA, Scales for Outcomes in Parkinson's Disease–Cognition (SCOPA-COG), Mini–Mental State Examination (MMSE), Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), and self-reported ability to take PD medications as prescribed. The neuropsychological battery included 8 core measures: memory (CVLT-II–Long Delay Free Recall),[7] attention (Digit Span–Longest Span Forward),[8] executive function–working memory (Letter–Number Sequencing),[8] executive function–cognitive flexibility (Visual Verbal Test–Total Number of Shifts),[9] executive function–inhibitory control (Color–Word Interference—Time to Complete Condition 3),[10] processing speed (Color–Word Interference—Time to Complete Condition 1),[10] visuospatial function (Visuospatial–Judgment of Line Orientation),[11] and language (Verbal Fluency–Category Fluency Condition).[10]

The diagnosis of MCI was made based on modified Petersen criteria requiring (1) a cognitive complaint from the subject or caregiver as assessed by the Neurobehavioral Inventory, (2) no functional impairment related to cognition as assessed by the modified DAD, and (3) performance at least 1.5 standard deviations below the reported normative mean on 1 or more of the a priori designated core neuropsychological tests.[12] This differs slightly from the more recently published criteria of the Movement Disorders Society Task Force, which require impairment on at least 2 neuropsychological tests from 1 or more cognitive domains to diagnose PD-MCI.[13]

The physician rated each subject's ability to report medication on the Pill Questionnaire according to 1 of 5 categories:

1. The patient is able to spontaneously and clearly describe the drugs, doses, and timing of the treatment.
2a. The patient needs some help from the examiner but is successful without clinically pertinent errors, and the caregiver verifies that the patient can take the medications safely and reliably.
2b. The patient needs some help from the examiner, and the caregiver verifies that the patient cannot take medications safely and reliably.
2c. The patient needs some help from the examiner, and the caregiver does not know whether the patient can take medications safely and reliably.
3. The patient is unable to describe medications even with help from the examiner.

Three measures were used as proxies for the complexity of a patient's current PD medication regimen: number of current PD medications, levodopa-equivalent dose (LED), and number of doses listed by the patient on the Pill Questionnaire.

We dichotomized Pill Questionnaire medication responses into accurate medication reporting: rating 1 versus inaccurate medication reporting: ratings 2a, 2b, 2c, and 3. Comparisons between these 2 groups were made using the Student t test for continuous variables, the 2-proportion z test for the frequency of impairment (>1.5 standard deviations below the normative mean) in core neuropsychological tests, and the chi-square test for the frequency of MCI. Adjusting for the effect of education, we assessed the relationship between ability to report medication on the Pill Questionnaire and PD-MCI (using logistic regression) or neuropsychological test z scores (linear regression), including years of education as an independent variable.

Results

Of 109 Parkinson's disease patients, 75 (68.8%) accurately described the drugs, doses, and timing of treatment (rating 1), 29 (26.6%) needed help describing medications but could take medications safely and reliably (rating 2a), 2 (1.8%) needed help describing medications and could not take medications safely and reliably (rating 2b), 1 (0.9%) needed help describing medications and the caregiver was unsure about their ability to take medications safely and reliably (rating 2c), and 2 (1.8%) were unable to describe their medications even with help (rating 3).

Subject characteristics are shown in Table 1. There were no significant differences in PD medication regimen complexity between patients with accurate and inaccurate medication reporting on the Pill Questionnaire: total mean number of doses listed by each patient (accurate reporting, 5.1 $\pm$ 2.9; inaccurate reporting, 6.0 $\pm$ 3.3; $P = .17$), number of medications for Parkinson's disease (accurate reporting, 1.6 $\pm$ 0.8; inaccurate reporting, 2.0 $\pm$ 0.9; $P = .07$), LED (Table 1) or total number of medications (accurate reporting, 6.6 $\pm$ 3.7; inaccurate reporting, 6.6 $\pm$ 4.3; $P = .93$). A slightly higher proportion of patients with inaccurate medication reporting on the Pill Questionnaire indicated problems remembering to take their medication as prescribed (accurate reporting, 9%; inaccurate reporting, 16%; $P = .3$).

Inaccurate medication reporting on the Pill Questionnaire was also associated with lower educational level, lower MoCA, and SCOPA-COG scores, and increased severity of Parkinson's disease (MDS-UPDRS total), particularly motor symptoms (UPDRS part III) and motor complications (UPDRS part IV) , in addition to reduced scores in tests of memory, attention, executive function–inhibitory control, processing

Table 1. Patient characteristics according to the Pill Questionnaire assessment

	Total (n = 109)	Accurate medication reporting[a] (n = 75)	Inaccurate medication reporting[b] (n = 34)	*P* value accurate versus inaccurate reporting
Age (y)	71.3 ± 5.2	70.9 ± 5.0	72.3 ± 5.5	.2
Male/Female (number)	74/35	53/22	21/13	—
Education (y)	15.9 ± 2.5	16.4 ± 2.0	14.9 ± 3.1	**.003**
Disease duration (y)	7.0 ± 5.2	6.7 ± 4.3	7.5 ± 6.9	.5
MDS-UPDRS Part I	6.3 ± 3.9	5.9 ± 3.7	6.9 ± 4.0	.2
MDS-UPDRS Part II	8.6 ± 5.7	8.0 ± 5.2	9.6 ± 6.1	.2
MDS-UPDRS Part III	27.4 ± 11.2	25.7 ± 11.6	30.6 ± 9.1	**.03**
MDS-UPDRS Part IV	2.3 ± 3.8	1.7 ± 3.0	3.7 ± 5.0	**.01**
MDS-UPDRS Total	44.5 ± 17.1	41.2 ± 16.0	50.8 ± 16.3	**.005**
Levodopa-equivalent dose (mg)	577.1 ± 418.5	563.1 ± 423.8	627.9 ± 430.6	.5
MMSE	28.1 ± 2.1	28.4 ± 1.6	27.7 ± 2.6	.1
MoCA	24.9 ± 3.1	25.4 ± 2.8	24.1 ± 3.3	**.04**
SCOPA-COG	27.0 ± 5.5	28.0 ± 5.0	24.8 ± 5.8	**.004**
MCI (number)				
Yes	59	35	24	**OR 2.74**
No	50	40	10	***P* = .0236**

Values are means with standard deviations unless otherwise indicated. Values in boldface indicate statistically significant differences between groups.
[a]Rating 1.
[b]Ratings 2a, 2b, 2c, or 3.
MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; MMSE, Mini–Mental State Examination; MoCA, Montreal Cognitive Assessment; SCOPA-COG, Scales for Outcomes in Parkinson's Disease–Cognition.

speed, visuospatial function, and language (Tables 1 and 2). After adjusting for level of education, inaccurate medication reporting on the Pill Questionnaire was associated with significantly reduced scores in executive function–inhibitory control ($P = .002$), processing speed (0.015), and language (0.007). Inaccurate medication reporting was associated with being classified as impaired (>1.5 SD below the normative mean) in memory, attention, executive function–inhibitory control, and language (Table 2). When individuals rated as 1 or 2a (able to take medications reliably without supervision) were compared with those rated as 2b, 2c, or 3 (unable or with uncertain ability to take medications reliably without supervision), those

Table 2. Frequency of impairment* in each cognitive domain and corresponding neuropsychological test by Pill Questionnaire performance

	Z scores			Number of patients scoring below 1.5 standard deviations from normative mean		
	Accurate medication reporting[a] (n = 75)	Inaccurate medication reporting[b] (n = 34)	*P* value[d] accurate versus inaccurate reporting	Accurate medication reporting[a] (n = 75)	Inaccurate medication reporting[b] (n = 34)	*P* value[d] accurate versus inaccurate reporting
Memory (*CVLT-II— Long Delay Free Recall*)[7]	0.19 ± 0.96	−0.32 ± 1.57	**.04**	5 (6.7%)	12 (35.3%)	**.0001**
Attention (*Digit Span—Longest Span Forward*)[8]	0.65 ± 0.83	0.23 ± 1.03	**.03**	0 (0%)	2 (5.8%)	**.04**
Executive function—working memory (*Letter-Number Sequencing*)[8]	0.48 ± 0.81	0.15 ± 1.02	.07	2 (2.7%)	2 (5.9%)	.4
Executive function—cognitive flexibility (*Visual Verbal Test—Total Number of Shifts*)[9]	−1.73 ± 1.84	−1.91 ± 2.20	.66	33 (44%)	18 (52.9%)	.4
Executive function—inhibitory control (*Color-Word Interference—Time to Complete Condition 3*)[10]	**0.33 ± 0.92**	**−0.33 ± 1.37**	**.004**	3 (4%)	5 (14.7%)	**.05**
Processing speed (*Color–Word Interference—Time to Complete Condition 1*)[10]	**−0.07 ± 0.89**	**−0.33 ± 1.08**	**.04**	4 (5.3%)	4 (11.8%)	.2
Visuospatial *(Visuospatial—Judgment of Line Orientation*)[11]	**−0.28 ± 1.57**	**−0.88 ± 1.16**	**.05**	13 (17.3%)	11 (32.4%)	.1
Language (*Verbal Fluency—Category Fluency Condition*)[10]	**0.45 ± 1.24**	**−0.51 ± 1.22**	**.003**	4 (5.3%)	6 (17.7%)	**.04**

Values in boldface show statistically significant differences between groups.
*Impairment on a neuropsychological tests is defined as standardized score ≥ 1.5 SD below mean from normative scores.
[a]Rating 1.
[b]Ratings 2a, 2b, 2c, or 3.
MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale.

scoring 2b, 2c, or 3 had significantly lower scores on core tests of memory, executive function–cognitive flexibility, and language and on the SCOPA-Cog (Supplementary Table 2).

Fifty-nine of 109 patients met our criteria for PD-MCI (54%). Inaccurate medication reporting on the Pill Questionnaire was associated with an odds ratio of 2.74 for PD-MCI (95% CI, 1.15–6.52; Table 1). The sensitivity and specificity of the Pill Questionnaire for detecting PD-MCI were 41% and 80%, respectively (positive predictive value, 71%; negative predictive value, 53%). After adjusting for years of education and total MDS-UPDRS scores, impaired medication reporting on the Pill Questionnaire was associated with an odds ratio of 2.4 for PD-MCI (95% CI, 0.91–5.88; $P = .06$). Inability to take medications reliably without supervision (2b, 2c, or 3) was associated with an odds ratio of 10.19 for PD-MCI after zero-cell correction (95% CI, 0.55–189.05; $P = .06$). Combining inaccurate medication reporting on the Pill Questionnaire with a MoCA score $\leq$ 26 improved the positive predictive value for detecting PD-MCI (to 92%) without further compromising sensitivity. In the same data set, the positive predictive value for PD-MCI of a MoCA score $\leq$ 26 alone was 67%. Following an inaccurate report on the Pill Questionnaire with the MMSE or SCOPA-Cog was not as helpful (Supplementary Table 1).

Discussion

Our analysis demonstrated that inaccurate medication reporting elicited by the Pill Questionnaire is associated with cognitive deficits, even in nondemented individuals. Patients with inaccurate medication reporting had lower scores on neuropsychological tests of memory, attention, and executive function—inhibitory control, processing speed, visuospatial function, and language and on cognitive screening tests (MoCA and SCOPA-Cog). There was no difference in performance on the MMSE, consistent with previous observations that the MoCA and SCOPA-Cog are more sensitive to the early cognitive changes in PD than the MMSE.[4]

In the current study PD-MCI was associated with inaccurate medication reporting on the Pill Questionnaire (ratings 2a, 2b, 2c, and 3). However, the Pill Questionnaire is insufficiently sensitive to be used as the sole screening tool and not specific enough to be used as a sole diagnostic test. Interestingly, inaccurate medication reporting on the Pill Questionnaire in conjunction with a MoCA score less than or equal to 26 was highly specific for PD-MCI, but this combination still had poor sensitivity.

As in any study of mild cognitive impairment, the results will vary depending on the criteria used. For example, some investigators require more than 1 cognitive test within a domain to be abnormal.[13–15] With more stringent criteria, the sensitivity of the Pill Questionnaire may be different. Our cohort was highly educated, and the Pill Questionnaire may perform differently in a less educated population of PD patients.

Although the deliberate use of the Pill Questionnaire to identify individuals with cognitive impairment is not recommended because of low sensitivity, neurologists routinely ask their patients about their PD medications early in the patient encounter, and it is common for patients to attempt to recall medications from memory without the aid of a list. Difficulty reporting a medication regimen should raise the suspicion of cognitive deficits because of the association with MCI and impairments in a number of cognitive domains.

References

1. Litvan I, Aarsland D, Adler CH, et al. MDS task force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI. Mov Disord. 2011;26:1814–1824.
2. Janvin CC, Larsen JP, Aarsland D, Hugdahl K. Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. Mov Disord. 2006;21:1343–1349.
3. Hoops S, Nazem S, Siderowf AD, et al. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. Neurology. 2009;73:1738–1745.
4. Dalrymple-Alford JC, MacAskill MR, Nakas CT, et al. The MoCA: well-suited screen for cognitive impairment in Parkinson disease. Neurology. 2010;75:1717–1725.
5. Dubois B, Burn D, Goetz C, et al. Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force. Mov Disord. 2007;22:2314–2324.
6. Dujardin K, Dubois B, Tison F, et al. Parkinson's disease dementia can be easily detected in routine clinical practice. Mov Disord. 2010;25:2769–2776.
7. Delis D, Kramer JH, Kaplan E, Ober B. The California Verbal Learning Test. 2nd ed. San Antonio, TX: The Psychological Corporation; 2000.
8. Wechsler D. Wechsler Memory Scale. 3rd ed. San Antonio, TX: The Psychological Corporation; 1997.
9. Wicklund AH, Johnson N, Weintraub S. Preservation of reasoning in primary progressive aphasia: further differencitation from Alzheimer's disease and the behavioral presentation of frontotemporal dementia. J Clin Exp Neuropsychol. 2004;26:347–355.
10. Delis DC, Kaplan E, Kramer JH. Delis–Kaplan Executive Function System (D-KEFS): Examiner's Manual. San Antonio, TX: The Psychological Corporation; 2001.
11. Benton AL, Sivan AB, Hamsher K, Varney NR, Spreen O. Contributions to Neuropsychological Assessment: A Clinical Manual. 2nd ed. New York: Oxford; 1994.
12. Caviness JN, Driver-Dunckley E, Connor DJ, et al. Defining mild cognitive impairment in Parkinson's disease. Mov Disord. 2007;22:1272–1277.
13. Litvan I, Goldman JG, Troster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord. 2012;27;349–356.
14. Dalrymple-Alford JC, Livingston L, MacAskill MR, et al. Characterizing mild cognitive impairment in Parkinson's disease. Mov Disord. 2011;26:629–636.
15. Liepelt-Scarfone I, Graeber S, Feseker A, et al. Influence of different cut-off values on the diagnosis of mild cognitive impairment in Parkinson's disease. Parkinsons Dis. 2011;2011:540843.