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A Recommended Scale for Cognitive Screening in Clinical Trials of Parkinson's Disease

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Abstract

Background—Cognitive impairment is common in Parkinson's disease (PD). There is a critical need for a brief, standard cognitive screening measure for use in PD trials whose primary focus is not on cognition.

Methods—The Parkinson Study Group (PSG) Cognitive/Psychiatric Working Group formed a Task Force to make recommendations for a cognitive scale that could screen for dementia and mild cognitive impairment in clinical trials of PD where cognition is not the primary outcome. This Task Force conducted a systematic literature search for cognitive assessments previously

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used in the PD population. Scales were then evaluated for their appropriateness to screen for

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cognitive deficits in clinical trials, including brief administration time (<15 minutes), assessment of the major cognitive domains, and potential to detect subtle cognitive impairment in PD.

Results—Five scales of global cognition met the predetermined screening criteria and were considered for review. Based on the Task Force’s evaluation criteria the Montreal Cognitive Assessment (MoCA), appeared to be the most suitable measure.

Conclusions—This Task Force recommends consideration of the MoCA as a minimum cognitive screening measure in clinical trials of PD where cognitive performance is not the primary outcome measure. The MoCA still requires further study of its diagnostic utility in PD populations but appears to be the most appropriate measure among the currently available brief cognitive assessments. Widespread adoption of a single instrument such as the MoCA in clinical trials can improve comparability between research studies on PD.

INTRODUCTION

Cognitive impairment is common in Parkinson’s disease (PD), and it is estimated that the majority of patients will develop dementia in the later stages of the disease.¹ Considering the high prevalence of cognitive impairment in PD and growing interest in the effects of medical and surgical therapies on cognitive dysfunction and motor symptoms in this population, there is a need for a brief cognitive test that can be consistently administered in clinical trials of PD. Currently, individual researchers have their own preferences for different cognitive tests, making it difficult to compare and cross-validate data between studies.

Kulisevsky and Pagonabarraga recently conducted a systematic review of cognitive scales used in PD,² and identified the Parkinson’s Disease-Cognitive Rating Scale (PD-CRS) as the optimal PD-specific scale for detecting early cognitive deficits in PD and tracking the transition to PD dementia. While this makes the PD-CRS suitable for clinical trials investigating progression of cognitive dysfunction in PD, its administration time (17 minutes in non-demented PD patients and 26 minutes in PDD patients)² makes it less appropriate for inclusion in clinical trials of PD not focused on cognition. Cognitive instruments used in such trials need to be brief (e.g., < 15 minutes) for the purpose of screening large numbers of participants for mild cognitive impairment and dementia, while allowing time for other motor assessments that are the primary focus of the research.

To address the growing challenge of identifying cognitive dysfunction in PD clinical trials, the Parkinson Study Group (PSG) Cognitive/Psychiatric Working Group formed a Task Force to develop recommendations on a cognitive scale that could efficiently screen for both dementia and mild cognitive impairment in treatment trials and other clinical research investigations of PD where cognition is not the primary outcome.

METHODS

The Task Force includes 9 movement disorders neurologists, one cognitive neurologist, 4 neuropsychologists, and one psychiatrist. In order to guide selection and review of candidate scales, the Task Force developed the following primary criteria (see Table): 1) the test must have been previously studied in a PD population; 2) the test should be able to stand alone in clinical trials, yet allow investigators to add additional cognitive assessments if indicated; 3) administration should be completed within 15 minutes in order to minimize the burden of testing in a patient undergoing a clinical trial; 4) all major cognitive domains (attention, memory, language, visual-perception and construction, and executive functions) should be assessed in order to screen for other causes of dementia, such as Alzheimer’s disease (AD), 5) the spectrum of cognitive impairment in PD, particularly subtle impairments involving

executive functions, should be measured by the test or tests. If there were several scales that met these 5 criteria, the Task Force considered the following secondary criteria in order to narrow the choices to one scale for recommendation: 1) the tool should have been evaluated in studies beyond those of its original developer, 2) psychometric performance data for PD should be available.

Literature Search Strategy and Review of Tests

A systematic search was conducted of PUBMED (1950 to January 2009) using the search terms “Cognitive Assessment” and “Parkinson’s disease” or “Parkinson disease” in the English language literature for cognitive tests that had previously been used in a PD population. 353 articles were retrieved and examined. In addition, *in press* peer-reviewed papers or published abstracts known to the task force members were included.

After this critical review and discussion of the scales, a report was prepared by the members of the Task Force and circulated to the Cognitive/Psychiatric Working Group for further evaluation. A final draft, including the Group’s recommendations, was written and submitted to the Executive Committee of the PSG for final approval before submission for peer-review publication.

RESULTS

The literature search identified ten scales for consideration: Addenbrooke’s Cognitive Evaluation (ACE),³ Alzheimer’s Disease Assessment Scale—cognitive (ADAS-cog),⁴ Cambridge Cognitive Assessment (CAMCOG),⁵ Mattis Dementia Rating Scale (DRS),⁶ Mini-Mental Parkinson (MMP),⁷ Mini-Mental State Exam (MMSE),⁸ Montreal Cognitive Assessment (MoCA),⁹ PD-CRS,¹⁰ Parkinson Neuropsychometric Dementia Assessment (PANDA),¹¹ and Scales for Outcomes in Parkinson’s disease—cognition (SCOPA-cog).¹² Each instrument includes components that assess multiple cognitive domains, but the summary scores provide measures of global cognitive function. Thus, each of these scales could stand alone.

Five of the ten scales (ACE,³ ADAS-cog,¹³ CAMCOG,⁵ DRS,¹⁴ and PD-CRS¹⁰) were excluded because administration time requires >15 minutes, leaving two generic instruments, the MMSE and MoCA, and three PD-specific instruments, the MMP, PANDA, and SCOPA-cog. The advantages and disadvantages of these 5 rating scales relative to the rest of the evaluation criteria are summarized (Table).

Mini-Mental State Exam (MMSE)

The MMSE is the most widely used screening measure for detecting dementia. While not developed specifically for PD patients, it is used consistently in PD studies and has the most empiric evidence among the rating scales considered. Available in 58 languages, the MMSE measures multiple cognitive domains on a 30-point scale: orientation (10 points), registration and short-term recall (6-points), attention and concentration (5 points), language (both oral and written) (8 points), and visuospatial function (1 point).⁸ It can be administered within 10 minutes. The MMSE test manual and forms are owned and copyrighted by Psychological Assessment Resources, Inc. (PAR). Alternate test versions of the MMSE are available.

The MMSE has good test-retest and inter-rater reliability in the general population.¹⁶ However, it has not been specifically validated in the PD population. Although influenced by age and education, age and education corrected normative data are available.¹⁷ A unique advantage of the MMSE relative to the other scales discussed is that it can measure

cognitive change over time in PD, especially in patients with dementia (about 2–2.5 points per annum)¹⁸ and is sensitive to treatment effects in clinical trials.^{19,20}

Despite its strengths, the MMSE does not measure the cognitive functions of reasoning, planning, and set shifting (e.g. executive functions), which are commonly impaired in PD patients early in the course of the disease.^{16,21} Furthermore, the naming task in the MMSE has not been validated against formal naming tests (i.e. Boston Naming Test) and thus may not detect a mild language deficit. Finally, the MMSE is relatively insensitive to mild cognitive changes.⁹

Montreal Cognitive Assessment (MoCA)

The MoCA was originally developed to screen for mild cognitive impairment (MCI) in the general population. Twenty-two language versions exist.⁹ It is free and may be used for non-profit research with prior written permission. A licensing agreement is required if the research is funded by a commercial entity. It is a 30-point test that can be administered in about 10 minutes, but unlike the MMSE, the MoCA also covers a range of executive functions. It has 6 orientation questions, and a 5 word memory recall task. A clock drawing task and a cube copy test assess visuospatial function. Attention/concentration is assessed using serial 7's, target tapping, and digit span forward and backward. Confrontation naming and repetition tasks assess language. Executive functions are evaluated using a shortened version of the Trail Making B test, phonemic fluency, and a verbal abstraction task. In non-PD samples, the MoCA has been shown to have excellent test-retest reliability and good internal consistency in patients with (MCI).⁹

Four studies were identified that used the MoCA in PD populations,^{22–25} and all suggest that the MoCA may be particularly sensitive to the mild cognitive changes seen in PD. The MoCA has demonstrated good test-retest, inter-rater reliability, and convergent validity in 48 subjects with PD.²² A recent study in PD that compared the abilities of the MoCA and MMSE to detect MCI and dementia compared to a neuropsychological battery reported that the MoCA had acceptable sensitivity (0.82) and specificity (0.75) for dementia screening using a cutoff of 24/25.²⁵ For MCI screening in PD, the MoCA had acceptable sensitivity (0.83), but low specificity (0.53) using a cutoff of 26/27, and the positive predictive (PPV) and negative predictive values (NPV) for detecting MCI were not explicitly stated.²⁵ The PPV was poor (PPV 46% and NPV 92%) for the “diagnosis of any cognitive disorder” using a 26/27 cutoff.

The main strengths of the MoCA are its rapid and easy administration, assessment of the broad range of cognitive domains, and its sensitivity to milder cognitive deficits and executive dysfunction in patients with PD. However, the naming task in the MoCA (3 animals) has not been properly validated and may not pick up mild language deficits. Cut-off values for dementia and MCI are also not firmly established.

Mini-Mental Parkinson (MMP)

The MMP is a brief screening test derived from the MMSE and developed specifically to assess cognition in PD.⁷ It is a 32-point test that takes approximately 10 minutes to complete.²⁶ Differences between the MMP and the MMSE include a time question on orientation instead of the season, a visual registration task based on picture cards, a fluency task where patients are asked to name 3 animals beginning with the same letter, visual memory recall instead of verbal memory recall, a set-shifting task where subjects are given a card with four images and asked to identify which image is different from the other 3, and a concept processing (similarities) task wherein subjects are given 3 groups of 3 words and asked which two words in each group are most closely related.

In its validation study, the MMP was validated against a comprehensive neuropsychological battery in 50 subjects with PD.⁷ The wide range of MMP total scores compared to the MMSE suggests it may be more sensitive to detecting the mild cognitive deficits seen in PD. Content validity and construct validity was assessed and inter-rater reliability was high ($r=0.84$), but no other psychometric properties were assessed.⁷ Despite being developed specifically for PD, the MMP has been evaluated in only one other study.²⁶

Advantages of the MMP include quick administration time and potential to detect early cognitive changes in PD. However, the MMP is still heavily weighted towards orientation, does not assess other cortically mediated functions such as language, and has limited data regarding psychometric performance in PD.

Parkinson Neuropsychometric Dementia Assessment (PANDA)

The PANDA was developed to be a brief assessment (~10 minutes) to detect subtle cognitive impairment and dementia in patients with PD in research and clinical care settings.¹¹ Four cognitive domains are tested: memory (verbal paired associate learning), executive functioning (alternating categorical fluency), visuospatial abilities (visual imagery), and working memory/attention (number sequencing). A fifth section screens for depressive symptoms (mood, interest, and drive).

Only two studies have used the PANDA in PD but initial data suggest that it is a reliable tool that is more sensitive than the MMSE for detecting cognitive impairment in patients with PD.^{11,27} Test-retest reliability is high ($r=.93$), as is inter-rater reliability ($r=.95$).¹¹ While sensitivity, specificity, and cut-off scores for dementia and MCI have been published, they are not firmly established. Moreover, the PANDA does not assess orientation, language, or visual construction.

Scales for Outcomes in Parkinson's disease-cognition (SCOPA-cog)

SCOPA-cog is a PD-specific scale that was developed for the purpose of comparing groups in research settings, not as a screening or diagnostic tool.¹² It is available without restrictions for use in research. The instrument consists of 10 items, with a maximum score of 43, and can be administered in approximately 10–15 minutes. Non-verbal and verbal memory and learning are assessed using a cube test (copying the order in which 4 cubes are pointed), backward digit span, and reading/recalling 10 words. Attention is assessed by saying the months backward and serial three subtractions. Aspects of executive functions measured include: complex motor planning, working memory, and verbal fluency. A figure assembly task to assess visuospatial function completes the scale. The SCOPA-cog is available in Dutch, English and Portuguese (Brazilian) versions.^{12,28,29}

The inclusion of specific tasks of executive function make the SCOPA-cog more likely to be sensitive to early cognitive changes in the PD population than the MMSE.¹² In its validation study, the SCOPA-cog was validated against the CAMCOG and had higher reproducibility than the MMSE (0.78 vs. 0.66) and greater internal consistency than the MMSE (0.83 vs. 0.62).¹² Although SCOPA-cog was developed specifically for a PD population, it has not been used extensively in PD.² Despite the SCOPA-cog's potential sensitivity to early cognitive changes in PD it has not been evaluated in PD patients with diagnoses of MCI or dementia to be able to determine sensitivity, specificity, or cut-off values and it does not measure orientation and language function.

CONCLUSIONS AND RECOMMENDATIONS

The purpose of this review was to identify and recommend a brief, standard cognitive measure that could be used to screen PD subjects for dementia and cognitive impairment in

research studies where cognitive performance is not the primary outcome measure. Of the 5 instruments reviewed, only the MoCA fulfilled the primary criteria established by the Task Force. Thus, the Task Force preliminarily recommends the MoCA as a minimum standard cognitive screening instrument in clinical trials of PD. It can be administered rapidly and has the potential to identify subtle executive dysfunction while also covering the major cognitive domains.

All available instruments that can be briefly administered have limitations. The MMSE has been used extensively in studies of patients with PD, can measure progression once patients develop dementia, and is sensitive to change in clinical trials. However, its deficiencies include a distinct ceiling effect and its inability to assess executive functions. Therefore, it is unlikely to detect MCI in PD, a primary concern if the instrument is to serve as a screening measure for mild cognitive dysfunction. While the MoCA, MMP, PANDA, and SCOPA-cog all appear suitable for detecting early cognitive dysfunction in PD, each has undergone limited cross-validation in PD samples. Some instruments (MoCA and MMSE) include language tasks, but do not assess this domain as adequately as longer and more comprehensive assessments. While all of the scales included in this review can be administered in less than 15 minutes, published administration times are likely based on non-demented populations and may take longer in demented PD participants.

Although preliminary data seems to suggest that the MoCA may be a poor screening measure for MCI in PD based on its reported low specificity (0.53) using a cutoff of 26/27,25 this study had several flaws that limit the strength of the conclusions that can be made regarding its utility to detect MCI. The diagnostic criteria for defining MCI has not been well established in PD and the requirement of self-reported cognitive decline in this study25 may require a degree of insight not commonly seen in patients with a neurodegenerative process affecting frontally-mediated functions such as meta-cognition. Additionally, the study had small numbers of subjects with cognitive impairment (only 12.9% PDD and 17.4% MCI out of 132 subjects), and a limited neuropsychological battery was used.25

A brief scale for screening dementia in PD (PDD-Short Screen) was recently published,30 which took 4.8–6.9 minutes to administer and had high sensitivity (0.898) and specificity (0.885) for diagnosing PDD. Unfortunately, it may not be sensitive enough to detect subtle executive dysfunction in PD and thus did not meet our Task Force's objectives.

The aim of this Task Force is complementary yet distinguishable from a recent review by Kulisevsky and Pagonabarraga that evaluated different instruments on their appropriateness to assess cognition throughout the course of PD.2 That review identified both SCOPA-cog and PD-CRS as the most appropriate for capturing early PD cognitive changes and PD-CRS as the most suitable for monitoring cognitive progression in PD. However, SCOPA-cog does not measure orientation or language function, which would be useful in a screening measure to rule out alternative causes for dementia, such as AD. The lengthier administration time of the PD-CRS precludes its use as a screening instrument in clinical trials of PD not focusing primarily on cognition. Our review is also different from the recent efforts of a Movement Disorders Society (MDS) Task Force on Dementia in Parkinson's Disease that established diagnostic criteria for dementia in PD31 as well as a practical approach to its diagnosis.32

Should the MoCA be utilized in clinical trials going forward, the dilemma of how to compare new data to existing trials that used the MMSE needs to be addressed. A potential strategy would be to transform MMSE and MoCA scores into equivalent z-scores,17 which would allow comparison of cognitive performance between the two groups. However, the absence of age and education normative data for the MoCA limits this practice. For now, the

most parsimonious strategy would be to administer both the MoCA and the MMSE until further evidence is available to demonstrate whether it is an appropriate tool. For existing clinical trial databases that have extensive MMSE data only, using age and education adjusted MMSE cut-offs for cognitive impairment may be helpful. In a recent study on cognitive impairment in the DATATOP study cohort,³³ Uc et al. found that subjects who developed cognitive impairment by age and education adjusted MMSE criteria showed significant decline on neuropsychological tests while the neuropsychological performance of non-impaired subjects remained stable.

This task force recommends consideration of the MoCA as a screening instrument for dementia and MCI in PD clinical studies where cognition is not the primary outcome measure. Widespread adoption of such an instrument in clinical trials will improve comparability among research studies on motor and non-motor aspects of PD. The MoCA still requires further study of its validity in PD populations to determine how well it detects MCI and dementia, and it could also benefit from the development of age and education normative data. Despite these flaws, the MoCA shows the most promise of the currently available brief cognitive assessments. Since the MoCA lacks data regarding sensitivity to change over time and to treatment, the Task Force does not recommend use of the MoCA as a stand-alone measure in PD trials investigating progression of cognitive impairment. If future evidence demonstrates that the MoCA is sensitive to longitudinal treatment effects and cognitive decline, then the MoCA may be considered for use as a primary outcome measure.

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Table

Evaluation criteria met for the reviewed scales

	MMSE	MoCA	MMP	PANDA	SCOPA-cog
Primary Criteria*					
Used in PD population	√	√	√	√	√
Could stand alone as minimum assessment	√	√	√	√	√
Administration in < 15 minutes	√	√	√	√	√
Assesses the major cognitive domains	o	√	o	o	o
Can identify subtle cognitive impairment in PD	o	√	√	√	√
Secondary Criteria					
Used in studies beyond original developers	√	√	√	o	√
Psychometric data available in PD	√	√	√	√	√

* the recommended scale should meet all primary criteria

√=met criterion, o=did not meet criterion