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Validity of the Mattis Dementia Rating Scale to Detect Mild Cognitive Impairment in Parkinson's Disease and REM Sleep Behavior Disorder

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Key Words
Dementia rating scale 2 · Mini-mental state examination · Mild cognitive impairment · Parkinson's disease · REM sleep behavior disorder

Abstract
Background/Aims: Mild cognitive impairment (MCI) is frequent in Parkinson's disease (PD) and idiopathic REM sleep behavior disorder (iRBD). However, only a few studies have evaluated the validity of brief cognitive measures to detect MCI in PD or iRBD using standard diagnostic criteria for MCI. Our aim was to evaluate the validity of the Mini-Mental State Examination (MMSE) and the Mattis Dementia Rating Scale (DRS-2) to detect MCI in PD and iRBD. ***Methods:*** Forty PD patients and 34 iRBD patients were studied. Receiver operating characteristic curves were created for both tests to assess their effectiveness in identifying MCI in PD and iRBD. ***Results:*** In PD, a normality cutoff of 138 on the DRS-2 yielded the best balance between sensitivity (72%) and specificity (86%) with a correct classification of 80%. In iRBD, the optimal normality cutoff was 141 on the DRS-2, with a sensitivity of 90%, a specificity of 71% and a correct classification of 82%. No cutoff for the MMSE was found to have acceptable sensitivity or specificity. ***Conclusion:*** The DRS-2 has satisfactory validity to detect MCI in PD or iRBD. The MMSE proved to be invalid as a screening test for MCI in both populations.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor symptoms such as resting tremor, postural instability, bradykinesia and rigidity. Nonmotor symptoms including sleep, neuropsychiatric, autonomic and gastrointestinal problems are also common in PD. Moreover, it is increasingly recognized that cognitive deficits are frequent in PD and that a substantial proportion of PD patients will eventually develop dementia [1, 2]. The presence of mild cognitive impairment (MCI), a risk factor for dementia [3, 4], has been estimated at 20–30% in PD patients in cross-sectional studies [5–7].

The Mini-Mental State Examination (MMSE) [8] has been proposed as a cognitive screening tool for brief clinical evaluation to detect dementia in PD [9]. However, the MMSE is not sensitive to dysexecutive syndrome [10], the

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main cognitive impairment in PD [11]. Accordingly, its validity to detect cognitive impairment in PD has been questioned [7, 12–16]. However, only a few of these studies used standard criteria and a comprehensive neuropsychological evaluation (i.e. more than one cognitive domain and at least two cognitive measures for each domain) to diagnose MCI [7, 15]. On the other hand, the Mattis Dementia Rating Scale (DRS-2) [17] has been proposed to assess cognitive global efficiency in PD in a research setting, longitudinal follow-up and further characterization of the cognitive profile [9]. The DRS-2 is based on performance across five domain subscales ('attention', 'initiation/perseveration', 'construction', 'conceptualization' and 'memory'). Administration may take 15–30 min to complete in subjects with MCI. Although the DRS-2 is useful for detecting dementia in PD [18, 19], its validity has never been studied in PD with MCI.

REM sleep behavior disorder (RBD) is a parasomnia characterized by excessive muscle activity during REM sleep leading to abnormal and complex motor behaviors associated with dream content [20]. Idiopathic RBD (iRBD) is a risk factor for the development of synucleinopathies such as Lewy body dementia, multiple system atrophy and PD [21]. Moreover, MCI affects approximately 50% of iRBD patients [22]. The validity of the MMSE to detect MCI in RBD is poor [23]. However, the validity of the DRS-2 to detect MCI in iRBD has never been studied.

In this study, we sought to determine the validity of the DRS-2 and MMSE to detect MCI in PD and iRBD patients. We also compared the discriminatory power of the MMSE score adjusted for age, sex and education for the detection of MCI.

Methods

Patient Selection

This study was conducted from 2002 to 2007 as part of a larger research project on cognitive impairment in PD and iRBD. All participants gave their informed consent according to the Helsinki Declaration and signed a consent form approved by the Hôpital du Sacré-Cœur research ethics board. Forty-nine PD patients from two specialized university hospital outpatient movement disorder clinics and 42 iRBD patients from the sleep clinic, Hôpital du Sacré-Cœur de Montréal, were initially recruited. Exclusion criteria were: the presence of a dementia or major depression according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision [24]; atypical PD, a history of stroke, head injury or brain tumor; a respiratory event index (apneas plus hypopneas) greater than 20; an abnormal EEG suggesting the presence of epilepsy; unstable diabetes or hypertension; encephalitis; age over 90 years; language other than French or English, and primary school uncompleted. Only iRBD patients (i.e. RBD not associated with narcolepsy, stroke, posttraumatic stress disorder, brainstem tumor or neurodegenerative disease, nor drug induced) were included in the study. PD patients were examined by neurologists specialized in movement disorders and met the United Kingdom Parkinson's Disease Society Brain Bank criteria for idiopathic PD [25]. All iRBD patients were examined by a sleep specialist and met the International Classification of Sleep Disorders, second edition, criteria for iRBD [20]. The Hoehn and Yahr scale was used to determine PD severity [26]. The Unified Parkinson's Disease Rating Scale, part III, was used to determine motor symptom severity [27]. Levodopa dose equivalents were determined for dopaminergic medication [28].

Neuropsychological Evaluation and MCI Criteria

All participants underwent an extensive neuropsychological evaluation by a neuropsychologist blinded to MCI diagnosis. PD patients were in the 'on' state for antiparkinsonian medication. The French version of the MMSE [8] and DRS-2 [17] were successively administered on the same day with an interval of approximately 1 h. The order of administration alternated. Orientation items (date, month, year, day, place and city) were cross-scored. For the DRS-2, the total score out of 144 points and the robust age- and education-corrected scaled scores (RAECSS; total score out of 18) [29] were considered. For the MMSE, the total score out of 30 points was used. We also assessed the discriminatory power of MMSE population-based norms adjusted for age and education (based on performance $\geq$1.5 standard deviations or SD below the standardized mean) [30] or adjusted for age, sex and education (based on performance in the percentile range $\leq$10) [31] to detect MCI in PD and iRBD.

The cognitive tests and variables included measures of three main cognitive domains: (1) attention and executive functions [digit span from the Wechsler Adult Intelligence Scale III (scaled score); a modified version of the Stroop Color Word Test (part III minus part I for times or errors) [32]; the trail-making test, part B (times); the semantic (animals, fruits/vegetables) and phonemic (P, F and L) verbal fluency test (number of items in 1 min)], (2) episodic verbal learning and memory [Rey Auditory Verbal Learning Test (sum of trials 1–5, list B, immediate recall, delayed recall and recognition)] and (3) visuospatial abilities [copy of the Rey-Osterrieth figure; block design from the Wechsler Adult Intelligence Scale III (scaled score); Bell test (number of omissions)] [22, 33].

We used a modified version of the MCI criteria [22, 34] including the presence of (1) a subjective cognitive complaint, by patient or informant, in the structured interview or on the Cognitive Failures Questionnaire [35] (based on a total score of >24, or the answer 3 = quite often or 4 = very often on at least 1 item); (2) objective evidence of cognitive decline defined as any 2 scores, in the same cognitive domain, $\geq$1.5 SD below the standardized mean (or a scaled score of $\leq$6 or a percentile range of $\leq$10); (3) preserved activities of daily living based on previous and actual capacities for housework, meal preparation, taking medication, shopping and managing money in the structured interview, and (4) cognitive deficits not better explained by another medical or psychiatric disorder or by medication use. MCI subtypes were defined as: nonamnestic MCI single domain; amnestic MCI single domain; nonamnestic MCI multiple domain and amnestic MCI multiple domain [34].

Table 1. Comparison between PD with and without MCI

	All PD (n = 40)	PD-MCI (n = 18)	PD-NoMCI (n = 22)	p[c]
Age[a], years	66.68 ± 8.36	67.72 ± 7.71	65.82 ± 8.95	ns
Education level[a], years	15.15 ± 3.21	15.06 ± 3.99	15.23 ± 2.51	ns
PD duration (symptoms onset)[b], years	5.74 ± 3.35	5.53 ± 3.76	5.91 ± 3.07	ns
Hoehn and Yahr scale score[a]	2.14 ± 0.77	2.15 ± 0.70	2.14 ± 0.83	ns
UPDRS part III 'on'[b]	17.63 ± 9.17	18.60 ± 7.36	16.95 ± 10.45	ns
Converted levodopa dosage[b], mg	403.18 ± 364.95	486.47 ± 427.55	338.82 ± 302.94	ns
MMSE score[a]	28.85 ± 1.00	28.39 ± 0.98	29.23 ± 0.87	0.007
DRS-2 total score[a]	137.35 ± 5.35	134.39 ± 6.25	139.77 ± 2.81	0.003
Attention score[a]	35.83 ± 1.06	35.33 ± 1.19	36.23 ± 0.75	0.006
Initiation score[a]	35.23 ± 2.27	34.22 ± 2.41	36.05 ± 1.81	0.01
Construction score[a]	5.85 ± 0.58	5.72 ± 0.83	5.95 ± 0.21	ns
Conceptualization score[a]	36.88 ± 3.00	35.83 ± 4.03	37.73 ± 1.35	0.05
Memory score[a]	23.58 ± 1.60	23.28 ± 1.78	23.82 ± 1.44	ns
DRS-2 RAECSS[a]	9.21 ± 3.25	7.17 ± 2.64	10.91 ± 2.86	<0.001

Values denote means ± SD unless specified otherwise. UPDRS-III = Unified Parkinson's Disease Rating Scale part III.
[a] t test. [b] Mann-Whitney test. [c] PD-MCI vs. PD-NoMCI.

Statistical Analysis

Between-group comparisons of sociodemographic, clinical and neuropsychological variables were performed using the independent samples t test or the Mann-Whitney test depending on whether the data were normally distributed. Receiver operator characteristic (ROC) curves were made to assess the sensitivity and specificity of the DRS-2 total score, the DRS-2 RAECSS and the MMSE total score to detect MCI in PD and iRBD patients. The optimal cutoff value was defined as the highest score when combining sensitivity, specificity and percentage of correctly classified patients. We also looked for the positive and negative predictive values, the percentage of correctly classified subjects and the area under the curve (AUC). Data are presented as means and SD. Statistical significance was set at $p < 0.05$. All analyses were performed using SPSS version 16.0 for Windows (SPSS, Chicago, Ill., USA).

Results

Nine PD patients (6 for atypical PD, 1 for dementia, 1 for sleep apnea and 1 for language other than French or English) and 8 iRBD patients (4 for dementia, 3 for primary school uncompleted and 1 for age over 90 years) were excluded. The participants were 40 PD patients (29 men) and 34 iRBD patients (29 men).

PD Patients

MCI was found in 45% of PD patients on neuropsychological evaluation (18/40; nonamnestic MCI single domain = 10, nonamnestic MCI multiple domain = 3, amnestic MCI single domain = 1, amnestic MCI multiple domain = 4). Results in PD patients with MCI (PD-MCI) and PD patients without MCI (PD-NoMCI) are presented in table 1. PD-MCI patients were comparable to PD-NoMCI patients on age, educational level, PD duration, PD severity, motor symptom severity and converted levodopa dosage. Compared with PD-NoMCI patients, PD-MCI patients performed worse on the DRS-2 total score, the DRS-2 RAECSS and the MMSE total score. PD-MCI patients also scored significantly lower on the attention, initiation and conceptualization DRS-2 subscales, whereas no significant differences were found for the construction and memory subscales. A ceiling effect was observed for the MMSE but not the DRS-2.

Using ROC curve analysis, the validity of each screening tool to detect MCI in PD was examined. The optimal normality cutoff value was 138 (137 indicating impairment) for the DRS-2 total score, with a sensitivity of 72% (95% CI: 0.58–0.86) and specificity of 86% (correct classification = 80%; AUC = 0.80). For the DRS-2 RAECSS, the optimal cutoff value was 8 (7 indicating impairment), with a sensitivity of 50% (95% CI: 0.35–0.65) and a specificity of 95% (correct classification = 75%; AUC = 0.82). For the MMSE total score, the optimal cutoff value was 30 (29 indicating impairment), with a sensitivity of 94% (95% CI: 0.87–1.01) and a specificity of 45% (correct classification = 65%; AUC = 0.70) (table 2).

Table 2. Discriminant validity of the DRS-2 and the MMSE for detecting MCI in PD

DRS-2 (total score)									
Cutoff	144/143	143/142	142/141	141/140	140/139	139/138	*138/137*	137/136	136/135
Sensitivity, %	100	100	89	89	83	72	*72*	61	44
Specificity, %	9	23	27	36	50	77	*86*	86	91
PPV, %	47	51	50	53	58	72	*81*	79	80
NPV, %	100	100	75	80	79	77	*79*	73	67
% correctly diagnosed	50	58	55	60	65	75	*80*	75	70
AUC	0.80 (0.66–0.94)								
DRS-2 RAECSS									
Cutoff	15/14	14/13	13/12	12/11	11/10	10/9	9/8	*8/7*	7/6
Sensitivity, %	100	100	100	100	94	78	61	*50*	33
Specificity, %	14	23	23	27	50	59	82	*95*	100
PPV, %	49	51	51	53	61	61	73	*90*	100
NPV, %	100	100	100	100	92	76	72	*70*	65
% correctly diagnosed	53	58	58	60	70	68	73	*75*	70
AUC	0.82 (0.69–0.96)								
MMSE									
Cutoff	*30/29*	29/28	28/27						
Sensitivity, %	*94*	39	28						
Specificity, %	*45*	82	95						
PPV, %	*59*	64	83						
NPV, %	*91*	62	62						
% correctly diagnosed	*68*	63	65						
AUC	0.70 (0.53–0.87)								

Values in parentheses denote 95% CI. Optimal cutoff values are set in italics. PPV = Positive predictive value; NPV = negative predictive value.

Table 3. Comparison between iRBD with and without MCI (t test)

	All iRBD (n = 34)	iRBD-MCI (n = 20)	iRBD-NoMCI (n = 14)	p[a]
Age, years	66.26 ± 7.11	66.80 ± 6.49	65.50 ± 8.09	ns
Education level, years	12.68 ± 3.46	11.95 ± 3.69	13.71 ± 2.92	ns
MMSE score	28.59 ± 1.18	28.15 ± 1.23	29.21 ± 0.80	0.008
DRS-2 total score	138.61 ± 4.31	134.30 ± 5.90	140.71 ± 2.09	<0.001
Attention score	35.94 ± 1.13	35.60 ± 1.31	36.43 ± 0.51	0.02
Initiation score	35.12 ± 2.66	34.60 ± 3.10	35.79 ± 1.67	ns
Construction score	5.97 ± 0.17	6.00 ± 0.00	5.93 ± 0.27	ns
Conceptualization score	36.85 ± 2.67	35.30 ± 2.76	38.14 ± 1.35	<0.001
Memory score	23.38 ± 1.94	22.75 ± 2.22	24.29 ± 0.91	0.01
DRS-2 RAECSS	9.80 ± 3.37	8.40 ± 3.47	11.93 ± 2.13	0.002

Values denote means ± SD unless specified otherwise. [a] iRBD-MCI vs. iRBD-NoMCI.

Table 4. Discriminant validity of the DRS-2 and MMSE for detecting MCI in iRBD

DRS-2 (total score)									
Cutoff	144/143	143/142	142/141	*141/140*	140/139	139/138	138/137	137/136	136/135
Sensitivity, %	100	90	90	*90*	80	75	65	65	60
Specificity, %	0	14	43	*71*	79	86	86	93	100
PPV, %	59	60	69	*82*	84	88	87	93	100
NPV, %	100	50	75	*83*	73	71	63	65	64
% correctly diagnosed	59	59	71	*82*	79	79	74	76	76
AUC	0.86 (0.73–0.98)								
DRS-2 RAECSS									
Cutoff	15/14	14/13	13/12	12/11	11/10	10/9	*9/8*	8/7	7/6
Sensitivity, %	95	90	85	80	75	70	*65*	50	20
Specificity, %	14	14	43	57	79	79	*100*	100	100
PPV, %	61	60	68	73	83	82	*100*	100	100
NPV, %	67	50	67	67	69	65	*67*	58	47
% correctly diagnosed	62	59	68	71	76	74	*79*	71	53
AUC	0.82 (0.68–0.96)								
MMSE									
Cutoff	30/29	*29/28*	28/27	27/26					
Sensitivity, %	85	*60*	30	10					
Specificity, %	43	*79*	100	100					
PPV, %	68	*80*	100	100					
NPV, %	67	*58*	50	44					
% correctly diagnosed	68	*68*	59	47					
AUC	0.75 (0.59–0.91)								

Values in parentheses denote 95% CI. Optimal cutoff values are set in italics. PPV = Positive predictive value; NPV = negative predictive value.

Of 18 PD-MCI patients, only 1 (6%) was detected using the MMSE population-based norms adjusted for age and education [30], and 3 out of 18 (17%) of the PD-MCI patients were detected using the MMSE norms adjusted for age, sex and education and adapted for a French Canadian population [31].

iRBD Patients

MCI was found in 59% of iRBD patients on neuropsychological evaluation (20/34; nonamnestic MCI single domain = 10, amnestic MCI multiple domain = 4, nonamnestic MCI multiple domain = 3, amnestic MCI single domain = 3). Results comparing iRBD patients with MCI (iRBD-MCI) with iRBD patients without MCI (iRBD-NoMCI) are presented in table 3. There was no group difference between iRBD-MCI patients and iRBD-NoMCI patients for age or educational level. iRBD-MCI patients had significantly lower total scores than iRBD-NoMCI patients on the DRS-2, the DRS-2 RAECSS and the MMSE. iRBD-MCI patients also scored significantly lower on the attention, conceptualization and memory DRS-2 subscales, whereas no group differences were found for the initiation and construction subscales. A ceiling effect was observed for the MMSE but not the DRS-2.

Using ROC curve analysis, the optimal normality cutoff value was 141 (140 indicating impairment) for the DRS-2 total score, with a sensitivity of 90% (95% CI: 0.80–0.100) and a specificity of 71% (correct classification = 82%; AUC = 0.86). For the DRS-2 RAECSS, the optimal cutoff value was 9 (8 indicating impairment), with a sensitivity of 65% (95% CI: 0.49–0.81) and a specificity of 100% (correct classification = 79%; AUC = 0.82). For the MMSE total score, the optimal cutoff value was 29 (28 indicating impairment), with a sensitivity of 60% (95% CI: 0.44–0.76) and a specificity of 79% (correct classification = 68%; AUC = 0.75) (table 4).

Of the 20 iRBD-MCI patients, only 3 (15%) were detected using the MMSE population-based norms adjusted for age and education [30], and 5 iRBD-MCI patients (25%) were detected using the MMSE norms adjusted for age, sex and education and adapted for a French Canadian population [31].

Discussion

This study evaluated the validity of the DRS-2 and the MMSE to detect MCI in PD and iRBD patients using standard criteria and neuropsychological evaluation to diagnose MCI. We found that the DRS-2 is superior to the MMSE in detecting MCI in PD and iRBD. In PD patients (based on the optimal cutoff value and the AUC), the DRS-2 total score was superior than the DRS-2 RAECSS for detection of MCI. In iRBD patients, the DRS-2 total score was also slightly superior than the DRS-2 RAECSS for detection of MCI. On the other hand, in both populations, no cutoff value for the MMSE reached acceptable sensitivity, specificity, correct classification or AUC.

In PD, the prevalence of MCI ranges from 20 to 30% in cross-sectional studies [5–7]. We found a higher prevalence of MCI in our PD population. However, our sample is relatively insufficient to provide a good approximation of prevalence, and there was probably a selection bias: many of our PD patients were referred for RBD, a probable risk factor for cognitive impairment in PD [22]. In both the general population and in PD patients, MCI is a risk factor for dementia [3, 4]. Longitudinal studies have estimated the cumulative prevalence of dementia in PD at approximately 75% [36–38]. In iRBD, at least 50% of patients met the MCI criteria [22]. Moreover, RBD is a risk factor for synuclein-mediated neurodegenerative diseases such as PD and Lewy body dementia. iRBD patients have an 18–45% risk of synucleinopathy at 5 years, increasing to 40–65% at 10 years [39–41]. Given the strong association between PD-MCI or iRBD and the development of dementia, there is a need to evaluate the validity of brief cognitive instruments to detect MCI and identify patients at risk for developing dementia. This is particularly important because nonpharmacological approaches have been developed to manage cognitive impairment in MCI [42].

Although the MMSE is widely used to detect cognitive impairment in aged populations, its validity to detect MCI has been questioned. Good sensitivity has always been obtained at the cost of lower specificity and vice versa [43, 44]. The MMSE has been recommended as a cognitive screening tool to detect dementia in PD [9]. Recognizing the poor sensitivity of the MMSE to executive dysfunction [10], a normality cutoff of 26 was proposed [9]. Moreover, for older and less educated patients, it was suggested to use population-based norms adjusted for age, sex and education.

Our results show that no cutoff value or population-based norm is valid to detect MCI in PD or iRBD. The validity of the MMSE has been questioned by other groups [12–16], although only a few of these studies used a comprehensive neuropsychological evaluation and standard criteria to detect and diagnose MCI [14, 15]. Hoops et al. [15] used the MMSE to detect MCI in PD and obtained an AUC (95% CI) of 0.72 (0.61–0.83), with an optimal normality cutoff value of 30 (sensitivity = 0.91; specificity = 0.38). These results are similar to those obtained in the present study on the MMSE. In iRBD, one study published by our group on a partially different cohort of iRBD patients showed that the MMSE was inadequate to detect MCI in that population [23]. Thus, our results and those from other groups show that the MMSE is not a valid instrument to screen for cognitive impairment or detect MCI in PD and iRBD. Among the other screening tests with similar administration time as the MMSE, the Montreal Cognitive Assessment [45] has shown better validity than the MMSE for detecting cognitive impairment in PD or iRBD [13–16, 46], although some authors found that the MMSE was also a good discriminator for cognitive impairment in PD [46]. However, longitudinal studies are needed to evaluate the validity of the Montreal Cognitive Assessment for following progression of cognitive impairment in these patients.

The validity of the DRS-2 to detect patients with MCI has not been systematically studied [43]. In PD, studies reported a DRS-2 total score lower than that of healthy individuals [18, 19, 47]. In PD with dementia, the DRS-2 is more sensitive than the MMSE to dysexecutive syndrome [36]. One study suggested a cutoff of $\leq$123 for the DRS-2 total score to differentiate PD patients with and without dementia [19]. To characterize the cognitive profile of PD patients with dementia for clinical monitoring, research studies or pharmacological trials, the DRS-2 has been recommended to test global efficiency [9], and a total score of $\geq$136 has been suggested to be considered normal [9]. Although the DRS-2 appears to be valid and reliable to detect dementia in PD, no studies had determined its validity in PD patients with MCI.

In our study, a normality cutoff of 138 for the DRS-2 total score yielded the best balance between good sensitivity (72%) and very good specificity (86%), with 80% correct classification in PD patients. This may suggest that the cutoff of 136 suggested to identify cognitively intact PD patients may miss some patients with MCI [9]. In PD, the presence of a cognitive complaint and a score of $\geq$138 on the DRS-2 may warrant a neuropsychological evaluation to further investigate and document the cognitive profile and detect MCI. An examination of the different subscales of the DRS-2 revealed that PD-MCI pa-

tients scored lower than PD-NoMCI patients on the attention, initiation and conceptualization subscales, whereas there were no differences on the memory and construction subscales. In line with these results, the predominant MCI subtype in our cohort of PD was nonamnestic MCI single domain with impaired attention and executive functions. This is consistent with the dysexecutive syndrome characterizing PD patients with cognitive impairment [11].

In iRBD, a normality cutoff of 141 for the DRS-2 total score provided a very good sensitivity (90%) with a moderate specificity (71%), with 82% correct classification. iRBD patients who score <141 on the DRS-2 but without cognitive complaint could also be given a comprehensive neuropsychological assessment to better characterize their cognitive profile and exclude the presence of MCI. A normality cutoff score on the DRS-2 of 139 or on the DRS-2 RAECSS of 9 would provide a higher specificity at a substantial cost to sensitivity. iRBD-MCI patients scored lower on the attention, conceptualization and memory DRS-2 subscales. Longitudinal studies would be beneficial to evaluate the responsiveness of the DRS-2 to follow the progression of cognitive impairment in PD and iRBD.

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Disclosure Statement

The authors report no conflict of interest.

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