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Potential reliability and validity of a modified version of the Unified Parkinson's Disease Rating Scale that could be administered remotely

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ABSTRACT

Background: By permitting remote assessments of patients and research participants, telemedicine has the potential to reshape clinical care and clinical trials for Parkinson disease. While the majority of the motor Unified Parkinson's Disease Rating Scale (UPDRS) items can be conducted visually, rigidity and retropulsion pull testing require hands-on assessment by the rater and are less feasible to perform remotely in patients' homes.

Methods: In a secondary data analysis of the Comparison of the Agonist pramipexole vs. Levodopa on Motor complications in Parkinson's Disease (CALM-PD) study, a randomized clinical trial, we assessed the cross-sectional (baseline and 2 years) and longitudinal (change from baseline to 2 years) reliability of a modified motor UPDRS (removing rigidity and retropulsion items) compared to the standard motor UPDRS (all items) using intraclass correlation coefficients (ICC), stratified by treatment group. Internal consistency of the modified UPDRS (mUPDRS) was measured using Cronbach's alpha, and concurrent validity was assessed using Pearson's correlation coefficient (r) between the standard motor UPDRS and mUPDRS.

Results: The mUPDRS versus standard motor UPDRS is cross-sectionally (ICC $\geq$ 0.92) and longitudinally (ICC $\geq$ 0.92) reliable for both treatment groups. High internal consistencies were also observed ($\alpha \geq 0.96$). The mUPDRS had high concurrent validity with the standard UPDRS at both time points and longitudinally ($r \geq 0.93$, $p < 0.0001$).

Conclusions: A modified version of the motor UPDRS without rigidity and retropulsion pull testing is reliable and valid and may lay the foundation for its use in remote assessments of patients and research participants.

1. Introduction

The high burden of clinical trials on participants with a neurological disease and their caregivers is a significant barrier to study participation. The costs of clinical trials and clinical drug development are rising rapidly [1], in part due to slow recruitment and poor retention of study participants and the resultant large sample sizes needed to demonstrate an effect. Home-based assessments via web-based video conferencing and remote mobility may reduce study costs by minimizing the number of required in-person visits, thereby enhancing enrollment and subsequently decreasing the time needed to meet enrollment goals, and decreasing administrative costs. A recent study suggested that home-based visits may be the most effective means of enhancing enrollment into clinical trials for individuals with neurodegenerative diseases [2]. Additionally, remote monitoring of clinical trial participants may permit the use of a single centralized rater for important clinical trial outcomes. A randomized, controlled trial of web-based video conferencing for the management of Parkinson's disease (PD) in community-dwelling individuals and nursing home residents suggested that remote assessment of the motor Unified Parkinson's Disease Rating Scale (UPDRS) is feasible, valid, and reliable (using a trained registered nurse to perform the rigidity assessment and conducting the pull test) compared to the in-person assessment [3,4].

While the majority of the motor UPDRS items can be conducted visually, rigidity and retropulsion pull testing require hands-on assessment by the rater. However, these tests may not add significant diagnostic or predictive benefit; specifically, an abnormal pull test was not associated with future fall risk [5] and rigidity, while responsive to dopaminergic therapy, is of unclear clinical and

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functional significance [6]. Prior to implementing a modified motor UPDRS (without rigidity or retropulsion pull testing) for remote assessment in clinical trials, it is necessary to establish its reliability and validity in the context of a clinical trial where an experimental therapy has been shown to significantly impact the standard UPDRS. Therefore, we evaluated the reliability and validity of the UPDRS without rigidity and pull testing through a secondary analysis of the Comparison of the Agonist pramipexole vs. Levodopa on Motor complications in Parkinson's Disease (CALM-PD) study, an RCT of levodopa versus pramipexole.

2. Methods

The CALM-PD study [7] compared the development of dopaminergic motor complications in 301 individuals with early PD randomized to initial levodopa or initial pramipexole. While the primary analysis demonstrated a lower incidence of motor complications with pramipexole, an early (10 weeks) and persistent benefit at 2 years on the total and motor UPDRS (5.0 and 3.9 point treatment effect, respectively) was observed favoring levodopa. This benefit persisted at the 4-year time point (5.9 for total and 4.9 for motor treatment effect) [8]. This study represents an ideal opportunity to assess whether the use of a modified UPDRS, with rigidity and pull testing removed, affects the results of a clinical trial where a profound effect on the outcome of interest is seen.

In the original CALM-PD study, UPDRS scores were evaluated via in-person clinic visits from baseline through 2 years of follow-up. All 14 items (items 18–31) of the motor UPDRS examination were assessed for each patient, defined as the standard (total) motor UPDRS. The modified motor UPDRS (mUPDRS) is defined as the sum of all motor items except neck rigidity, right upper extremity rigidity, left upper extremity rigidity, right lower extremity rigidity, left lower extremity rigidity (all measured by item 22) and retropulsion pull test for postural stability (item 30).

2.1. Reliability and consistency

To establish the cross-sectional reliability and assess the agreement between the standard motor UPDRS and mUPDRS at baseline and 2 years for both the levodopa ($n = 150$) and pramipexole ($n = 151$) treatment groups, the intraclass correlation coefficient (ICC) and 95% confidence intervals (CI) were calculated. Longitudinal reliability was assessed by calculating the ICC of the change in scores from baseline to 2 years, stratified by treatment groups (levodopa: $n = 131$ and pramipexole: $n = 127$ due to loss to follow-up), between the standard motor UPDRS and mUPDRS. The threshold for reliability was set by an ICC greater than or equal to 0.7 ("excellent agreement") [9]. The MIXED procedure in SAS version 9.2 (SAS Institute, Inc., Cary, NC) was used for ICC calculations. Internal consistency (homogeneity of items in relation to the measure) was measured using Cronbach's alpha for the mUPDRS at baseline, 2-year follow-up, and longitudinally (change between baseline and 2-year follow-up). A value of 0.80 or higher was considered highly consistent.

2.2. Validity

To assess concurrent validity, the motor mUPDRS was correlated with the standard motor UPDRS. Pearson's correlation coefficients (r) and 95% CIs were calculated using the CORR procedure. The magnitude of correlation coefficients was expected to be high ($r > 0.80$) to demonstrate strong convergent validity.

2.3. Kappa and percent agreement

Agreement on the direction of individual change from baseline to 2-year follow-up was assessed between the standard and mUPDRS. A decline in UPDRS score from baseline to 2-year follow-up meant improved motor function while an increase in UPDRS score meant a worsening of motor function. Analyses were stratified by treatment group and performed using the kappa test in PROC FREQ to obtain kappa coefficients and 95% confidence intervals. Percent agreement was calculated by summing the concordant (diagonal) elements and dividing by the sample size for that treatment. Kappa estimates above 0.8 and percent agreement above 90% were considered "excellent agreement" [10].

3. Results

The distribution of UPDRS motor item scores by treatment group is shown in Table 1. All motor items, except for speech in the pramipexole treatment group, demonstrate improvement in function from baseline to 2 years. Improvements were seen the most for rigidity, finger taps, hand pronate/supinate, and body bradykinesia, which was consistent between treatment groups. Total motor

Table 1
Distribution of UPDRS motor item scores by treatment group at baseline and 2-year follow-up.

UPDRS item (measure)	Levodopa (Mean ± SD)			Pramipexole (Mean ± SD)		
	Baseline ($N = 150$)	2-year ($N = 131$)	Δ ($N = 131$)	Baseline ($N = 151$)	2-year ($N = 127$)	Δ ($N = 127$)
18 (speech)	0.85 ± 0.64	0.60 ± 0.68	−0.24 ± 0.61	0.85 ± 0.67	0.88 ± 0.73	0.03 ± 0.57
19 (facial expression)	1.29 ± 0.70	0.92 ± 0.78	−0.37 ± 0.82	1.36 ± 0.74	1.24 ± 0.73	−0.11 ± 0.63
20a (tremor at rest: face, lips, chin)	0.23 ± 0.55	0.10 ± 0.35	−0.13 ± 0.46	0.12 ± 0.37	0.04 ± 0.20	−0.06 ± 0.27
20b (tremor at rest: R hand)	0.94 ± 1.01	0.55 ± 0.83	−0.32 ± 0.75	0.92 ± 1.04	0.50 ± 0.72	−0.43 ± 0.90
20c (tremor at rest: L hand)	0.73 ± 0.89	0.40 ± 0.68	−0.37 ± 0.75	0.79 ± 1.00	0.50 ± 0.79	−0.24 ± 0.72
20d (tremor at rest: R foot)	0.24 ± 0.57	0.11 ± 0.40	−0.10 ± 0.56	0.18 ± 0.49	0.05 ± 0.23	−0.14 ± 0.47
20e (tremor at rest: L foot)	0.23 ± 0.55	0.13 ± 0.40	−0.13 ± 0.57	0.20 ± 0.48	0.10 ± 0.40	−0.08 ± 0.39
21a (action tremor: R)	0.57 ± 0.74	0.34 ± 0.59	−0.22 ± 0.64	0.49 ± 0.68	0.30 ± 0.53	−0.20 ± 0.62
21b (action tremor: L)	0.58 ± 0.65	0.33 ± 0.53	−0.26 ± 0.59	0.52 ± 0.63	0.33 ± 0.56	−0.20 ± 0.49
22a (rigidity: neck)	1.06 ± 0.80	0.82 ± 0.82	−0.21 ± 0.69	1.09 ± 0.81	0.89 ± 0.80	−0.20 ± 0.78
22b (rigidity: R upper extremity)	1.25 ± 0.82	0.83 ± 0.78	−0.37 ± 0.74	1.30 ± 0.78	0.99 ± 0.75	−0.30 ± 0.71
22c (rigidity: L upper extremity)	1.18 ± 0.84	0.76 ± 0.75	−0.42 ± 0.80	1.14 ± 0.82	0.89 ± 0.80	−0.21 ± 0.61
22d (rigidity: R lower extremity)	0.80 ± 0.83	0.50 ± 0.69	−0.27 ± 0.78	0.78 ± 0.77	0.67 ± 0.79	−0.10 ± 0.72
22e (rigidity: L lower extremity)	0.74 ± 0.82	0.54 ± 0.71	−0.22 ± 0.82	0.81 ± 0.83	0.68 ± 0.82	−0.08 ± 0.70
23a (finger taps: R)	1.25 ± 0.97	0.79 ± 0.82	−0.46 ± 0.84	1.26 ± 0.85	0.84 ± 0.74	−0.41 ± 0.75
23b (finger taps: L)	1.25 ± 0.95	0.87 ± 0.79	−0.41 ± 0.90	1.16 ± 0.90	0.85 ± 0.84	−0.28 ± 0.90
24a (hand grips: R)	0.90 ± 0.84	0.51 ± 0.74	−0.39 ± 0.79	0.99 ± 0.78	0.77 ± 0.74	−0.23 ± 0.69
24b (hand grips: L)	1.00 ± 0.88	0.63 ± 0.74	−0.39 ± 0.89	0.98 ± 0.87	0.79 ± 0.72	−0.14 ± 0.73
25a (hand pronate/supinate: R)	0.93 ± 0.85	0.50 ± 0.75	−0.42 ± 0.73	1.02 ± 0.79	0.71 ± 0.76	−0.30 ± 0.79
25b (hand pronate/supinate: L)	1.00 ± 0.92	0.58 ± 0.71	−0.42 ± 0.82	1.00 ± 0.91	0.81 ± 0.83	−0.18 ± 0.87
26a (leg agility: R)	0.71 ± 0.78	0.42 ± 0.64	−0.30 ± 0.79	0.87 ± 0.80	0.56 ± 0.70	−0.29 ± 0.77
26b (leg agility: L)	0.84 ± 0.78	0.55 ± 0.68	−0.32 ± 0.86	0.83 ± 0.77	0.71 ± 0.83	−0.09 ± 0.70
27 (arise from chair)	0.22 ± 0.42	0.12 ± 0.31	−0.08 ± 0.40	0.28 ± 0.47	0.23 ± 0.38	0.01 ± 0.42
28 (posture)	0.69 ± 0.62	0.51 ± 0.60	−0.17 ± 0.61	0.75 ± 0.66	0.67 ± 0.62	−0.01 ± 0.55
29 (gait)	0.61 ± 0.57	0.31 ± 0.44	−0.29 ± 0.50	0.65 ± 0.58	0.50 ± 0.56	−0.13 ± 0.49
30 (postural stability)	0.28 ± 0.55	0.13 ± 0.35	−0.09 ± 0.45	0.29 ± 0.52	0.18 ± 0.42	−0.09 ± 0.46
31 (body bradykinesia)	1.59 ± 0.67	1.00 ± 0.80	−0.59 ± 0.81	1.69 ± 0.72	1.30 ± 0.76	−0.37 ± 0.70
18-31 (standard motor UPDRS)	21.97 ± 9.64	13.85 ± 8.98	−8.12 ± 8.47	22.27 ± 9.16	16.97 ± 8.89	−4.73 ± 7.47
18-31, excl. 22 & 30 (modified motor UPDRS)	16.66 ± 7.42	10.27 ± 6.91	−6.30 ± 7.40	16.85 ± 7.04	12.69 ± 6.66	−3.74 ± 5.90

UPDRS, Unified Parkinson's Disease Rating Scale; SD, standard deviation; R, right; L, left.