Weighting MDS-UPDRS Motor Items for Optimal Sensitivity to Parkinson's Disease Progression in Untreated Patients Using Parkinson's Progression Markers Initiative Data

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Introduction

- Parkinson's Disease (PD) symptoms and rates of progression can vary substantially across individuals,[1] which complicates the study of disease-modifying therapies (DMTs) in clinical trials
- The MDS-UPDRS is a cornerstone measure used in clinical trials that assesses a range of outcomes in PD patients across the spectrum of disease (motor, non-motor and activities of daily living)
- However, the comprehensive nature of MDS-UPDRS makes it challenging to detect small but meaningful changes in more specific groups of PD patients (e.g., early-stage disease), over time periods feasible for clinical trials
- To address this challenge, there is precedent for the use of composite scores in other neurodegenerative diseases that are optimized to disease stage, treatment status and symptom presentation[2,3]
- Composite scores can be highly sensitive to detect small but meaningful changes in disease progression

DMT, disease modifying therapy; **MDS-UPDRS**, The Movement Disorder Society Unified Parkinson's Disease Rating Scale; **PD**, Parkinson's disease.

1. The Michael J Fox Foundation. Symptoms. n.d.; https://www.michaelifox.org/symptoms. 2. Schobel SA, Palermo G, Auinger P, et al. Motor, cognitive, and functional declines contribute to a single progressive factor in early HD. *Neurology*. 2017;89(24):2495-2502. 3. Wang J, Logovinsky V, Hendrix SB, et al. ADCOMS: a composite clinical outcome for prodromal Alzheimer's disease trials. *J Neurol Neurosurg Psychiatry*. 2016;87(9):993-999.

Objective

To demonstrate how composite scales can better detect meaningful changes in motor progression among untreated PD patients

PD, Parkinson's disease

Methods

Study Participants and Data

- Data: PPMI PD cohort from July 1, 2010 to July 1, 2023
- Subject eligibility criteria:
  - Hoehn & Yahr stage 1 or 2
  - No previous or current DT use
  - Time from PD diagnosis less than two years
- Patients censored once DT initiated (excluding MAO-B inhibitors)
- Components of the MDS-UPDRS scale (© 2008 MDS) in the motor composite scale (MCS):
  - Part II (motor experiences of daily living, 13 items)
  - Part III (motor examination, 33 scores based on 18 items)
- Patients were required to have baseline and ≥1 post-baseline visits with complete data on Part II and Part III, within 3 years of follow-up

Statistical Analysis

- A linear decline model was fit using partial least squares (PLS) regression methods with temporal change as the outcome and MDS-UPDRS Parts II and III items as explanatory variables
- The MCS combined the explanatory variables selected from the PLS regression with PLS coefficients serving as weighting factors
- Wold's criterion was used to remove scale items under a variable importance in projection (VIP) threshold of 0.5
- The mean to standard deviation ratio (MSDR) was computed for change values of the new score and used in a power calculation
- All analyses were conducted in R v4.2.2

DT, dopaminergic therapy; **MAO-B**, monoamine oxidase-B; **MCS**, motor composite scale; **MDS**, International Parkinson and Movement Disorder Society; **MDS-UPDRS**, The Movement Disorder Society Unified Parkinson's Disease Rating Scale; **MSDR**, Mean to Standard Deviation Ratio; **PD**, Parkinson's disease; **PPMI**, Parkinson's Progression Markers Initiative, **PLS**, partial least squares; **VIP**, variable importance in projection.

Results: Demographic and Baseline Characteristics for Untreated Patients With PD, From the PPMI Dataset

	N=426
Age in years, mean (SD)	62.7 (9.1)
Sex, n (%)	
Male	293 (69)
Female	133 (31)
Age at diagnosis, mean (SD)	61.7 (9.1)
Race	
White	396 (93)
Multiracial	10 (2)
Black/African American	8 (2)
Asian	5 (1)
Native American	1 (0)
Not specified	6 (1)
Time since diagnosis (years), mean (SD)	0.6 (0.5)
Hoehn & Yahr stage, n (%)	
1	159 (37)
2	267 (63)
MDS-UPDRS Part II score, mean (SD)	5.3 (4.0)
MDS-UPDRS Part III score, mean (SD)	20.8 (8.9)

- 426 eligible PPMI participants included
- Predominantly white males aged 63 years, diagnosed in the previous year with Hoehn & Yahr stage 2

MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; **PD**, Parkinson's disease; **PPMI**, Parkinson's Progression Markers Initiative; **SD**, standard deviation.

Results: PLS Regression

PART II
Motor Experiences of Daily Living

1. Speech
2. Salivation & drooling
3. Chewing & swallowing
4. Eating tasks
5. Dressing
6. Hygiene
7. Handwriting
8. Doing hobbies and other activities
9. Turning in bed
10. Tremor
11. Getting out of bed, car, or deep chair
12. Walking and balance
13. Freezing

PART III
Motor Examinations

1. Speech
2. Facial expression
3. Rigidity of neck and four extremities
4. Finger taps
5. Hand movements
6. Pronation/supination
7. Toe tapping
8. Leg agility
9. Arising from chair
10. Gait
11. Freezing of gait
12. Postural stability
13. Posture
14. Global spontaneity of movement
15. Postural tremor of hands
16. Kinetic tremor of hands
17. Rest tremor amplitude
18. Constancy of rest tremor

- 18 non-responsive items were removed
- 61% (28 of 46) items were included in the MCS

LLE, left lower extremity**; LUE,** left upper extremity**; MCS**, motor composite score; **MSDR**, mean to standard deviation ratio; **PD**, Parkinson's disease; **PLS**, partial least squares; **RUE**, right upper extremity; **VIP**, variable importance in projection.

MCS VIP Scores and PLS Coefficients Among Untreated PD Patients, VIP Cut-off 0.5

Item	MSDR at 1 year	VIP	PLS weight	% contribution
2.9 Turning in bed	0.3498	0.8853	0.7629	9.4
3.1 Speech	0.3683	0.9706	0.6261	7.7
3.17b Rest tremor amplitude — LUE	0.3329	1.0614	0.5510	6.8
3.8b Leg agility — Left leg	0.3061	1.3672	0.5328	6.6
3.17a Rest tremor amplitude — RUE	0.2711	1.0651	0.5075	6.3
2.11 Getting out of bed, a car, or a deep chair	0.2208	0.9876	0.4674	5.8
3.6b Pronation-Supination — Left hand	0.3842	1.3425	0.4484	5.5
2.10 Tremor	0.2322	0.8414	0.3556	4.4
2.12 Walking and balance	0.2723	0.6476	0.3358	4.2
3.13 Posture	0.1708	0.7745	0.3251	4.0
3.2 Facial expression	0.2019	1.0356	0.3164	3.9
2.1 Speech	0.2420	0.6893	0.3144	3.9
3.5b Hand movements — Left hand	0.3332	1.4373	0.3107	3.8
2.7 Handwriting	0.2456	1.1884	0.3042	3.8
3.3e Rigidity — LLE	0.1430	1.1031	0.2782	3.4
3.7a Toe tapping — Right foot	0.1784	1.3510	0.2586	3.2
2.2 Saliva and drooling	0.2288	0.8720	0.2335	2.9
3.18 Constancy of rest tremor	0.3316	1.5598	0.2289	2.8
2.4 Eating tasks	0.2947	0.7090	0.2227	2.8
3.3b Rigidity — RUE	0.1834	0.8314	0.2116	2.6
3.14 Global spontaneity of movement	0.2734	0.9049	0.1519	1.9
3.3c Rigidity — LUE	0.3370	1.0914	0.0694	0.9
3.7b Toe tapping — Left foot	0.2227	1.3155	0.0597	0.7
2.5 Dressing	0.3113	0.7396	0.0599	0.7
3.5a Hand movements — Right hand	0.2268	1.1942	0.0464	0.6
3.3a Rigidity — Neck	0.2428	0.9632	0.0521	0.6
3.4b Finger tapping — Left hand	0.3876	1.3037	0.0279	0.3
3.4a Finger tapping — Right hand	0.2000	1.1148	0.0240	0.3
Overall MSDR	**0.8612**			

Results: PLS regression

Model weight contribution of MCS

- 37.9% from Part II
- 61.9% from Part III

Most highly weighted items from Part II

- Turning in bed (9.4%)
- Getting out of bed/car/chair (5.8%)
- Tremor (4.4%)

Most highly weighted items from Part III

- Speech (7.7%)
- Rest tremor amplitude — left upper extremity (6.8%)
- Leg agility — left (6.6%)

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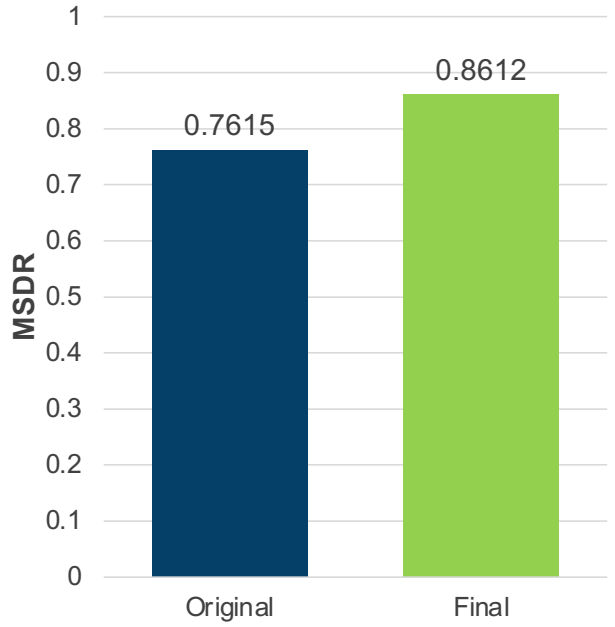
Results: Scale Performance

- 13.1% increase in MSDR at 1-year
  - Original MSDR 0.7615 (MDS-UPDRS Parts II and III combined)
  - Weighted MCS MSDR 0.8612
- Corresponds to:
  - 22% sample size decrease
  - Power improvement of 8% at 80% initial power

Change in MSDR for the MDS-UPDRS Parts II and III, Untreated PD Patients



MCS, motor composite scale; **MDS-UPDRS**, The Movement Disorder Society Unified Parkinson's Disease Rating Scale; **MSDR**, mean to standard deviation ratio; **PD**, Parkinson's disease.

Discussion

- The MCS is optimized for patients with early PD who have not initiated levodopa
- An MCS derived in treated patients with PD would be expected to differ, in terms of the items included and their relative contribution to the overall composite scale
- The improved MSDR indicates a more sensitive scale for disease progression in untreated PD patients based on a shorter tool (28 items vs. 46)
- Accompanying reduction in sample side and improvements in power can have significant implications for clinical trial design
- Trial efficiency is valuable in PD, given the difficulties in accurately measuring disease progression during the typical length of a DMT trial

DMT, disease modifying therapy; **MCS**, motor composite scale; **MDS-UPDRS**, The Movement Disorder Society Unified Parkinson's Disease Rating Scale; **MSDR**, mean to standard deviation ratio; **PD**, Parkinson's disease.

Conclusions

- Endpoints derived from the MCS measure clinically meaningful progression with greater sensitivity compared to the original MDS-UPDRS Part II and III
- Turning in bed, speech and rest tremor amplitude are the items with greatest sensitivity to disease progression in untreated patients with PD
- Composite scales can improve detection of clinical decline when applied in similar patient populations and are valuable for the assessment of DMTs

Acknowledgements

Data source: Parkinson's Progression Markers Initiative (PPMI): Ongoing, international, multicenter natural history cohort primarily funded by the Michael J. Fox Foundation. https://ppmi-info.org

Instrument: MDS-UPDRS scale (© 2008 International Parkinson and Movement Disorder Society)

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Thank you!