Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

A Placebo-Controlled Study to Assess the Sensitivity of Finger Tapping to Medication Effects in Parkinson's Disease

Eva Thijssen, MSc,[1,2] Soma Makai-Bölöni, MSc,[1,2] Emilie van Brummelen, PharmD, PhD,[1] Jonas den Heijer, MD, PhD,[1,2] Yalcin Yavuz, MSc,[1] Robert-Jan Doll, PhD,[1] and Geert Jan Groeneveld, MD, PhD[1,2,]*

ABSTRACT: Background: Movement Disorder Society–Unified Parkinson's Rating Scale Part III (MDS-UPDRS III) is the gold standard for assessing medication effects in patients with Parkinson's disease (PD). However, short and rater-independent measurements would be ideal for future trials.

Objectives: To assess the ability of 3 different finger tapping tasks to detect levodopa/carbidopa-induced changes over time and to determine their correlation and compare their discriminatory power with MDS-UPDRS III.

Methods: This was a randomized, double-blind, crossover study in 20 patients with PD receiving levodopa/carbidopa and placebo capsules after overnight medication withdrawal. Pre- and up to 3.5 hours postdose, MDS-UPDRS III and tapping tasks were performed. Tasks included 2 touchscreen-based alternate finger tapping tasks (index finger versus index–middle finger tapping) and a thumb–index finger task using a goniometer.

Results: In the alternate index finger tapping task, levodopa/carbidopa compared with placebo resulted in significantly faster (total taps: 12.5 [95% confidence interval, CI, 6.7–18.2]) and less accurate tapping (total spatial error: 240 mm [95% CI, 123–357 mm]) with improved rhythm (intertap interval standard deviation [SD], −16.3% [95% CI, −29.9% to 0.0%]). In the thumb–index finger task, tapping was significantly faster (mean opening velocity, 151 degree/s [64–237 degree/s]), with a higher mean amplitude (8.4 degrees [3.7–13.0 degrees]) and improved rhythm (intertap interval SD, −46.4% [95% CI, −63.7% to −20.9%]). The speed-related endpoints showed a moderate-to-strong correlation with the MDS-UPDRS III ($r = 0.45–0.70$). The effect sizes of total taps and spatial error in the alternate index finger tapping task and opening velocity in the thumb–index finger task were comparable with the MDS-UPDRS III. In contrast, the MDS-UPDRS III performed better than the alternate index–middle finger task.

Conclusion: The alternate index finger and the thumb–index finger tapping tasks provide short, rater-independent measurements that are sensitive to levodopa/carbidopa effects with a similar effect size as the MDS-UPDRS III.

The Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is considered the gold standard for assessing (dopaminergic) medication effects.[1] Part III of the scale is often used in clinical trials to show motor improvements after medication intake. However, Part III requires a trained rater who preferably assesses a patient throughout the entire trial to avoid interrater variability. In addition, the assessment takes a relatively long time (ie, approximately 15 minutes, but depends on the patient's clinical state). This makes accurate time-response assessment of fast-acting agents challenging, especially when

[1]*Centre for Human Drug Research, Leiden, Netherlands;* [2]*Leiden University Medical Centre, Leiden, Netherlands*

***Correspondence to:** Prof. Geert Jan Groeneveld, Centre for Human Drug Research, Zernikedreef 8, 2333CL Leiden, the Netherlands; E-mail: ggroeneveld@chdr.nl.

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safety and pharmacokinetic measurements also need to be performed. Hence, a short, rater-independent measurement would be ideal for use in clinical trials.

Literature has shown that finger tapping can be used to show differences between healthy controls and patients with PD[2–7] and between medication states (*on*/*off*).[3,5,6,8,9] Moreover, various finger tapping configurations have shown a correlation with the MDS-UPDRS Part III.[3–6,8,10] However, the set-up and devices used for these tapping tasks vary among studies, and it is unclear which is most suitable for the determination of medication effects in randomized placebo-controlled trials.

In this randomized, double-blind, placebo-controlled trial, we assessed the response to dopaminergic medication during an induced *off* state in patients with PD by using the gold standard MDS-UPDRS III as well as 3 different tapping tasks. For this, 2 touchscreen-based alternate finger tapping tasks (with 2.5 or 20 cm between targets) and a task using a goniometer that assesses angular movement during thumb–index finger tapping were developed in house. The aim was to validate these tapping tasks by demonstrating their ability to detect and quantify acute pharmacodynamic effects over time. Moreover, we evaluated whether the finger tapping endpoints correlated with MDS-UPDRS III.

Methods

This study is registered in the Netherlands Trial Register (Trial NL8617) and was conducted at the Centre for Human Drug Research (Leiden, the Netherlands) between July and November 2020.

Study Design

This was a randomized, double-blind, placebo-controlled, 2-way crossover study in 20 patients with PD. A sample size of 18 was considered sufficient to show a treatment effect based on a paired *t* test with 80% power and a 2-sided α level of 5%, assuming an expected difference on the best response of 8 total taps (standard deviation [SD] = 7) between placebo and treatment (Lipp et al[11]). To be conservative, it was decided to include 20 patients. The study consisted of a screening visit followed by 2 treatment periods of 2 days each, with a 1-week washout between periods. Patients were randomly assigned 1:1 to 1 of 2 treatment sequences (levodopa/carbidopa–placebo or vice versa). The randomization code was generated using SAS version 9.4 (SAS Institute, Cary, NC) by a study-independent statistician. Patients were instructed to withhold their own anti-Parkinson medication in the evening prior to treatment in both treatment periods. Patients were dosed the next morning when in an *off* state, as assessed by the physician. Patients were allowed to resume their own medications 110 minutes after dosing, or, if feasible for the patient, after the last efficacy assessments 210 minutes postdose.

Participants

Patients with PD with self-described motor fluctuations, recognizable *off* periods, and aged between 20 and 85 years with Hoehn and Yahr stages I to III were eligible for participation. In addition, patients had to be levodopa responsive as evidenced by current or historical use of levodopa. Reasons to exclude a patient were a previous intolerance, a potentially relevant interaction of comedication with or a contraindication to levodopa and/or carbidopa. Patients were ineligible when the levodopa equivalent dose (LED) of their morning medication exceeded 500 mg.

Investigational Drugs

To ensure blinding, levodopa/carbidopa 100/25 mg (Sinemet, MSD, Haarlem, the Netherlands) tablets were overencapsulated in 00 gelatin (Swedish orange) capsules. Similarly, placebo tablets were overencapsulated. Patients received a semi-individualized dose based on the LED of their morning medication. To calculate the LED, conversion factors as described by Tomlinson et al[12] were used. For long-acting dopamine agonists, only 25% of their LED was included because only their acute effect was of importance for calculation of the morning LED. Finally, the LED was multiplied by 1.25 to ensure a supramaximal dose was given that was at least 25% higher than the usually administered morning dose (to ensure *off*–*on* transition). This supramaximal LED was rounded up to a whole number of levodopa/carbidopa 100/25 mg (or placebo) capsules that was required for that patient. Because food and especially proteins can affect the absorption of levodopa, study drug administration occurred at least 1 hour after finishing a protein-restricted breakfast, and food was not allowed until 1 hour after dosing.

Safety

Patients enrolled in this study were already using levodopa or had used it in the past. Therefore, they were expected to tolerate the study treatment well. Nonetheless, patient safety was evaluated by the monitoring of adverse events throughout the study and by examining the patient's vital signs, electrocardiograms, and physical/neurological examination before discharge. As no notable changes were observed, these data are not shown.

Outcome Measures

MDS-UPDRS

MDS-UPDRS Part III was used to assess motor function. Physicians administering the scale were trained in its use. To the degree feasible, the same physician evaluated a patient during both treatment periods at day −1 (day before dosing) and at day 1 predose and 10, 30, 60, 90, and 210 minutes postdose. The last measurement was only performed when the patients had not yet resumed their own medications.

Touchscreen-Based Tapping Tasks[13]

1. Alternate index and middle finger tapping: task in which the patient was instructed to alternately tap with the index and middle finger on 2 circles (radius, 1.2 cm) spaced 2.5-cm apart (Fig. 1A).
2. Alternate index finger tapping: task in which the patient was instructed to alternately tap with the index finger on 2 circles (radius, 1.7 cm) spaced 20-cm apart (Fig. 1B).

For both tasks, the instructions were to tap as accurately and as fast as possible for 30 seconds with the hand most affected by PD (or the dominant hand if both sides were equally affected). Calculated endpoints were the following: total number of taps, total taps inside the target, ratio of good:total taps, number of halts, mean intertap interval, SD of intertap intervals, intertap interval change, mean spatial error, SD of spatial error, spatial error change, and total spatial error. Refer to Table S1 for a description of each endpoint.

Thumb–Index Finger Tapping

A goniometer (Biometrics Ltd, Newport, UK) placed on the proximal phalanx and metacarpal of the index finger of the most affected (or dominant if both sides were equally affected) hand measured the angle of the index finger (Fig. 1C). Patients were instructed to tap the index finger on the thumb as quickly and widely as possible for 15 seconds. Calculated endpoints included the following: total number of taps, mean intertap interval, SD of intertap intervals, intertap interval change, mean tapping amplitude, tapping amplitude change, peak frequency area under the curve (AUC), angle frequency change, and mean opening and closing velocity (Table S1).

Patients were trained on all 3 tapping tasks twice on day −1 and once on day 1 predose. These measurements were not used in the analysis. Finger tapping tasks included in the analyses were performed on day 1 predose (double baseline) and approximately 10, 25, 45, 60, 75, 90, 105, and 210 minutes postdose (if the time points coincided with MDS-UPDRS III, then finger tapping tasks were performed first, followed by MDS-UPDRS III). The last measurement was only performed when the patients had not yet resumed their own medications.

Data Exclusion

In case the ratio of good:total taps was <0.3 in the alternate index and middle finger tapping task, intertap interval parameters (mean, SD, change) and number of halts could not be reliably calculated and so were excluded from analysis. One patient seemed unable to correctly perform and/or the device did not correctly record the alternate index and middle finger tapping, so this task was completely excluded from the analysis for this patient.

Statistical Analysis

Analyses were performed using SAS version 9.4. To detect significant treatment effects on the primary endpoints, each endpoint was analyzed using a mixed-model analysis of variance with period, treatment, time, and treatment × time as fixed factors; subject and subject × time as random factors; and the average baseline measurement as a covariate. Homoscedasticity assumption of the mixed-modeling framework was relaxed by allowing separate variance estimates for each treatment. In the model, the contrast levodopa/carbidopa versus placebo was calculated based on all postdose measurements. In case of nonnormality, endpoints with positive numerical results were reanalyzed after log transformation. For 10 endpoints, no models could be fitted because they violated the normality assumption, even after log transformation.

Pearson's or Spearman's (in case of nonnormal or log-normal data) correlation was used to evaluate the relationship between finger tapping endpoints and MDS-UPDRS III at a selected time point (90 minutes for MDS-UPDRS and 105 minutes [after completion of MDS-UPDRS at 90 minutes] for tapping). Correlation analysis was performed for placebo and levodopa/

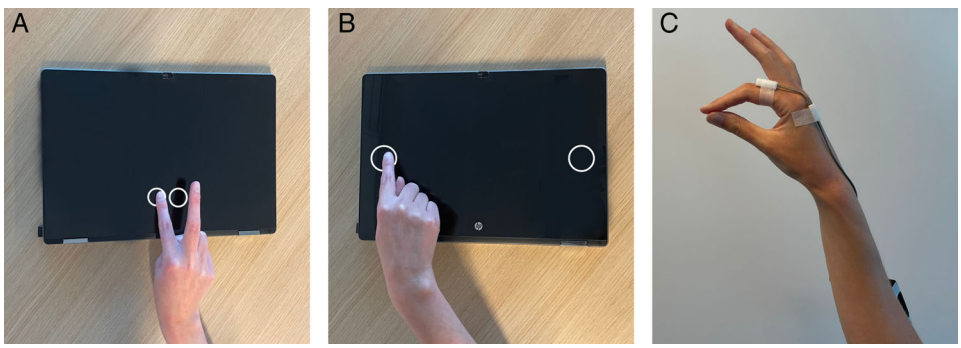

FIG. 1. Depiction of the 3 finger tapping tasks: alternate index and middle finger tapping (**A**), alternate index finger tapping (**B**), and thumb–index finger tapping (**C**).

carbidopa separately. The strength of the correlation was classified as weak ($r < 0.40$), moderate ($r = 0.40$–0.59), strong ($r = 0.60$–0.79), or very strong ($r = 0.80$–1.0).

For both analyses, a P value of ≤0.05 was used as a cutoff for determining significance. No correction for multiple testing was performed because of the exploratory nature of this study.

Standardized effect sizes were calculated by dividing the least squares means (LSMs) difference (levodopa/carbidopa–placebo) by the pooled SD of the treatment effect. The pooled SD was calculated with the formula described by Brown et al.[14] A Hedge's g correction was done to account for small sample size. Effect sizes were calculated for the comparison of endpoints and tasks but are not intended for future power calculations (model-based estimates to be used).

Results

Baseline Characteristics

The number of patients screened, randomized, completed, and analyzed are summarized in the Consolidated Standards of Reporting Trials flow diagram in Figure S1. Table 1 outlines the demographics and baseline characteristics of the 20 patients with PD who completed the study. Most (95%) patients received a levodopa-containing agent as part of their regular medication regimen. Supramaximal morning LED ranged between 47 and 391 mg. Therefore, patients received between 1 and 4 capsules of levodopa/carbidopa 100/25 mg and placebo in a randomized order.

Overall Task Performance

For 6 of 20 patients with PD, the alternate tapping task with the index and middle finger was sometimes difficult to correctly perform. Difficulty was being defined as having a ratio of good:total taps less than 0.3 on at least 4 of 22 performed tests (but this reached up to 17 of 22 tests). Difficulties were approximately equally divided over placebo and levodopa/carbidopa tests. One patient seemed unable to correctly perform and/or the device did not correctly record the alternate index and middle finger tapping. This was concluded based on taps only being recorded during the first few seconds or by gaps of >10 seconds where no taps were recorded (in the absence of freezing). With the alternate index finger tapping and thumb–index finger tapping tasks, the patients usually did not experience any difficulties. However, the goniometer devices used for the thumb–index finger tapping task turned out to be fragile and broke in a few instances. This led to missing data for 1 patient after placebo and 2 patients after levodopa/carbidopa treatment.

Treatment and Treatment × Time Effects

After placebo treatment, 14 of 20 patients had to resume their own Parkinson's medication prior to the last assessment planned at 3.5 hours postdose. After levodopa/carbidopa, this was 6 of

TABLE 1 *Demographics and Baseline Characteristics*

Baseline characteristics	All Patients with PD (n = 20)
Age, years	
Median (range)	61 (48–70)
Mean (SD)	60.6 (6.0)
BMI, kg/m^2	
Median (range)	27 (23–30)
Mean (SD)	26.5 (2.5)
Sex, n/n (%/%)	
Female/male	6/14 (30/70)
Race, n (%)	
White	20 (100)
Hoehn and Yahr stage at screening, n (%)	
Stage 1	7 (35)
Stage 2	7 (35)
Stage 3	6 (30)
MDS-UPDRS III total score on the day prior to dosing (ie, when using regular medication)	
Median (range), placebo treatment	23 (7–52)
Mean (SD), placebo treatment	24.2 (13.1)
Median (range), active treatment	22 (5–70)
Mean (SD), active treatment	24.6 (14.7)
Concomitant PD medication, n (%)	
Levodopa-containing agents	19 (95)
Dopamine agonists	14 (70)
COMT inhibitors	4 (20)
MAO-B inhibitors	2 (10)
Amantadine	4 (20)
Deep brain stimulation (bilateral subthalamic nucleus)	2 (10)
Levodopa-equivalent dose, mg[a]	
Median (range)	275 (47–391)
Mean (SD)	246.9 (112.5)
Number of capsules[b]	
Median (range)	3 (1–4)
Mean (SD)	3 (1)

[a]Supramaximal levodopa equivalent dose of the morning medication (for calculation, refer to the Methods).
[b]Number of levodopa/carbidopa 100/25 mg or placebo capsules administered in this study.
Abbreviations: PD, Parkinson's disease; SD, standard deviation; BMI, body mass index; MDS-UPDRS III, Movement Disorder Society–Unified Parkinson's Disease Rating Scale Part III; COMT, catechol-O-methyltransferase; MAO-B, monoamine oxidase B.

TABLE 2 *Per Endpoint, Least Square Means, Least Square Means Change from Baseline, P Values of the Treatment and Treatment × Time Effects, and the Estimated Difference for the Levodopa/Carbidopa–Placebo Contrast with Its 95% CI Are Shown*

Category	Parameter (Unit)[a]	Least Square Means		Treatment *P* Value	Treatment × Time *P* Value	Contrast Levodopa/Carbidopa vs. Placebo (95% CI)	Least Square Means Change from Baseline	
		Placebo	Levodopa/Carbidopa				Placebo	Levodopa/Carbidopa
MDS-UPDRS III total score								
Gold standard	MDS-UPDRS III	34.3	27.0	**0.0014**	**<.0001**	−7.3 (−11.6 to −3.0)	−0.7	−8.0
Alternate index and middle finger tapping[b]								
Speed	Total number of taps	81.3	87.5	0.2173	**0.0052**	6.3 (−3.9 to 16.4)	−8.9	−2.7
	Mean intertap interval, ms	389.450	317.338	**0.0198**	0.1106	−18.5% (−31.2% to −3.5%)	15.3%	−6.0%
Accuracy	Total taps inside target	75.0	86.6	**0.0308**	**0.0001**	11.6 (1.1–22.1)	−10.3	1.4
	Ratio good:total taps	0.586	0.724	**0.0006**	**<.0001**	0.138 (0.065–0.211)	−0.1	0.0
	Total spatial error, mm	470.380	428.462	0.2629	0.1974	−41.918 (−116.88 to 33.0479)	−6.2	−48.1
	Mean spatial error, mm	5.635	4.958	0.0950	0.3893	−12.0% (−24.4%–2.4%)	10.6%	−2.7%
Rhythm	Intertap interval SD, ms	219.731	162.780	**0.0304**	0.2219	−25.9% (−43.4% to −3.0%)	21.6%	−9.9%
	Spatial error SD, mm	2.179	1.998	0.4203	0.1024	−8.3% (−26.2% to 13.9%)	1.6%	−6.9%
	Number of halts	3.2	3.4	0.6975	0.2483	0.2 (−0.7 to 1.1)	−0.1	0.0
Alternate index finger tapping[c]								
Speed	Total number of taps	66.1	78.6	**0.0001**	**<.0001**	12.5 (6.7–18.2)	−2.4	10.0
Accuracy	Total taps inside target	55.5	63.2	**0.0260**	**<.0001**	7.7 (1.0–14.4)	−2.5	5.1
	Total spatial error, mm	718.994	959.262	**0.0002**	**<.0001**	240.269 (123.264–357.274)	−29.7	210.6
	Mean spatial error, mm	10.816	12.015	**0.0205**	0.6719	1.199 (0.195–2.203)	0.0	1.2
Rhythm	Intertap interval SD, ms	52.286	43.758	**0.0494**	**0.0307**	−16.3% (−29.9% to −0.0%)	8.9%	−8.8%
	Spatial error SD, mm	4.544	4.889	0.2830	0.1083	7.6% (−6.1% to 23.3%)	3.7%	11.6%
Thumb–index finger tapping[d]								
Speed	Total number of taps	46.1	52.6	0.0633	**<.0001**	6.5 (−0.4 to 13.4)	−1.5	5.0
	Mean opening velocity, degree/s	372.194	522.695	**0.0013**	**<.0001**	150.501 (64.236–236.766)	−62.9	87.6
	Mean closing velocity, degree/s	479.066	658.973	**0.0028**	**<.0001**	179.907 (67.004–292.809)	−90.4	89.5

(Continues)

TABLE 2 *Continued*

Category	Parameter (Unit)[a]	Least Square Means		Treatment *P* Value	Treatment × Time *P* Value	Contrast Levodopa/Carbidopa vs. Placebo (95% CI)	Least Square Means Change from Baseline	
		Placebo	Levodopa/Carbidopa				Placebo	Levodopa/Carbidopa
Amplitude	Mean tapping amplitude, degree	27.365	35.723	**0.0009**	**<.0001**	8.358 (3.725–12.990)	−4.9	3.4
	Peak frequency AUC, degree^2	107.403	187.776	**0.0089**	**0.0034**	80.373 (21.862–138.885)	−44.9	35.5
Rhythm	Intertap interval SD, ms	62.416	33.439	**0.0028**	**0.0004**	−46.4% (−63.7% to −20.9%)	24.8%	−33.1%
Fatigue	Tapping amplitude change, degree/s	−0.339	−0.499	0.1781	0.9049	−0.160 (−0.397–0.077)	0.0	−0.2

P values < 0.05 are shown in bold.
[a]For log-transformed parameters, geometric least square means are given, and estimates of the contrast with their 95% confidence intervals are back-transformed and therefore given in percentages.
[b]The analysis results of intertap interval change (ms/min) and spatial error change (mm/min) have not been reported because they violated the normality assumption.
[c]The analysis results of the ratio of good:total taps, intertap interval change (ms/min), mean intertap interval (ms), number of halts, and spatial error change (mm/min) have not been reported because they violated the normality assumption.
[d]The analysis results of angle frequency change (Hz/min), intertap interval change (ms/min), and mean intertap interval mean (ms) have not been reported because they violated the normality assumption.
Abbreviations: 95% CI, 95% confidence interval; MDS-UPDRS III, Movement Disorder Society–Unified Parkinson's Disease Rating Scale Part III; SD, standard deviation; AUC, area under the curve.

20, meaning that the MDS-UPDRS III and finger tapping measurements at 3.5 hours were performed in n = 14 levodopa/carbidopa-treated and n = 6 placebo-treated patients.

Table 2 shows treatment and treatment × time effects for the gold standard MDS-UPDRS III and the 3 tapping tasks. In Figure 2, the LSMs (geometric LSMs for back-transformed data) change from baseline data over time are depicted for MDS-UPDRS III and a subset of 3 endpoints of each tapping task that showed to be significant in Table 2. For graphs of the other finger tapping endpoints, refer to Figure S2.

The MDS-UPDRS III showed a significant treatment effect and treatment × time interaction effect (Table 2) and is also visualized in Figure 2A. For the alternate index and middle finger tapping task, it was shown that levodopa/carbidopa compared with placebo resulted in significantly faster (ie, lower mean intertap interval) and more accurate tapping (ie, more total taps inside target and higher ratio of good:total taps) (Table 2, Fig. 2B). No significant treatment effect but a significant treatment × time interaction effect was found for the total number of taps, indicating that at least at 1 time point there was a significant difference between placebo and levodopa/carbidopa. Although a significantly lower intertap interval SD, that is, improved rhythm, was found for levodopa/carbidopa compared with placebo, it did not show a clear time-related response (Fig. 2B). Spatial error and number of halts were not significantly different between active and placebo treatments.

Also in the alternate index finger tapping task, significantly faster tapping (increased total number of taps, and as a result, total taps inside the target) was observed after levodopa/carbidopa compared with placebo treatment (Table 2, Fig. 2C). In contrast, accuracy was significantly reduced as observed by a higher mean and total spatial error. Lastly, levodopa/carbidopa compared with placebo resulted in a better tapping rhythm as observed by a lower SD of the intertap intervals, which showed a clear time-related response.

In the thumb–index finger tapping task, levodopa/carbidopa not only resulted in significantly faster tapping (higher mean opening and closing velocities) but also resulted in an increased mean tapping amplitude (Table 2, Fig. 2D). Another measure of amplitude, peak frequency AUC, was also significantly higher after levodopa/carbidopa than placebo treatment. As in the alternate index and middle finger tapping task, the total number of taps did not show a significant overall treatment effect but did show a significant treatment × time interaction effect. SD of the intertap intervals was again lower in the levodopa/carbidopa than in the placebo group, indicating improved rhythm. No significant treatment effect on fatigue, that is, a decrease in tapping amplitude over time, was observed.

To enable the comparison of endpoints within and between tasks, standardized mean differences (Hedge's g) between levodopa/carbidopa and placebo treatment were calculated (Figure S3). This shows that alternate index finger tapping and thumb–index finger tapping had higher standardized effect sizes than alternate index and middle finger tapping. The endpoint in the alternate index and middle finger tapping task with the highest standardized effect size was the ratio of good:total taps.

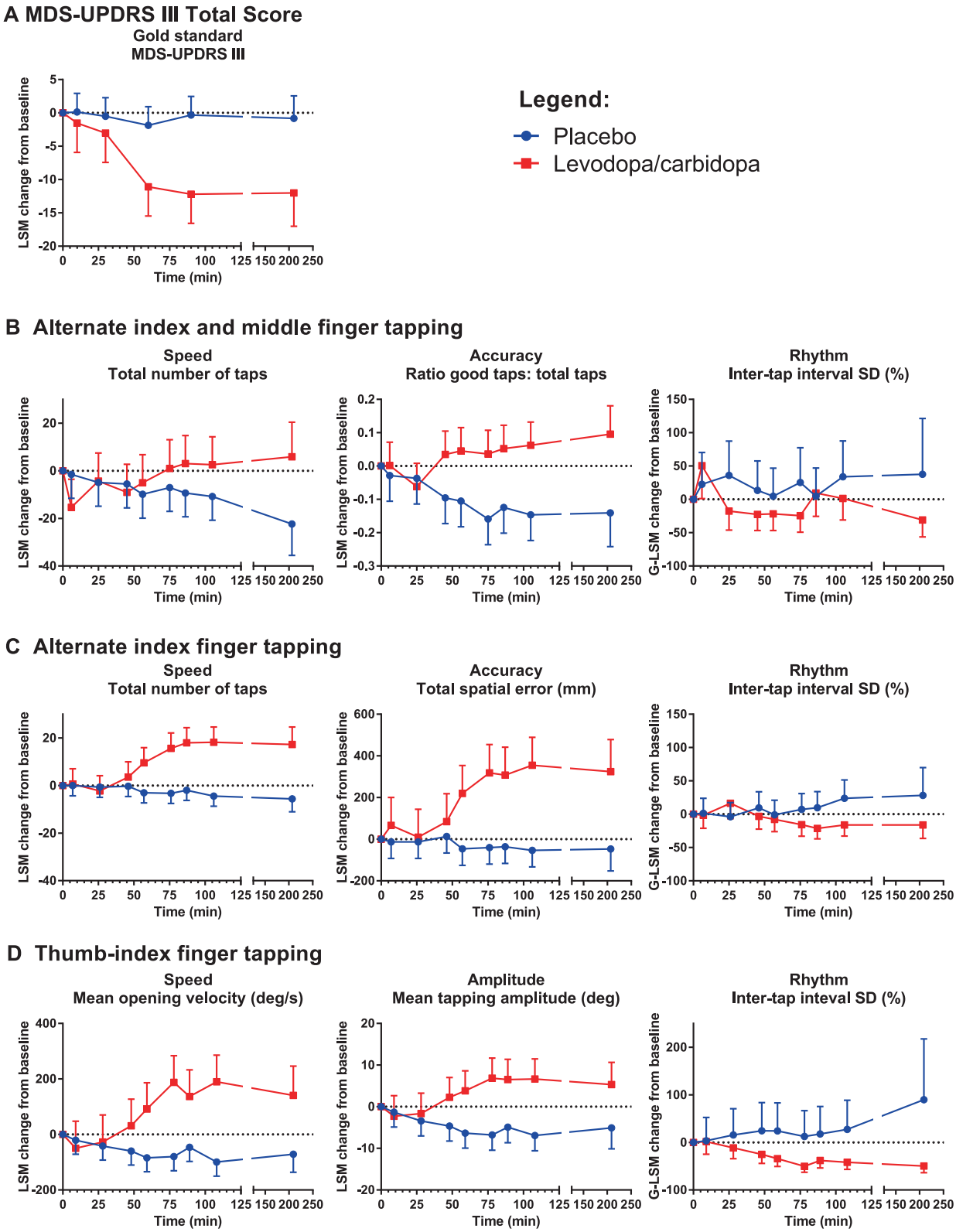

FIG. 2. (G-)LSM change from baseline with 95% confidence intervals plotted over time for MDS-UPDRS III (**A**) and for 3 endpoints of the alternate index and middle finger tapping (**B**), alternate index finger tapping (**C**), and thumb–index finger task (**D**). (G-)LSM, (geometric–) least square means; LSM, least square means; MDS-UPDRS III, Movement Disorder Society–Unified Parkinson's Disease Rating Scale Part III; SD, standard deviation.

TABLE 3 *Correlation Between Each Finger Tapping Endpoint and MDS-UPDRS III Total Score*

		Placebo		Levodopa/Carbidopa	
Category	**Parameter**	***r***	***P* value**	***r***	***P* value**
Alternate index and middle finger tapping					
Speed	Total number of taps	0.08	0.7381	0.31	0.1935
	Mean intertap interval	−0.11	0.6599	−0.41	0.1001
Accuracy	Total taps inside target	0.06	0.8165	0.28	0.2478
	Ratio good:total taps	−0.17	0.4899	−0.23	0.3379
	Total spatial error	0.30	0.2159	0.50	**0.0306**
	Mean spatial error	0.35	0.1389	0.32	0.1769
Rhythm	Intertap interval SD	−0.06	0.8101	−0.10	0.6889
	Spatial error SD	−0.10	0.6931	0.02	0.9401
	Number of halts	0.22	0.4029	0.22	0.3959
Fatigue	*Intertap interval change*	0.14	0.5928	0.23	0.3758
	Spatial error change	−0.04	0.8635	0.37	0.1189
Alternate index finger tapping					
Speed	Total number of taps	−0.45	**0.0454**	−0.45	**0.0457**
	Mean intertap interval	0.50	**0.0249**	0.21	0.3764
Accuracy	Total taps inside target	−0.39	0.0849	−0.55	**0.0120**
	Ratio good:total taps	−0.24	0.3140	−0.45	**0.0446**
	Total spatial error	−0.23	0.3365	−0.04	0.8528
	Mean spatial error	0.11	0.6482	0.29	0.2123
Rhythm	Intertap interval SD	0.25	0.2822	0.32	0.1733
	Spatial error SD	−0.06	0.7906	0.10	0.6784
	Number of halts	−0.16	0.5022	−0.10	0.6703
Fatigue	*Intertap interval change*	−0.05	0.8397	−0.26	0.2661
	Spatial error change	0.12	0.6143	0.16	0.4984
Thumb–index finger tapping					
Speed	Total number of taps	−0.65	**0.0024**	−0.21	0.4255
	Mean intertap interval	0.70	**0.0013**	0.17	0.5249
	Mean opening velocity	−0.66	**0.0027**	−0.24	0.3628
	Mean closing velocity	−0.65	**0.0025**	−0.50	**0.0426**
Amplitude	Mean tapping amplitude	−0.27	0.2748	−0.41	0.1021
	Peak frequency AUC	−0.28	0.2376	−0.29	0.2553
Rhythm	Intertap interval SD	0.45	0.0586	0.66	**0.0037**
Fatigue	*Intertap interval change*	−0.09	0.7160	−0.22	0.3886
	Tapping amplitude change	−0.11	0.6577	0.11	0.6732
	Angle frequency change	0.08	0.7418	0.26	0.3201

P values < 0.05 are shown in bold.
Correlation coefficient *r* and *P* value are given for both the placebo and the levodopa/carbidopa group. For parameters in italics, no model could be fitted.
Abbreviations: MDS-UPDRS III, Movement Disorder Society–Unified Parkinson's Disease Rating Scale Part III; SD, standard deviation; AUC, area under the curve.

For alternate index finger tapping, these were total number of taps and total spatial error. For thumb–index finger tapping, the opening and closing velocity had the highest standardized effect sizes, followed by the amplitude endpoints and intertap interval SD. Of these endpoints, 4 had a standardized effect size that was similar to that of the MDS-UPDRS III, namely, the total number of taps and the total spatial error in the alternate index finger tapping task and the opening and closing velocity in the thumb–index finger tapping task.

Correlation with MDS-UPDRS III

At 1.5 hours postdose, none of the alternate index and middle finger tapping endpoints correlated with MDS-UPDRS III total score except for total spatial error after levodopa/carbidopa treatment (Pearson's $r = 0.50$, $P = 0.0306$) (Table 3).

In the alternate index finger tapping task, the total number of taps showed a significant moderate correlation with MDS-UPDRS III in both the placebo (Pearson's $r = -0.45$, $P = 0.0454$) and levodopa/carbidopa (Pearson's $r = -0.45$, $P = 0.0457$) group. Similarly, the mean intertap interval was significantly correlated with MDS-UPDRS III, but only in the placebo group (Spearman's $r = 0.50$, $P = 0.0249$). The accuracy parameters total taps inside the target and ratio of good:total taps significantly correlated with MDS-UPDRS III in the levodopa/carbidopa group (Pearson's $r = -0.55$ [$P = 0.0120$] and Spearman's $r = -0.45$ [$P = 0.0446$], respectively). For the other accuracy and rhythm parameters, no correlation was found.

In the thumb–index finger tapping task, all speed parameters had a strong correlation with MDS-UPDRS III in the placebo group (r ranging between -0.65 and 0.70). Closing velocity also showed a moderate correlation with MDS-UPDRS III in the levodopa/carbidopa group (Pearson's $r = -0.50$, $P = 0.0426$). No other significant correlations were found except for a strong correlation of intertap interval SD with MDS-UPDRS III in the levodopa/carbidopa group (Spearman's $r = 0.66$, $P = 0.0037$).

Discussion

In this randomized, placebo-controlled trial, we assessed the ability of 3 different finger tapping tasks to detect and quantify acute pharmacodynamic effects of dopaminergic medication. Moreover, we investigated whether the finger tapping endpoints correlated with the MDS-UPDRS III score. The advantage of finger tapping over the MDS-UPDRS III is its short duration and rater independence. The short duration allows for frequent assessments and thus for a better detection of the onset of pharmacodynamic effects. Because no trained rater is required, it is logistically easier to perform the task during a clinical trial, but also allows for testing at home. To our knowledge, this is the first time these tapping tasks have been directly compared with the MDS-UPDRS III in a placebo-controlled study.

Both the alternate index finger tapping and thumb–index finger tapping tasks showed significant differences between levodopa/carbidopa and placebo treatment, with effect sizes comparable with the MDS-UPDRS III. Patients with PD were able to perform both tasks without difficulties. The goniometer used for the thumb–index finger tapping task was quite fragile and broke several times. In a clinical trial setting where backup devices are available this is not a major problem, but it does make the task unsuitable for at-home testing. In contrast, the alternate index finger tapping only requires a touchscreen tablet and therefore would also be suitable for the testing of medication effects or disease progression over time in an at-home setting.

For the alternate index finger tapping task, endpoints relating to speed (ie, total number of taps) and accuracy (ie, total spatial error) performed best. An increased speed was associated with reduced accuracy. Such a trade-off between speed and accuracy has previously been described in patients with PD,[6,15] although not consistently.[8] Different results between studies might have been obtained due to differences in the test set-up as well as in how accuracy was calculated (eg, on a continuous scale vs. inside/outside target). In the alternate index finger tapping task, rhythm was also significantly improved (ie, lower geometric mean of intertap interval SD) after levodopa/carbidopa compared with placebo, albeit with a lower effect size than the speed and accuracy endpoints. The total number of taps correlated moderately with the MDS-UPDRS III. In contrast, the total spatial error and the intertap interval SD, which showed significant treatment effects with a time-related response, did not correlate with MDS-UPDRS III. This might be because they quantify aspects of tapping performance that are not captured by (parts of) the MDS-UPDRS III. Therefore, despite the absence of a correlation, they can be valuable additional endpoints in drug efficacy trials. Particularly the total spatial error can be a valuable endpoint because it has an effect size comparable with that of the MDS-UPDRS III.

In the thumb–index finger tapping task, levodopa/carbidopa compared with placebo resulted in faster tapping with a bigger amplitude and improved rhythm. This is in line with previously reported results on thumb–index finger tapping when *on* and *off* states were compared.[5,9] When comparing all endpoints, mean opening and closing velocity had the largest effect sizes, which were comparable with that of the MDS-UPDRS III. In addition, both endpoints showed a moderate-to-strong correlation with the MDS-UPDRS III. The SD of the intertap intervals also showed a significant difference between levodopa/carbidopa and placebo, but with a smaller effect size than the opening and closing velocity. Moreover, the intertap interval SD showed a strong correlation with the MDS-UPDRS III in the levodopa/carbidopa group and a trend toward a moderate correlation in the placebo group. The mean tapping amplitude and peak frequency AUC, both measures of amplitude, showed a significant treatment effect with a similar effect size. Because they performed equally, but the peak frequency AUC requires a more difficult formula and therefore might be harder to interpret, the mean tapping amplitude is preferred for use in future studies. Mean tapping amplitude did not correlate with MDS-UPDRS III, which was in contrast to the strong correlation ($r = -0.79$) reported by Ling et al in patients with PD when *off*.[5] No medication effects on fatigue, that is, a change in tapping amplitude over time, were observed. This is in line with what is reported

for other thumb–index finger tapping tasks.[5,9] However, the lack of an effect might be related to the relatively short task duration of 15 seconds in all of these tasks. By increasing the task duration, one might enhance fatigue and thereby leave more room to show improvement by medication.

Of the 3 tapping tasks, the alternate index and middle finger tapping task performed the worst, that is, had the lowest effect sizes. Its effect sizes were also below that of the gold standard MDS-UPDRS III. Moreover, the task was sometimes difficult to perform for the patients with PD, resulting in a high percentage of same-sided double taps. This is likely the result of the patients not lifting their fingers from the touchscreen before tapping with the other finger, resulting in 2 fingers touching the screen simultaneously. With the used setup, this was recorded as a single tap. The number of tests with more than 70% of same-sided double taps (ie, a ratio of good:total taps <0.3) was approximately balanced over placebo and levodopa/carbidopa treatment. Nevertheless, the ratio of good:total taps on a continuous scale was significantly different between placebo and levodopa/carbidopa treatment and showed a time-related response. The same holds true for the total taps inside the target, albeit with a lower effect size. In contrast, the mean and SD of the intertap intervals showed a significant treatment effect, but no clear time-related response, making it possible that these were chance findings due to multiple testing. None of the alternate index and middle finger tapping endpoints with significant treatment or treatment × time interaction effects showed a correlation with the MDS-UPDRS III score. Overall, the problems with correctly performing/recording the alternate index and middle finger tapping task, combined with the relatively small effect sizes, make the task in its current configuration the least suitable for efficacy studies including patients with PD.

In conclusion, the alternate index finger tapping and thumb–index finger tapping tasks provide short, rater-independent measurements that are sensitive to dopaminergic medication effects and have a similar effect size as the MDS-UPDRS III. When including these tasks in future trials, at least the following endpoints should be included: total number of taps and total spatial error (for alternate index finger tapping), opening or closing velocity, mean tapping amplitude, and intertap interval SD (for thumb–index finger tapping). Although spatial error and amplitude did not correlate with MDS-UPDRS III, they should be included in future placebo-controlled efficacy trials because they show a clear difference between active and placebo treatment as well as a time-related response. Because these measurements only take 15 to 30 seconds, they can be performed repeatedly during clinical trials and are therefore expected to better detect the onset of effect and time to reach maximum effect than the MDS-UPDRS III. The alternate index finger tapping task may also be suitable for testing new drugs or monitoring disease progression in an at-home setting.

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

E.T.: 1A-C, 2A, 2C, 3A
S.M.-B.: 1A-C, 2A, 2C, 3B
R.-J.D.: 1A-C, 2A, 2C, 3B
E.B.: 1A-C, 2A, 3B
J.H.: 1A, 1C, 2A, 3B
Y.Y.: 1A, 2A-B, 3B
G.J.G.: 1A-C, 2A, 2C, 3B

Disclosures

Ethical Compliance Statement: The study was performed in compliance with Good Clinical Practice and approved by the Independent Ethics Committee of Foundation Beoordeling Ethiek Biomedisch Onderzoek (BEBO). Informed consent was obtained from all participants prior to study participation. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

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

Supplemental Figure S1. Consolidated Standards of Reporting Trials flow chart.

Supplemental Figure S2. (Geometric–) Least squares means ([G-]LSMs) change from baseline with 95% confidence intervals plotted over time for the endpoints of the alternate index and middle finger tapping, alternate index finger tapping, and thumb–index finger tapping that were not depicted in Figure 2.

Supplemental Figure S3. Standardized effect sizes (Hedge's g) with 95% confidence interval (CI) depicted for the endpoints of the alternate index and middle finger tapping, alternate index finger tapping, thumb–index finger tapping, and Movement Disorder Society–Unified Parkinson's Rating Scale Part III.

Supplemental Table S1. Description of finger tapping endpoints.