Journal of Neurology (2018) 265:1343–1352
https://doi.org/10.1007/s00415-018-8848-1

ORIGINAL COMMUNICATION

Supervised versus unsupervised technology-based levodopa monitoring in Parkinson's disease: an intrasubject comparison

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Received: 12 December 2017 / Revised: 3 March 2018 / Accepted: 22 March 2018 / Published online: 29 March 2018

Abstract

We aimed to assess the intrasubject reproducibility of a technology-based levodopa (LD) therapeutic monitoring protocol administered in supervised versus unsupervised conditions in patients with Parkinson's disease (PD). The study design was pilot, intrasubject, single center, open and prospective. Twenty patients were recruited. Patients performed a standardized monitoring protocol instrumented by an ad hoc embedded platform after their usual first morning LD dose in two different randomized ambulatory sessions: one under a physician's supervision, the other self-administered. The protocol is made up of serial motor and non-motor tests, including alternate finger tapping, Timed Up and Go test, and measurement of blood pressure. Primary motor outcomes included comparisons of intrasubject LD subacute motor response patterns over the 3-h test in the two experimental conditions. Secondary outcomes were the number of intrasession serial test repetitions due to technical or handling errors and patients' satisfaction with the unsupervised LD monitoring protocol. Intrasubject LD motor response patterns were concordant between the two study sessions in all patients but one. Platform handling problems averaged 4% of total planned serial tests for both sessions. Ninety-five percent of patients were satisfied with the self-administered LD monitoring protocol. To our knowledge, this study is the first to explore the potential of unsupervised technology-based objective motor and non-motor tasks to monitor subacute LD dosing effects in PD patients. The results are promising for future telemedicine applications.

Keywords Parkinson's disease · Levodopa · Alternate finger tapping test · Timed Up and Go test · Information and communication technology · Therapeutic drug monitoring

Introduction

Recent years have seen a growing interest in quantitative, user-friendly, technology-based tools to assess the clinical status and therapeutic response of people with Parkinson's disease (PD), possibly even in a home setting [1–3].

Simple rapid motor performance tests, such as alternate finger tapping [4–6] and the Timed Up and Go (TUG) test [7], have proved reliable tools for objective monitoring of an individual's motor skills along PD progression. The alternate finger tapping test has been used in our laboratory for years in therapeutic drug monitoring (TDM) to quantify the relationship between levodopa (LD) dose and its motor effect (time to onset, duration and magnitude) [8–10]. These objective variables are useful to tailor drug treatment from the early disease stages in PD patients and modify LD therapy according to disease progression to establish the minimum dose required over time [11]. Gradual drug dosing changes

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00415-018-8848-1) contains supplementary material, which is available to authorized users.

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paralleling patients' objectively assessed clinical needs can help to simplify pharmacologic treatment. This will result in facilitating therapy adherence and reducing the risks of both acute and chronic adverse effects [12].

Moreover, advances in wearable technology, including smartphones and smartwatches, have fostered the development of monitoring systems able to evaluate movement patterns objectively, even remotely [1]. We recently explored the use of a single wearable sensor for the objective monitoring of anti-PD therapies. The sensitivity and specificity of the device proved promising in identifying and quantifying LD-induced dyskinesias (LIDs), one of the most disabling adverse effects of chronic LD treatment [13].

One of the current limitations of wearable devices lies in their real-life application for continuous uncontrolled monitoring over 24 h or more [2]. This approach cannot take into account several confounding variables that may occur, with the risk of collecting a huge amount of instrumental data difficult to understand and use in clinical practice.

Our experimental approach in the context of LD therapeutic monitoring in PD is to discipline the collection of objective measurements of motor and non-motor performances within standardized protocols applicable in an ambulatory setting and possibly transferable to the patient's home.

Our project aimed to assess intrasubject reproducibility of a standardized ambulatory LD monitoring protocol administered in supervised versus unsupervised conditions. The protocol was designed as a potentially home-based service instrumented by an ad hoc integrated information and communication technology (ICT) platform for patients to self-administer motor and non-motor tests.

Methods

The study design was pilot, intrasubject, randomized, single center, open and prospective (protocol number 15111, Ethics Committee of the Bologna-Imola Local Health Trust). The protocol was proposed to 20 PD patients referred to the Institute of Neurological Sciences of Bologna. Written informed consent was obtained from each subject. Inclusion criteria were age ≤ 80 years; diagnosis of possible or probable PD according to the criteria of Gelb [14]; Hoehn and Yahr stage $\leq$ III; chronic stable therapy with LD + benserazide (BZ) or carbidopa (CD) > 3 months; overall positive response to LD therapy, defined as an improvement of at least 20% in Unified Parkinson's Disease Rating Scale (UPDRS)-motor section III compared to LD-naive condition, at a pre-LD UPDRS < 20, or an improvement of $\geq 30\%$ at a pre-LD UPDRS ≥ 20 [15]; absence of physical handicaps hampering the execution of the tests; written informed consent, including video recording. Exclusion criteria were psychiatric and/or cognitive disorders (mini mental test score < 24) [16].

Interventions and comparisons

Patients were trained to use the ICT platform in parallel with recruitment by the physician in charge of clinical study management (GL), on a different day from the two intrasubject study sessions.

The ICT platform is based on tablet PC, a smartphone and a Bluetooth sphygmomanometer. The smartphone acts as a wearable inertial sensor. The system automatically starts and manages the assessment procedure by means of textual, vocal and video instructions. The smartphone and the sphygmomanometer automatically connect to the tablet when the assessment protocol starts. Vocal and video guidance is provided to the patient on how to wear the smartphone by means of the Neoprene waist belt round the lower back (L5) and on how to perform motor and non-motor tests. The user also receives a confirmatory pop-up for notifying the actual intake of the LD test dose; the system waits for the user to confirm the intake before continuing with the assessment procedure (Online Resource, Technical description of the ICT platform, Figs. 1–10S).

Patients underwent TDM of their first morning fasting dose of LD + BZ or CD, taken 12 h apart from the last LD dose and possible concomitant anti-PD co-therapy [9].

Motor and non-motor effects elicited by the same LD dose were measured in two different randomized sessions, at most 2 weeks apart: (a) under the supervision of a physician (session A); (b) self-administered (session B). Randomization was handled by a laboratory operator not involved in patients' assessment by sequentially drawing from a box of sealed envelopes containing the order session: A/B (session A first); B/A (session B first).

In the supervised condition, the physician provided the patient with all the instructions and assistance to correctly use the ICT platform. In the unsupervised condition, the patient followed him-/herself video and audio instructions supplied by the platform.

During the entire evaluation protocol for both study sessions patients' movements were monitored and collected by the smartphone worn on the lower back.

The LD monitoring protocol is based on a battery of objective serial tests and measurements, including (Table 1):

1. Finger tapping test (total number of times in 1 min that the index finger of the subject's most affected hand can alternately touch two buttons spaced 20 cm apart).
2. TUG test, the time taken to rise from an armless chair, walk 3 m, return to the chair and finally sit.
3. Dyskinesia monitoring, 30-s sensor assessment post-tapping test and sitting position.
4. Reaction time tests, measure of both recognition time, i.e., the latency between the light turned on and the start

Table 1 Protocol of levodopa therapeutic monitoring in patients with Parkinson's disease

Time	Alternate finger tapping test	Timed Up and Go test	Dyskinesia monitoring	Reaction time tests	Blood pressure and heart rate measurement	Drug dose intake	Breakfast
$T-10$	x[a]	x[a]	x		x		
$T-5$	x[a]	x[a]	x	x			
$T0$						x	
$T+15$	x	x	x				
$T+30$	x	x	x				x (30–45 min post-dosing)
$T+45$	x	x	x				
$T+60$	x	x	x	x	x		
$T+75$	x	x	x				
$T+90$	x	x	x				
$T+120$	x	x	x	x			
$T+150$	x	x	x				
$T+180$	x	x	x	x			

$T-10$, $T-5$, baseline pre-levodopa dose measurements

[a]Average values

of the movement (release of the central start button by the index finger) and movement time, i.e., the time from initiation to completion of the movement (switching the lighted button off).

5. Measurement of blood pressure and heart rate (sitting position) before LD dose intake and 1 h post-dosing.

Tapping and reaction time tests are measured and collected by the tablet PC. TUG test performances are monitored and recorded by the smartphone. Trunk acceleration and angular velocity are also recorded by the smartphone for 30 s immediately after completion of the serial tapping test when the patient is waiting seated in front of the tablet. Signals are then processed to identify possible LIDs [13] (Online Resource, Technical description of the ICT platform: Measurement of trunk kinematics).

Tapping and TUG tests are performed at 15-min intervals for the first hour, then half-hourly. The aim is to obtain the most accurate picture of the LD dose motor response pattern reflecting the rapid rise and fall of plasma LD concentrations, especially at the more advanced stages of the disease [8, 9]. Based on our previous experience [8], reaction time tests are recorded hourly as ancillary measurements; in particular, poor reaction times may predict or assess patients' cognitive impairment [17].

Blood pressure and heart rate are measured in seated condition by a digital blood pressure monitor with a Bluetooth connection before LD dosing and after 1 h to check for potential drug hypotensive effects [18].

Study sessions of patients presenting LIDs from ambulatory screening were videotaped for subsequent offline evaluation according to the Clinical Dyskinesia Rating Scale (CDRS) [19], a 0–4-point rating scale for upper and lower extremities, trunk, head, neck and orofacial region, with a maximum score of 28.

UPDRS-III was administered to each patient before LD dosing in both sessions, and 1 h after drug dose during the supervised session.

Patient satisfaction was measured by administration of an ad hoc questionnaire (0–4-level scale) on the feasibility of an unsupervised ICT platform and its potential use at home.

Data analysis

Two different objective motor profiles were identified after LD dose intake in PD patients:

1. A clinically significant subacute response (R1 pattern) [9] characterized by a sustained ($\geq$ 30 min) increase in tapping frequency and/or decrease in TUG total duration $\geq$ 15% over baseline values.
2. A clinically non-significant subacute response (R2 pattern) characterized by a variation in tapping frequency and/or TUG total duration < 15% of baseline values.

Study of primary motor response outcome was the comparison of intrasubject clinically subacute motor response patterns in supervised vs unsupervised conditions elicited by the LD dose.

Variables considered for R1 patterns: (a) latency to onset of subacute motor response, i.e., the time taken for tapping frequency to increase and or TUG total time to decrease $\geq$ 15% of baseline values; (b) duration of motor response, calculated as the time from onset of response to the return within 15% of baseline values. When no return to baseline was observed, response duration was approximated to

180 min, i.e., the maximum length of the TDM protocol, for subsequent statistical comparisons [9]; (c) the overall extent of motor response, estimated by the area under the 3-h tapping and/or TUG effect–time curve (AUC_E), according to the linear trapezoidal rule, corrected for baseline measures.

Variable considered for R2 patterns: mean frequency of serial tapping tests and mean total time of serial TUG tasks over the 3-h monitoring period.

Secondary outcomes included: percentage of intrasession serial motor and non-motor test errors/repetitions due to technical or handling problems out of the total number of tests performed for each session; percentage of patients expressing an overall satisfaction score of "3" (satisfied, 0–4 level scale) in the ad hoc questionnaire on the feasibility of an unsupervised ICT platform and its potential use at home.

Statistical analysis

When data were consistent with a normal distribution and equal variances, means and standard deviations (SD) were calculated and the significance of differences was assessed by Student's paired *t* test. When deviation from a normal distribution was found, medians and 25th–75th percentiles were calculated and statistical comparisons were performed by Wilcoxon signed ranked test. Significance was set at $p < 0.05$.

Results

Table 2 summarizes the demographic and clinical characteristics of enrolled patients (11 women, 9 men, age 47–76 years, PD symptoms duration 0.5–15 years, LD therapy duration 0.5–14 years, Hoehn and Yahr stage I–III). Conversion of all concomitant antiparkinsonian drugs into LD equivalent daily dose was done according to Tomlinson et al. [20].

The two sessions were regularly carried out and completed by all patients. According to UPDRS-III assessment before LD dose intake, no significant differences in performances were found between the 2 study days, spaced out from a minimum of five up to a maximum of 14 days, with median scores (25th–75th percentiles) of 22 (13–28) for both sessions. With the only exception described below, no concurrent clinical upsets or possibly LD-related side effects were observed in any patient at either session.

A clinically significant subacute LD response to tapping test was noted in 12 patients in both study sessions, whereas TUG test was consistently affected by LD dose only in two patients (nos. 5 and 14). A clinically significant tapping motor response was observed in patient no. 12 in the supervised condition, whereas no significant response was noted in the unsupervised session. This patient had felt a gastric upset after LD dose intake during the unsupervised session, which might reflect an irregular drug dose bioavailability and matched motor response. Table 3 reports the intrasubject comparisons of latency to onset, duration and AUC of tapping effect in this subset of patients. Latency to onset of tapping effect ranged from 30 to 90 min in both sessions, while intrasubject maximum difference in tapping effect onset was 15 min in all patients. Tapping motor response did not return to baseline values within the examination period in eight patients at either session. Duration of tapping effect ranged from 60 to 75 min (session A and B, respectively) to approximately 180 min. Intrasubject differences in tapping effect duration ranged from 15 to 45 min in the remaining patients. Median values of both latency and duration of tapping response were similar in the two sessions. Similarly, intrasubject AUCs of tapping effect were comparable, with the exception of patient no. 12. Mean values of tapping AUCs did not differ significantly in the two experimental conditions. Overall, the objective motor picture of subacute LD dosing obtained was in agreement with the subjective perception expressed by patients on chronic treatment (Table 2). Figure 1a depicts a typical LD subacute tapping response profile in one representative patient of this subgroup.

A clinically non-significant subacute response to both tapping and TUG tests was noted in seven patients in the two sessions. Intrasubject comparisons of mean frequency of serial tapping tests and mean TUG total time over the 3-h monitoring period did not reveal significant differences (Table 4). The results of LD objective monitoring in this subgroup were in line with patients' routine LD dosing effect perception in four cases (nos. 6, 7, 8 and 11), whereas subjective perception in the remaining three patients was mainly based on alleviation of tremor (nos. 2, 13 and 16) and LIDs (no. 16). Figure 1b depicts the LD subacute tapping response profile in one representative patient of this subgroup.

Motor response was complicated by LIDs in four patients (nos. 4, 8, 16 and 18). Intermittent, low-severity LIDs (maximum 0.5–1 score of CDRS scale) were restricted to the lower extremities (nos. 4 and 8) or head and neck (no. 16) and could not be detected by the single sensor in three patients [13]. Patient no. 18 showed more severe LIDs in lower and upper extremities and trunk detected by the sensor and whose temporal profile overlapped with CDRS assessment from videotapes in both sessions (Fig. 11S, Online Resource).

Measurements of blood pressure (systolic, diastolic) and heart rate (beats per minute) parameters were consistent in the two study sessions and did not reveal any clinically significant difference either before or 1 h after LD dosing (Table 1S, Online Resource).

Very low percentages of technical problems and execution errors were detected in the use of the ICT platform

Table 2 Demographic and clinical characteristics of patients

Pt. no.	Sex	Age (years)	PD duration (years)	PD motor subtypes	H&Y stage	LD therapy duration (years)	LD dose (mg/day)	Anti-PD co-therapies	LD equivalent dose (mg/day)	UPDRS pre-/post-LD dose		Subjective response to LD dosing	Education	Profession	Familiarity with electronic devices
1	F	61	1	B/R	I	1	200	–	200	5	4	Yes[a]	H-s diploma	Retired (former office worker)	Moderate
2	M	51	4	T	II	3	200	Pramipexole ER	357	18	13	Yes[b] (T)	H-s diploma	Office worker	Good
3	F	47	0.5	B/R	I	0.5	200	–	200	6	4	Yes[a]	Degree	Accountant	Good
4	F	69	4	B/R	II	3	300	Pramipexole	345	15	10	Yes[a]	Primary school certificate	Retired (former dress maker)	None
5	M	63	4	B/R	II	4	200	Pramipexole ER	305	24	16	Yes[a]	H-s diploma	Retired (former bank clerk)	Moderate
6	M	73	4	B/R	II	3	250	Pramipexole ER	355	22	17	No	H-s diploma	Retired (former company manager)	Moderate
7	F	65	2	B/R	II	1	300	–	300	10	8	No	H-s diploma	Retired (former nurse)	Moderate
8	M	75	6	B/R	II	5	400	Rotigotine	640	29	26	No	Degree	Retired (former dentist)	Moderate
9	M	58	3	B/R	II	1	200	–	200	25	18	Yes[a]	H-s diploma	Public administration manager	Moderate
10	F	62	4	B/R	II	4	200	–	200	17	8	Yes[a]	H-s diploma	Retired (former teacher)	Moderate
11	F	76	7	B/R/T	II	6	300	Ropinirole, pramipexole ER	362	29	22	No	Degree	Retired (former teacher)	Good
12	F	65	2	B/R (axial)	II	2	450	Pramipexole	505	36	33	No	H-s diploma	Retired (former office worker)	None
13	M	67	5	T	I	5	200	Pramipexole ER	410	12	10	Yes[a] (T)	H-s diploma	Retired (former bank clerk)	Moderate

Table 2 (continued)

Pt. no.	Sex	Age (years)	PD duration (years)	PD motor subtypes	H&Y stage	LD therapy duration (years)	LD dose (mg/day)	Anti-PD co-therapies	LD equivalent dose (mg/day)	UPDRS pre-/post-LD dose	Subjective response to LD dosing	Education	Profession	Familiarity with electronic devices
14	M	52	6	B/R	III	3	500	Rotigotine	740	39 24	Yes[b]	H-s diploma	Warehouse worker	Good
15	F	67	1	B/R	II	1	200	Pramipexole ER	305	19 15	No	H-s diploma	Retired (former office worker)	Moderate
16	M	62	7	B/R/T (axial)	II	6	300	Trihexyphenidyl	300	21 12	Yes[b] (T, D)	Secondary school certificate	Sales agent	Moderate
17	F	47	5	B/R/T	I	4	200	Pramipexole ER	410	10 4	Yes[a]	H-s diploma	Office worker	Good
18	M	65	15	B/R	III	14	450	Pramipexole ER	660	42 24	Yes[b]	Secondary school certificate	Retired (former workman)	None
19	F	65	8	B/R	II	7	300	Amantadine, rotigotine, rasagiline	720	26 16	Yes[b]	Degree	Retired (former physician)	Good
20	F	57	7	B/R	II	4	200	–	200	16 11	Yes[a]	H-s diploma	Office worker	Moderate

PD Parkinson's disease, *H&Y* Hohen and Yahr clinical stage, *LD* levodopa, *ER* extended release, *UPDRS* Unified Parkinson's Disease Rating Scale, motor section III, administered before and 1 h after LD dosing, *H-s* high school, *(T)* subjective response based on tremor symptom, *(D)* subjective response based on levodopa-induced dyskinesias

[a]Perception of time to onset of first morning dose effect, no wearing-off

[b]Perception of time to onset and offset of LD dose effect

Table 3 Intrasubject finger tapping outcomes in patients with a clinically significant levodopa subacute response

Pt. no.	LD test dose (mg)	Latency to onset of effect (min)		Effect duration (min)		AUC_E [(tap/min) x min]		UPDRS		Randomization sequence
		A	B	A	B	A	B	A	B	
1	100	30	30	180	180	4785	3202	5	5	A/B
3	100	60	45	180	180	4155	3915	6	6	B/A
4	100	45	45	180	180	3495	3607	15	15	A/B
5	100	45	45	135	180	2377	3525	24	22	A/B
9	100	90	90	180	180	1967	2167	25	25	B/A
10	100	30	45	150	180	2910	2715	17	17	A/B
12	200	45	–	180	–	4605	1528	36	36	A/B
14	100	30	45	60	75	2355	3157	39	35	A/B
15	100	75	60	180	180	2212	3315	19	19	A/B
17	100	60	75	180	180	3622	3337	10	8	B/A
18	125	45	30	105	120	2925	2527	42	40	A/B
19	100	45	60	180	180	4065	3518	26	26	B/A
20	100	30	30	180	180	6652	7612	16	16	B/A
		45[a] (30–60)	45[a] (34–60)	180[a] (138–180)	180[a] (180–180)	3548 ± 1316[b]	3394 ± 1427[b]			
p		N.S.		N.S.		N.S.				

Pt patient, *LD* levodopa, *A* supervised session, *B* unsupervised session, AUC_E area under the tapping effect–time curve (3 h), corrected for baseline values, *UPDRS* Unified Parkinson's Disease Rating Scale, motor section III, administered before LD dose intake, *N.S.* not significant ($p \geq 0.05$)

[a]Median (25–75th percentiles)

[b]Mean ± standard deviation

(Table 2S, Online Resource). A potential interference of LIDs on blood pressure measurements was observed in patient no. 18. These problems averaged 4% of the total number of planned serial measurements for both study sessions.

Patient satisfaction with the instrumented TDM protocol feasibility was high: 19 patients (95%) expressed an overall satisfaction ranging from 3 to 4 (satisfied to very satisfied).

Discussion

The overall results of our pilot clinical study are encouraging in terms of intrasubject reproducibility, feasibility and patients' satisfaction with self-administered instrumented LD monitoring protocol.

Intrasubject ICT-based LD motor response patterns were concordant between the two study sessions in all patients but one. A clinically significant subacute LD motor response was consistently detectable in 12 patients on the basis of alternate finger tapping test. In line with our experience of objective LD monitoring [8–10], this test proved to be more sensitive than TUG in detecting subtle subacute motor effects elicited by LD dosing at the mild to moderate disease stages of PD.

No clinically significant first morning LD subacute motor response was noted in seven patients at either session. The mild and short duration of PD symptoms may account for the lack of a subacute LD tapping effect in at least three of these patients, in line with subjective motor perception. An LD-compensated stable clinical situation during the day is common at the early "LD honeymoon" PD stages [21]. We are aware that the tapping test can be not adequate to monitor LD effects on tremor, the main clinical symptom affecting the remaining patients of this subgroup. To this end, further analyses are needed to assess the reliability of sensor measurements in subacute LD tremor effect monitoring, which were beyond the aim of this pilot study. At present, UPDRS is still the common reference scale in clinical trials of therapeutic interventions in PD and development of both quantitative and semiquantitative tools for assessing PD features. It has been observed that the scale is adequate to assess moderate and severe impairments, while its utility may be limited at the early PD stages, where deficits are subtle. To date, the minimal clinically relevant difference between two assessments that has an impact on PD disability has not been fully established for the UPDRS across the different stages of the disease [15, 22]. As previously pinpointed, the 20–30% UPDRS change from baseline used in some clinical trials to define "LD responders" has been arbitrarily defined and

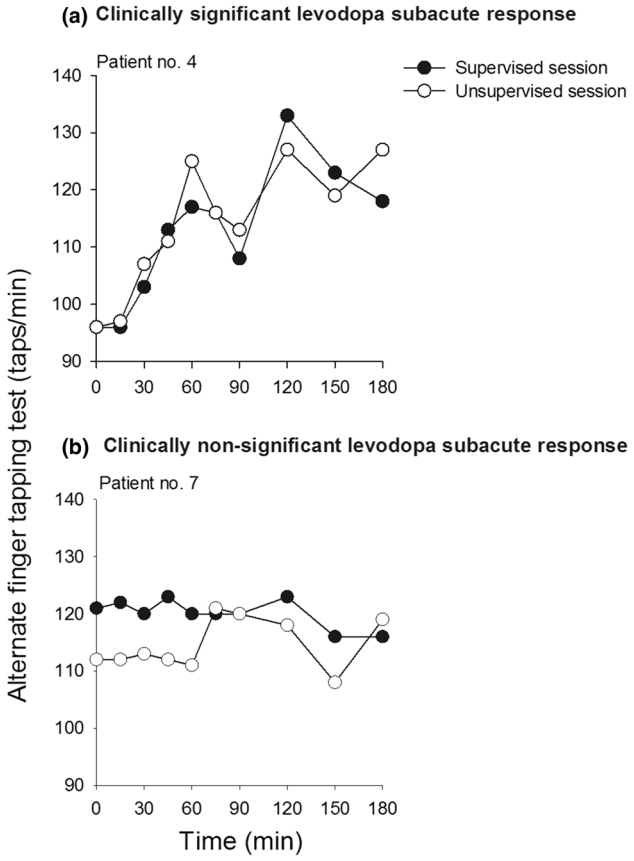

Fig. 1 Levodopa tapping response pattern in two representative patients: **a** clinically significant levodopa subacute response; **b** clinically non-significant levodopa subacute response

may not represent a minimal change of clinical significance on an individual basis [15, 22].

Alternate finger tapping measurements [23, 24] and gait performance [23] monitored by smartphones [23] or tablet PC [24] have been proposed as feasible self-administered tools to monitor PD symptoms severity. To our knowledge, this study is the first to explore the potential of unsupervised technology-based tapping and TUG tasks to monitor subacute LD dosing motor effects in PD patients.

Evidence gained on the feasibility of ICT-LD monitoring was also positive, as suggested by both the very low percentage of technical problems and execution errors and the high level of patient satisfaction with the self-administered protocol.

The main strengths of our study are the synergy between technological development and clinical application, reinforced by patients' participation and involvement. The patient sample was balanced in terms of both education level and familiarity with electronic devices. In addition, intrasubject motor and non-motor effects were measured and compared by a standardized protocol [2, 25] taking into account the time of LD dose intake and the time lapse between dose intake and meal ingestion. These variables are crucial for the purpose of understanding the drug motor and non-motor response profile over the day.

One limitation of our study is the patient sample that is mainly representative of the mild and moderate stages of PD, while more advanced patients are less represented. We recognized this potential limit during clinical protocol design, considering the exploratory characteristics of the pilot clinical study, and the unknowns deriving from self-administered instrumented LD monitoring.

Table 4 Intrasubject motor outcomes in patients with a clinically non-significant levodopa subacute response

Pt. no.	LD test dose (mg)	Mean frequency of serial tapping tests (taps/min)		Mean total time of serial TUG tests (s)		UPDRS		Randomization sequence
		A	B	A	B	A	B	
2	100	155	145	9.58	9.28	18	18	B/A
6	100	108	138	11.7	11.7	22	22	B/A
7	100	120	115	10.4	10.9	10	10	B/A
8	100	113	137	13.3	11.5	29	28	A/B
11	100	112	112	13.2	13.5	29	28	A/B
13	100	95	94	10.6	10.1	12	12	B/A
16	150	238	240	12.2	12.2	22	22	B/A
	[a]	134 ± 49	140 ± 47	11.5 ± 1.4	11.3 ± 1.4			
p		N.S.		N.S.				

Pt patient, *LD* levodopa, *A* supervised session, *B* unsupervised session, *TUG* Timed Up and Go test, *UPDRS* Unified Parkinson's Disease Rating Scale, motor section III, administered before LD dose intake, *N.S.* not significant ($p \geq 0.05$)

[a]Mean values ± standard deviation

Lastly, the effect of the environment on TDM performance cannot be ruled out. Motor, non-motor outcomes and handling of ICT-LD monitoring were comparable in an ambulatory supervised versus unsupervised setting. However, the unsupervised condition may not be entirely representative of the at-home application [2, 26], which will be specifically explored in future studies. The ultimate goal of our research is the implementation of our ICT-LD therapeutic monitoring protocol directly in the patient's home during longitudinal follow-up. In addition, we plan to transfer the ICT platform to other clinical centers specialized in movement disorders, to standardize protocols for the objective measurement of anti-PD therapeutic interventions [27].

Acknowledgements Grant no. 451bis/2015 from "Fondazione del Monte di Bologna e Ravenna" is gratefully acknowledged. We thank the patients who participated in the study for their active cooperation. This study was presented at the 18th Annual Congress of the Italian Society of Clinical Movement Analysis (SIAMOC), Politecnico di Torino, Turin, Italy, 4th–7th October 2017. Anne Collins edited the English text.

Compliance with ethical standards

Conflicts of interest G. Lopane and M. Corzani received a Grant from "Fondazione del Monte di Bologna e Ravenna" (Grant no. 451bis/2015). The other authors declare that they have no conflict of interest.

Ethical standards The study was approved by the Ethics Committee of the Bologna-Imola Local Health Trust (Protocol number 15111) and was performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments. Patients gave their written informed consent to study participation.

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