The role of Personal KinetiGraph™ fluctuator score in quantifying the progression of motor fluctuations in Parkinson's disease

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Summary

Motor fluctuations (MF) are important determinants of quality of life in Parkinson's disease (PD). To determine whether the Personal Kineti Graph (PKG), a wearable motion tracking device, can define MF progression, we correlated PKG fluctuator scores (FS) with clinical motor fluctuator profiles in a case-control cohort study. 54 subjects completed a 6-day PKG trial and completed a standardized motor diary. We distinguished non-fluctuators (NF), early (EF), moderate (MF) and troublesome fluctuators (TF), based on Wearing Off Questionnaire and Movement Disorders Society-Unified Parkinson's Disease Rating Scale scores. PKG FS significantly differentiated EF and TF, as well as dyskinetic and non-dyskinetic subjects. Motor diaries could not distinguish the four study groups on the basis of average OFF time, while average time with dyskinesia distinguished NF and MF. In conclusion, PKG FS can distinguish EF from TF, as well as dyskinetic from non-dyskinetic patients, but cannot discriminate subtler MF. PKG may provide objective MF measures for routine PD management and clinical trials.

KEY WORDS: dyskinesias, motor fluctuations, Parkinson's disease, wearable device, wearing-off.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder, typically characterized by motor deficits including bradykinesia, rigidity and resting tremor. These motor symptoms are easily treated in the early stages of the disease using dopaminergic medications, including levodopa. However, approximately 40% of PD patients develop fluctuations of response to levodopa and dyskinesia after 4-6 years of treatment, and 70% after long-term treatment of 9 years or longer (Schrag and Quinn, 2000; Ahlskog and Muenter, 2001; Pahwa and Lyons, 2009). Motor fluctuations, including "wearing-off" (WO) and dyskinesia, coincide with greater disease severity and disability, while poorer quality of life results from the inability to rely on predictable medication effects (Hechtner et al., 2014; Stocchi et al., 2014). Signs and symptoms of fluctuations vary and it is thought that WO may be under-recognized (Stocchi et al., 2014), as direct observation in the outpatient clinic may be unrevealing and patient recall incomplete and unreliable (Stacy et al., 2005; Matthews et al., 2015).

In this context, the use of a wearable device might provide desirable information on the occurrence of daily motor fluctuations, without the need to depend on patient or caregiver memory or understanding of pathological events (i.e. tremor *vs* dyskinesia). Among other wearable devices, the Personal KinetiGraph™ (PKG™) system (Global Kinetics Corporation, Melbourne, Australia) was developed in response to the lack of objective measurement tools for movement disorder symptoms beyond direct clinical observation. Worn continuously like a wristwatch, it quantifies the kinematics of PD symptoms, including tremor, bradykinesia and dyskinesia. The raw data collected by the device logger (the "watch") is translated by a proprietary algorithm (Griffiths et al., 2012) into a multi-page printable graph with fluctuation scores (FS), which can distinguish between PD patients with motor fluctuations and those without (Horne et al., 2015). The device includes a medication reminder, an event marker and can also monitor activity associated with movement during sleep (Kotschet et al., 2014).

In prior studies, FS proved able to distinguish between fluctuating and non-fluctuating patients with high sensitivity and selectivity, showing improvements associated with activation of deep brain stimulators (Griffiths et al., 2012; Horne et al., 2015). The present study aimed to correlate PKG scores with more detailed fluctuator profiles, in order to determine whether PKG FS cut-offs can define the progression of PD fluctuation stages.

Materials and methods

Subjects

We conducted a case-control cohort study of 60 PD patients attending the Movement Disorders Clinic at Cedars-Sinai Medical Center. The Cedars-Sinai Institutional Review Board approved the project prior to initiation. Informed consent was obtained prior to enrolling each patient in the study. All subjects met the UK Brain Bank diagnostic criteria for PD (Hughes et al., 1992, 2001) and were actively treated with dopaminergic medications. Subjects were excluded if they had levodopa non-responsive tremor-predominant PD, used a walking aid with the most bradykinetic upper extremity, or presented painful limitation with that limb, since any restricted movement of that upper limb would affect PKG scores. Subjects were also excluded if they were using advanced therapies (such as deep brain stimulation, or an apomorphine or levodopa pump).

Using the Wearing Off Questionnaire (WOQ9) (Stacy et al., 2008; Antonini et al., 2011), and the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part IV - Complications of Therapy (Goetz et al., 2008), subjects were categorized into four groups characterized by progressive motor fluctuation severity. We distinguished non-fluctuators (NF, WOQ9 < 2 and MDS-UPDRS IV = 0), early fluctuators (EF, WOQ9 ≥ 2 and MDS-UPDRS IV = 0), moderate fluctuators (MF, WOQ9 ≥ 2 and MDS-UPDRS IV.1 + IV.2 ≤ 2), and troublesome fluctuators (TF, WOQ9 ≥ 2 and MDS-UPDRS IV.1 + IV.2 ≥ 3). Each subject was trained in the completion of a 48-hour patient's PD symptom diary, in which they could enter the following: asleep, OFF, ON, or ON with dyskinesia. In addition, we performed a K-mean cluster analysis (Everitt et al., 2001) including as variables the combined WOQ9 plus MDS-UPDRS IV scores and FS.

PKG system

The PKG watch is a medical device that looks like a wristwatch. Its features and algorithm have previously been described (Griffiths et al., 2012). The PKG watch was programmed for each subject and dispensed by clinic staff. Each subject received one and was trained in its use. They were then required to wear the device for six days before mailing it with the completed motor diary back to the clinic. The watch was worn on the most affected upper limb, or the dominant upper limb if symptoms were symmetrical. Subjects were asked to wear the PKG watch at all times, including during sleep, but not when bathing. Subjects were asked to get out of bed each morning prior to taking their first dose of levodopa.

Data collection

Subject demographics were collected and each subject completed the WOQ9 and the MDS-UPDRS in ON medication condition with the support of a trained neurologist (ET, EH or MT). On the basis of motor diary data, average percentage OFF time and average percentage dyskinesia time per day were calculated as: OFF time (or dyskinesia time)/(24 – time asleep). Subjects who did not complete both days of the motor diary were excluded from the secondary analysis.

At the end of the recording period, PKG data were downloaded and analyzed using a proprietary algorithm to translate raw movement data collected by the PKG Data Logger into a multi-page, printable output of the patient's movement over the wear period. The algorithm produces bradykinesia scores (BS), dyskinesia scores (DS), and fluctuation scores (FS) every two minutes with bradykinesia interquartile range (BS_IQ) and dyskinesia interquartile range (DS_IQ), in addition to other quantitative and qualitative movement information (Griffiths et al., 2012). Subjects who wore the watch < 5 days were excluded from data analysis.

During the course of the study, high DS were observed in patients who denied having dyskinesia. Further review of individual data revealed that periods of activity consistently recognized as dyskinesia by the PKG corresponded in reality to periods of exercise. An independent, blinded evaluation of PKG scores was performed to rate the influence of exercise. Each PKG dataset was evaluated for the presence of probable exercise between 900 and 1800 hours.

Exercise was defined on PKG as an abrupt ON and abrupt OFF of a DS peak that exceeded the 90th percentile. If exercise was present, the investigator also rated its qualitative impact on the FS or DS because DK peaks that are long enough or intense enough may impact median summary scores over the aforementioned 9 - hour period. For example, if exercise was present lasting 90 minutes, with a DS otherwise of 5 and a large interquartile range, then it is expected that exercise will increase the median DS by 2-4 points. Thus, by assessing duration and intensity of DK peaks relative to DK behavior during non-peak time periods, we were able to estimate the impact of exercise on FS and DS and express it using the following qualitative scale: 0 – no exercise; 1 – exercise, but with minimal effect on FS or DS; 2 – exercise with modest effect, changing DS by 1-2 points; 3 – exercise, affecting DS by > 2 points; and 4 – exercise with a great effect on FS or DS. A *post-hoc* FS, BS, and DS analysis was performed excluding the effect of exercise.

Statistical analysis

PKG score mean, standard deviation and interquartile ranges were calculated. One-way ANOVA and Tukey's Honest Significant Difference (HSD) were used to compare PKG and motor diary scores between different fluctuator groups. Further analysis by two-tailed t-test was done by grouping subjects into non-dyskinetic and dyskinetic groups. A significance level of $p < 0.05$ was used. A second one-way ANOVA and Tukey's HSD evaluated differences between fluctuator groups after correction for exercise. This second analysis was additionally performed for the cluster analysis derived groupings.

Results

Six subjects were excluded from the analysis due to incomplete PKG data. The remaining 54 subjects were initially categorized into the pre-determined four groups as follows: NF (n=14), EF (n=15), MF (n=15), and TF (n=10, Fig. 1). As expected, the groups varied significantly in terms of disease duration, which was progressively longer with increasing severity of clinical fluctuation, and levodopa equivalent dose (LED). LED was more than double in TF as compared with NF, while EF and MF reported equivalent daily dosages. MDS-UPDRS score increased significantly with the severity of fluctuations, with the highest scores recorded in the TF group (Table I).

Of the 54 subjects who successfully completed the PKG study period and returned the watch, 39 also completed and returned valid two-day motor diaries. No patient completed only the motor diary without returning the watch. Therefore, the return rate was much higher for the PKG watch (88%) than for the motor diary (65%). The largest proportion of motor diaries excluded due to incorrect completion belonged to the TF group (5 of 10, 50%); compliance improved progressively with decreasing severity of fluctuations (Table II). Five patients reported WO in the motor diaries that was not reported on the WOQ9. No patient reported dyskinesia in the motor diaries that was not reported in the MDS-UPDRS IV. Due to the limitations of the diary method, motor diaries failed to distinguish clearly between the four groups on

Table I - Demographic and clinical data.

Demographic element	Non-fluctuators (n=14)	Early fluctuators (n=14)	Moderate fluctuators (n=15)	Troublesome fluctuators (n=10)	Cohort (n=53)	p value
Age	70 ± 9	68 ± 13	68 ± 9	66 ± 11	68 ± 10	0.86
Gender, male (female); % male	8(6) 57%	10(4) 71%	11(4) 73%	7(3) 70%	37(17) 69%	
Disease duration, years	4.2 ± 4.3	7.3 ± 4.4	7.2 ± 4.0	8.6 ± 3.2	6.8 ± 4.2	0.056
Most affected upper limb						
• left	8	10	9	6	33	
• right	5	4	6	4	20	
• NR	1	0	0	0	1	
LED (mg)	531 ± 201	831 ± 607	799 ± 386	1324 ± 685	839 ± 538	0.003
MDS-UPDRS I	7.1 ± 6.7	7.4 ± 4.5	13.8 ± 5.7	14.8 ± 5.9	10.4 ± 6.6	0.001
II	9.6 ± 7.5	11.4 ± 6.8	14.9 ± 6.4	12.5 ± 4.8	12.2 ± 6.7	0.19
III	14.9 ± 10.5	14.5 ± 7.8	16.7 ± 7.5	17.9 ± 10.7	16.0 ± 8.9	0.78
IV	0.5 ± 1.4	5.5 ± 3.1	9.1 ± 3.7	12.7 ± 3.5	6.4 ± 5.2	< 0.001
Total	32.1 ± 22.5	39.5 ± 14.9	54.5 ± 15.1	65.0 ± 14.5	46.2 ± 20.6	< 0.001

Abbreviations: NR, not reported; LED, levodopa equivalent dose; MDS-UPDRS, Movement Disorders Society-United Parkinson Disease Rating Scale

Table II - Motor diary results.

Diary element	Non- fluctuators (n=9)	Early fluctuators (n=14)	Moderate fluctuators (n=9)	Troublesome fluctuators (n=5)	p value
Average OFF time	2.2 ± 2.7	3.1 ± 2.2	3.4 ± 2.2	4.1 ± 1.1	0.45
Hours	11.0 ± 13.0	20.3 ± 14.5	16.6 ± 7.9	24.0 ± 7.5	0.64
%					
Average dyskinesia					
Hours	0.3 ± 0.7	0.9 ± 1.5	3.0 ± 1.4	3.3 ± 2.5	<0.001
%	1.7 ± 4.3	5.5 ± 8.9	20.0 ± 9.4	20.7 ± 18.2	<0.001

the basis of their average OFF time, either in absolute or percentage terms (Table II). The diaries distinguished NF from MF for average dyskinesia time, although average dyskinesia time was similar in MF and TF (Table II). Interestingly, the NF group reported an average of 2.2 hours OFF time per day (range 0-16 hours), despite having a WOQ9 score < 2. Two NF also reported dyskinesia.

In the 39 subjects who returned both watch and diary, FS analysis revealed a progressive average score increase from NF to TF (7.3 to 9.6, p = 0.012), although the EF had lower FS than the NF, with the difference between EF and TF being significant (Table III). One-way ANOVA for DS was significant (p = 0.031), however Tukey's HSD was not, possibly due to the small group size. BS_IQ and DS_IQ differed between EF and NF (p = 0.019, p = 0.026), while BS_IQ was equivalent in all groups, as expected (Table III). Further analysis based on grouping of non-dyskinetic (NF, EF) and dyskinetic (MF, TF) subjects demonstrated significant differences in FS, DS, DS_IQ and BS. However, when comparing the scores of NF *versus* all fluctuators (EF, MF, TF), there was no significant difference in any of the PKG scores (Table III).

Post-hoc analysis revealed no exercise interference in 46 patients. Seven subjects with exercise scores greater than 0 were excluded from a second analysis designed to limit the influence of exercise. This led to a small reduction in the size of the NF, MF and TF groups (Table III). Repeat one-way ANOVA showed that FS, DS_IQ

Table III - Personal KinetiGraph (PKG™) scores.

Summary score	Non- fluctuators (n=14, 12)	Early fluctuators (n=14, 14)	Moderate fluctuators (n=15, 12)	Troublesome fluctuators (n=10, 9)	p value	Tukey HSD
FS	7.3 ± 2.4	6.3 ± 1.6	8.8 ± 2.6	9.6 ± 3.8	*0.01*	EF/TF
No Ex	6.6 ± 1.8	6.3 ± 1.6	8.7 ± 2.9	9.4 ± 4.0	*<0.02*	
DS	1.4 ± 1.1	1.1 ± 0.8	3.0 ± 3.3	3.5 ± 3.1	*0.03*	None
No Ex	1.1 ± 0.7	1.2 ± 0.8	3.1 ± 3.6	3.0 ± 3.0	<0.06	
DS_IQ	5.0 ± 3.9	3.4 ± 2.0	9.3 ± 9.6	11.5 ± 10.3	*0.03*	EF/TF
No Ex	3.8 ± 2.7	3.6 ± 2.0	9.4 ± 10.6	10.9 ± 10.8	*<0.05*	
BS	30.9 ± 6.7	31.4 ± 5.3	26.5 ± 7.5	23.93 ± 6.2	*0.02*	EF/TF
No Ex	31.7 ± 6.8	30.6 ± 4.8	26.2 ± 7.7	24.1 ± 6.5	*<0.03*	None
BS_IQ	17.3 ± 3.4	16.6 ± 2.8	16.6 ± 4.0	17.3 ± 4.6	0.9	N/A
No Ex	16.9 ± 2.3	16.3 ± 2.7	16.4 ± 4.1	17.5 ± 4.9	0.85	
	No Dyskinesias (NF + EF)		Dyskinesias (MF + TF)			
FS	6.8 ± 2.1		9.1 ± 3.1		*<0.005*	
No Ex	6.4 ± 1.7		9.0 ± 3.3		*<0.005*	
DS	1.2 ± 1.0		3.2 ± 3.2		*<0.01*	
No Ex	1.1 ± 0.7		3.1 ± 3.3		*0.01*	
DS_IQ	4.2 ± 3.1		10.1 ± 9.7		*<0.01*	
No Ex	3.7 ± 2.3		10.0 ± 10.4		*0.01*	
BS	31.3 ± 6.0		25.5 ± 7.0		*<0.005*	
No Ex	31.1 ± 5.7		25.3 ± 7.2		*<0.005*	
BS_IQ	17.0 ± 3.1		16.9 ± 4.2		0.97	
No Ex	16.6 ± 2.5		16.9 ± 4.4		0.81	
	Non-fluctuators	Fluctuators (EF + MF + TF)				
FS	7.3 ± 2.4	8.1 ± 3.0			0.36	
No Ex	6.6 ± 1.8	7.9 ± 3.1			0.09	
DS	1.4 ± 1.1	2.4 ± 2.8			0.05	
No Ex	1.1 ± 0.7	2.4 ± 2.8			*0.02*	
DS_IQ	5.0 ± 3.9	7.7 ± 8.5			0.11	
No Ex	3.8 ± 2.7	7.6 ± 8.8			*0.03*	
BS	30.9 ± 6.7	27.6 ± 7.0			0.13	
No Ex	31.7 ± 6.8	27.3 ± 6.8			0.06	
BS_IQ	17.3 ± 3.4	16.8 ± 3.7			0.63	
No Ex	16.9 ± 2.3	16.7 ± 3.8			0.83	

Abbreviations: FS, fluctuation score; DS, dyskinesia score; DS_IQ, dyskinesia score interquartile range; BS, bradykinesia score; BS_IQ, bradykinesia score interquartile range; No Ex=no exercise interference; N/A, not applicable

and BS were still significantly different across study groups (Table III). Inter-group analysis confirmed that FS was still different for EF *vs* TF ($p = 0.017$). Interestingly, the FS in the NF changed the most (7.3 to 6.6), while other groups changed minimally (Fig. 2). Significance of PKG scores comparing non-dyskinetic *vs* dyskinetic groups did not change after excluding exercisers (Table III). However, DS and DS_IQ became significant after excluding exercisers ($p = 0.017$, $p = 0.031$).

Finally, a cluster analysis was performed on the 40 "fluctuators" with a positive combined WOQ9+ MDS-UPDRS IV score. The analysis revealed four distinct clusters, namely mild fluctuators (WOQ9 + MDS-UPDRS IV ≤7) accounting for 27% of the study population, moderate fluctuators (WOQ9 + MDS-UPDRS IV >7 and ≤14) accounting for 18%, and troublesome fluctuators (WOQ9 + MDS-UPDRS IV >14) accounting for 45%, in addition to a smaller cluster of high fluctuation score outliers accounting for 10% of the study population (Fig. 3A). One-way ANOVA showed that FS values failed to significantly differentiate the three clusters with progressive clinical fluctuation scores (Fig. 3B).

Discussion

Fluctuations of response to levodopa, including wearing off and dyskinesias, are common in PD as the disease progresses. Their accurate recognition is vital in order to stage PD severity and determine treatment changes and candidacy for advanced therapies. Due to their variability over time, the identification of motor fluctuations is currently highly dependent on the ability of patients and caregivers to report them correctly. Therefore, there is a clear need for technology that can monitor motor fluctuations over time, providing accurate feedback to the clinician in charge of adapting therapy to the ever-evolving demands of the disease.

Our data shows that FS can accurately distinguish between some types of fluctuators, in particular dyskinetic *versus* non-dyskinetic patients. This result confirms previous observations in deep brain stimulation surgery candidates, who would have likely qualified as MF or TF in our study (Horne et al., 2015), but suggests that the PKG may not be able to consistently distinguish between NF and milder stages of fluctuation (EF). No study using wearable devices previously attempted to separate groups of fluctuators into more than a binary system, and the inability to differentiate between multiple subgroups may be explained by the subjective nature of the defining characteristics for each of them. In addition, the attempt to define fluctuation severity in more detail resulted in smaller sample group sizes, possibly affecting the statistical power of the analysis. While more complex scales may have proved more sensitive (Stacy et al., 2005; Antonini et al., 2011), WO questionnaires always depend on the accuracy of the study subject's reporting, which may occasionally be in question,

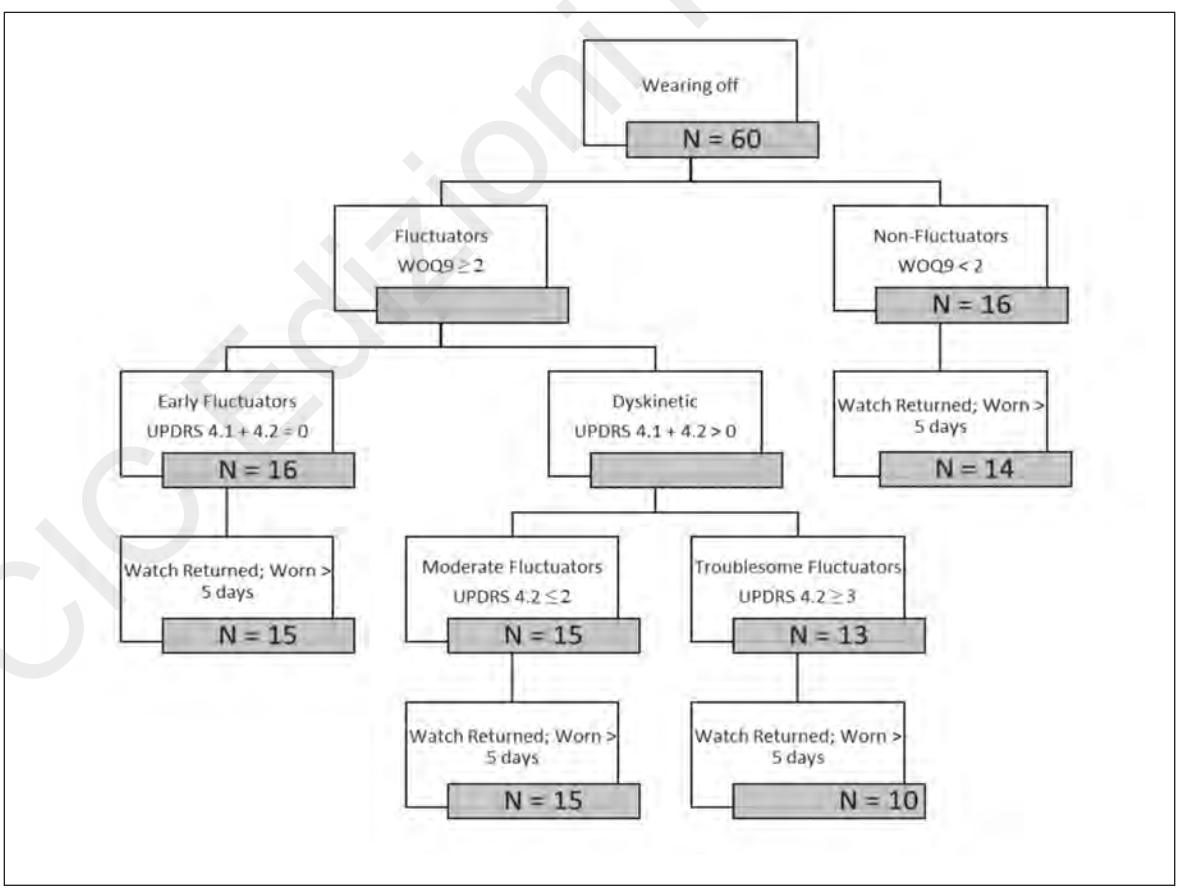

Figure 1 - Study design algorithm and subject categorization.

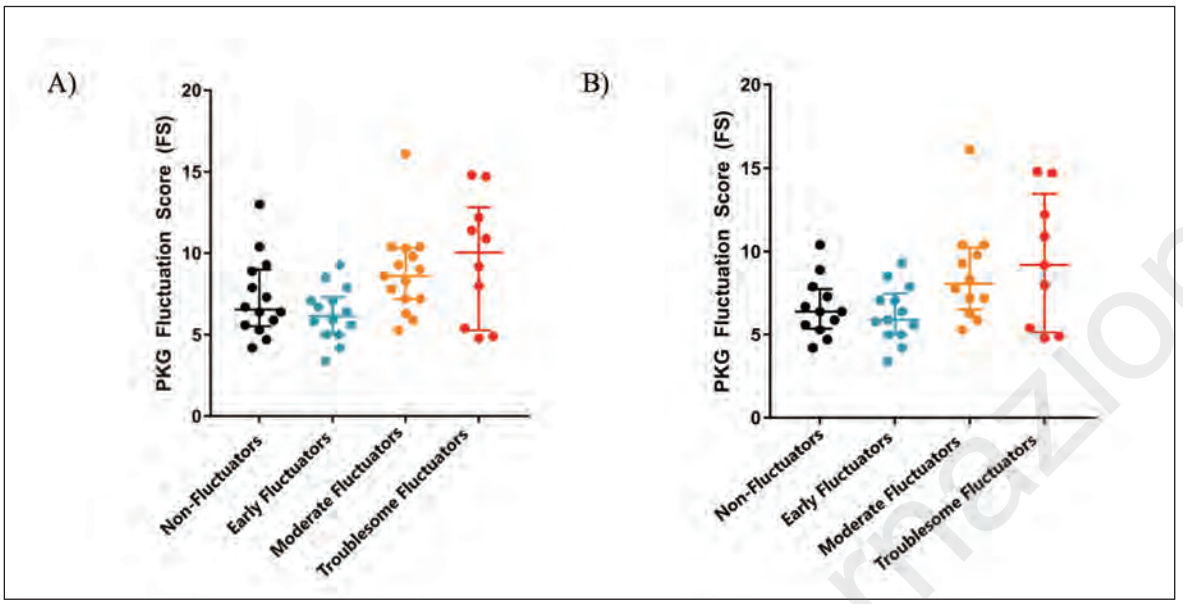

Figure 2 - Graphs showing the median and interquartile range of PKG fluctuation scores in the four subgroups of PD patients recruited in the study. A) Entire cohort; B) results excluding exercisers.

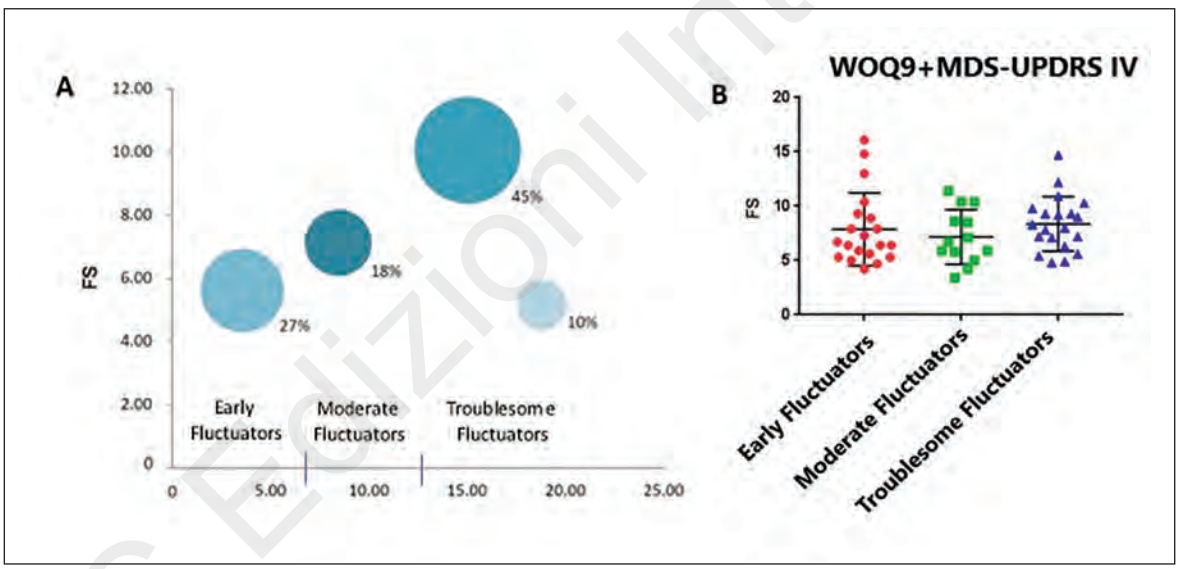

Figure 3 - A) Identified cluster profiles and sizes (% of total sample); B) graph showing the median and interquartile range of PKG fluctuations scores in the three subgroups of PD patients defined by cluster analysis.

especially as cognitive impairment becomes more obvious (Stocchi et al., 2014; Matthews et al., 2015; Altavista et al., 2015).

Significant discrepancies emerged between the WOQ9 survey, motor diaries and automated motion data recording with the PKG device. For example, FS differences did not correlate with motor diary scores, a discrepancy that parallels the previously reported low correlation of diary to PKG recording (Ossig et al., 2016). In addition, despite our asking for only two diaries instead of the six conventionally used, compliance was lower than the levels reported in previous diary validation studies (Hauser et al., 2004). In the absence of a standardized method for hourly reminders to fill out motor diaries, it is possible that diaries were completed in hindsight, which would further diminish their reliability. The return rate of the PKG watch was much higher compared with the motor diary, suggesting that wearable devices might improve compliance in "at home" fluctuation studies. Furthermore, wearable devices transcend language barriers, cognitive barriers, as well as time constraints in the clinic. The crucial nature of an accurate technique for quantifying and describing the presence and severity of motor fluctuations for medical treatment as well as clinical trials cannot be overemphasized (Lieber et al., 2015; Espay et al., 2016).

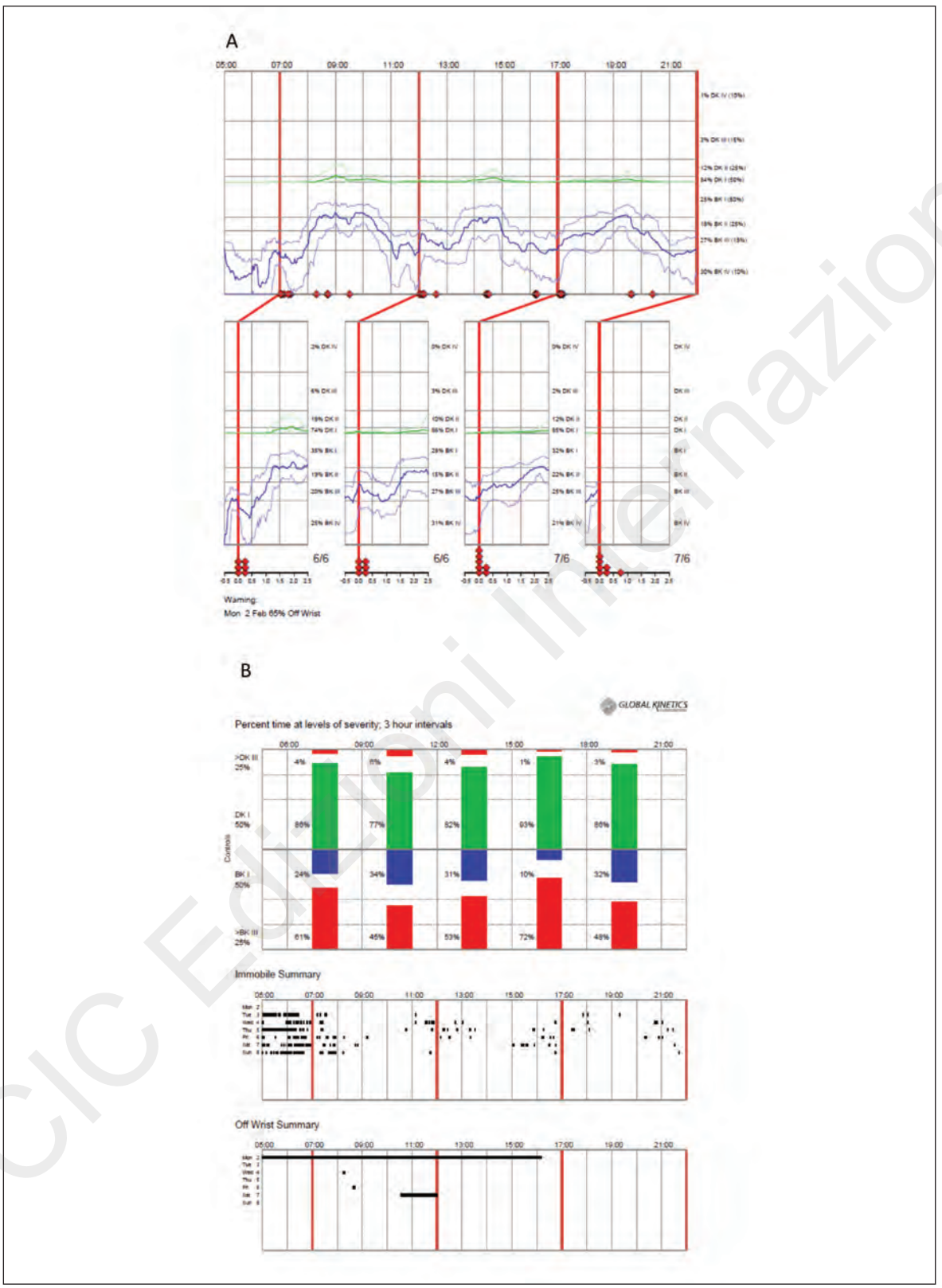

Figure 4 - Qualitative analysis of PKG output data. A) Graphical representation of BS, DS in quartile ranges during awake hours. Medication administration times are marked as red lines, with red dots marking times patient takes medications. B) Bar chart presents the same data in average percent time spent in each quartile range. Time spent immobile, and time that the watch is off the wrist is also represented in bar form.

We found the FS to be unable to truly detect certain subtleties of daily motor fluctuations. Just as one WO questionnaire cannot capture the depth and range of motor fluctuations, FS may not completely grasp each patient's individual response to levodopa and the state of their PD. FS may be influenced by factors other than bradykinesia and dyskinesia, including exercise and, potentially, tremor (Braybrook et al., 2016). Study subjects were asked not to abstain from exercise or to remove the device during exercise, which likely introduced significant motion artifacts requiring adjustments in the analysis and interpretation of the data. These limitations suggest that other, more qualitative components of the PKG (Fig. 4) may be fundamental in order to glean all the information contributing to motor fluctuations and to changing medical management. Other limitations of our study include the exclusion of subjects with tremor-predominant PD and those using a walking frame. The latter category, in particular, may include subjects most likely experiencing motor fluctuations. In addition, we did not request caregivers to fill out parallel diaries, which could have added a point of comparison and limited loss of patient-derived data.

Despite these limitations, FS were useful in differentiating dyskinetic from non-dyskinetic patients, and dyskinesia is, of course, a key motor complication leading to medication adjustments or referral for advanced surgical therapies. However, the device was unable to significantly differentiate between the NF and EF groups, limiting its role in the diagnosis of milder motor fluctuations. Our data support the use of FS as an objective tool to be used to capture and quantify these motor fluctuations as a triage mechanism. Future studies will need to investigate the influence of exercise and walking aids on fluctuation scores.

Acknowledgements

Professor Malcolm Horne, BMedSci Hons, PhD, MBBS (Hons), FRACP and Deputy Director of the Florey Neuroscience Institute and Neurologist at St. Vincent's Hospital in Melbourne served as an independent, blinded physician for PKG exercise evaluations. Technomics Research LLC provided interim statistical planning and analysis services. VitaMedical LLC provided medical writing and illustration services. Cedars-Sinai Clinical & Translational Research Center provided final statistical analysis services.

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