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Effect of using a wearable device on clinical decision-making and motor symptoms in patients with Parkinson's disease starting transdermal rotigotine patch: A pilot study

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ABSTRACT

Background: Feedback from wearable biosensors may help assess motor function in Parkinson's disease (PD) patients and titrate medication. Kinesia 360 continuously monitors motor symptoms via wrist and ankle sensors.
Methods: PD0049 was a 12-week pilot study to investigate whether using Kinesia 360 at home could improve motor symptom management in PD patients starting transdermal dopamine agonist rotigotine. Adults with PD and insufficiently controlled motor symptoms (prescribed rotigotine) were randomized 1:1 to Control Group (CG) or Experimental Group (EG) before starting rotigotine. Motor symptoms were assessed in all patients at baseline and Week 12 (W12) using Unified PD Rating Scale (UPDRS) III and Kinesia ONE, which measures standardized motor tasks via a sensor on the index finger. Between baseline and W12, EG used Kinesia 360 at home; clinicians used the data to supplement standard care in adjusting rotigotine dosage.
Results: At W12, least squares mean improvements in UPDRS II (−2.1 vs 0.5, $p = 0.004$) and UPDRS III (−5.3 vs −1.0, $p = 0.134$) were clinically meaningfully greater, and mean rotigotine dosage higher (4.8 vs 3.9 mg/24 h) in EG (n = 19) vs CG (n = 20). Mean rotigotine dosage increase (+2.8 vs + 1.9 mg/24 h) and mean number of dosage changes (2.8 vs 1.8) during the study were higher in EG vs CG. Tolerability and retention rates were similar.
Conclusion: Continuous, objective, motor symptom monitoring using a wearable biosensor as an adjunct to standard care may enhance clinical decision-making, and may improve outcomes in PD patients starting rotigotine.

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1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by motor and nonmotor symptoms [1]. Motor symptoms reflect nigrostriatal dopaminergic degeneration, and improve with dopaminergic replacement therapy with levodopa and/or dopamine agonists.

Rotigotine is a non-ergoline dopamine receptor agonist [2]. The rotigotine transdermal patch is approved in the EU for treatment of early-stage idiopathic PD as monotherapy or in combination with levodopa over the disease course, through to late stages when “on-off” fluctuations occur with levodopa, and in the US for treatment of PD. In early-stage PD, dosing consists of one daily dosage initiated at 2 mg/24 h, increased in weekly increments of 2 mg/24 h to an effective dosage of up to 6 mg/24 h; dosing in advanced-stage PD comprises one daily dosage initiated at 4 mg/24 h increased in weekly increments of 2 mg/24 h to an effective dosage of up to 8 mg/24 h (US prescribing information) [3].

Optimizing patient response to rotigotine and improving clinical outcomes depends on identifying an optimal dose based on efficacy and tolerability. Response to treatment titration is typically assessed by querying patients and their caregivers, but may be limited by recall and subjective impressions of response. Assessment is also limited by the clinician's ability to accurately assess motor function on interval examinations. Because motor symptoms vary by time of day and other factors, examination at a clinic visit provides a limited snapshot of a patient's daily symptoms.

Wearable devices can provide objective, quantitative, more continuous monitoring of motor symptoms and fluctuations during everyday activities [4–6]. Wearable technologies may allow clinicians to make more accurate motor assessments, which could improve personalized medication titration and augment shared clinical decision-making. Patients with PD perceive the potential benefits of wearables to include improved understanding about their disease for better self-management and increased confidence in their health professional's clinical decision-making [7].

Kinesia ONE (Fig. S1A, supplementary materials) and Kinesia 360 (Fig. S1B) (Great Lakes NeuroTechnologies Inc., Cleveland, OH, USA) are systems that include wearable sensors for measuring PD motor symptoms. Kinesia ONE measures tremor, bradykinesia, and dyskinesia using a sensor worn on one finger during standardized motor tasks. It provides objective tracking of a subset of the Unified Parkinson's Disease Rating Scale (UPDRS) Part III [8] items. Kinesia 360 allows continuous motor symptom monitoring throughout the day during activities of daily living (ADL) using sensor bands worn on the wrist and ankle on one side of the body.

PD0049 was a 12-week pilot study to investigate whether motor symptom management in patients with PD starting transdermal rotigotine could be improved by using Kinesia 360 at home (ClinicalTrials.gov identifier: NCT03103919).

2. Methods

2.1. Eligibility

Participants were male or female patients with PD aged ≥18 years who were newly prescribed transdermal rotigotine for clinically significant motor symptoms insufficiently controlled by current therapy, and who had an average of triplicate measurements of Kinesia ONE resting tremor and finger tapping scores > 1.0. Prior but not current rotigotine treatment was permitted. Exclusion criteria included current participation in any study with an investigational medicinal product or device; any medical, neurological, or psychiatric condition that could jeopardize or would compromise the patient's ability to participate in the study; and prior deep brain stimulation.

An institutional review board approved the study protocol. The study was conducted in accordance with the principles of the Declaration of Helsinki; all enrolled participants provided informed consent.

2.2. Objectives

Primary objectives were to evaluate:

- Whether PD motor symptoms in patients starting transdermal rotigotine could be improved by using feedback of motor symptom data from Kinesia 360 presented to patients and clinicians, in addition to standard care, versus only standard care
- Rotigotine dosing regimen when using feedback from Kinesia 360 in addition to standard care versus only standard care
- Whether patients were more likely to continue using transdermal rotigotine if Kinesia 360 data were used to provide them with feedback on their motor symptoms, and were used in addition to standard care for titrating their dosing regimen.

Other objectives are described in Text S1, supplementary materials.

2.3. Design

Study schema is presented in Fig. S2. On Day 1, eligible patients were randomized 1:1 to the Control Group (CG) or Experimental Group (EG). Both groups used Kinesia ONE in clinic at Visit 1 (screening visit) and Visit 2 (Week 12) to measure motor performance during specific motor tasks (Text S2). The Kinesia ONE results were used as study outcomes but not provided to clinicians for titrating the dosing regimen. Other assessments performed at the two visits included the UPDRS [8], 39-Item Parkinson's Disease Questionnaire (PDQ-39) [9], and 13-Item Patient Activation Measure (PAM-13) [10], which quantifies the extent to which patients are informed about and involved in their healthcare. To reflect routine management, the timing of the assessments was not specified to be in either the “on” or the “off” state. The investigators did not determine whether patients were fluctuators at baseline or their motor state (“on” or “off”). Patients not on levodopa who needed additional motor treatment and patients on levodopa with “off” time (ie, fluctuators) were both prescribed rotigotine at a regular clinic visit and then enrolled. For fluctuators, their motor state on entry was not controlled to minimize disruption of the usual clinical practice follow-up.

Between the two visits, the EG used Kinesia 360 throughout the day while awake. Details of Kinesia 360 are given in Text S3. Patients were asked to use the device on at least two consecutive days in each of Weeks 1 (baseline), 2, 3, 4, and 11, but were free to use it as often as they liked between these time points before Visit 2 (Week 12).

Kinesia 360 data reports were accessed by patients via a mobile application and by investigators through a web portal. These showed tremor, slowness, dyskinesia, and walking severity (color-coded green to yellow to red with increasing severity) and duration (percent of day detected), averaged by day or by rotigotine dose (Figs. S3A and B). The investigators used these data to provide feedback to patients on their motor symptoms and to supplement standard care to titrate the optimal rotigotine dosage. Investigators were encouraged to phone patients to discuss motor symptom reports and potential rotigotine dosage adjustments based on clinical judgment.

The CG did not use Kinesia 360, and the investigators used only standard care to titrate the optimal rotigotine dosage.

Patients in both study groups could start rotigotine 2 or 4 mg/24 h (at the investigator's discretion according to disease stage), preferably on Day 1 (but no later than Day 4) for the CG and on Day 4 for the EG. Baseline was Days 2–4. Evaluations concluded 12 weeks after the start of rotigotine treatment (Visit 2).

This study was conducted in the US from March 2017 to January 2018.

2.4. Outcomes

Primary outcome measures included:

- Change from baseline to Week 12 in UPDRS III motor score
- Change from baseline to Week 12 in Kinesia ONE variables (listed in Text S4)
- Rotigotine dosage at Week 12
- Number of rotigotine dosage changes between baseline and Week 12
- Discontinuation of rotigotine during the study.

Safety variables were occurrence of treatment-emergent adverse events (TEAEs) during the study.

Other outcome measures included change from baseline to Week 12 in:

- UPDRS II ADL score
- Kinesia 360-derived motor scores by time for the EG (listed in Text S5)
- PDQ-39 scores
- PAM-13 score.

2.5. Statistical analyses

As this pilot study was exploratory in nature, no formal sample size estimation was performed. The planned sample size of approximately 40 patients was chosen to obtain an impression of the effect of the device(s) on the efficacy variables based on experience from similar exploratory studies involving dopaminergic therapies. All analyses were exploratory.

Efficacy was analyzed for the Full Analysis Set (FAS – all participants with at least one valid baseline and at least one valid post-baseline efficacy measurement) mainly using an analysis of covariance (ANCOVA) with baseline as a covariate, “center” as factor, and “group” (CG and EG) as main factor. Kinesia 360-based efficacy data are presented descriptively for the EG, by time point.

Safety analyses were performed on the Safety Set (SS – all enrolled patients who received at least one rotigotine dose).

Post hoc analyses were performed for UPDRS II and III in advanced and early PD subgroups, using the above-mentioned ANCOVA model. PD stage was defined by the presence or absence of concomitant levodopa at baseline (advanced and early PD, respectively).

Rotigotine dosage at Week 12 was analyzed for long and short duration Kinesia 360 wear time subgroups (derived from median wear time), among EG patients treated with rotigotine for more than 10 weeks.

3. Results

3.1. Participant disposition and characteristics

The study screened 57 patients from eight sites, 40 of whom were randomized (Fig. S4). Of these, 39 were included in the SS and in the FAS: 20 in the CG and 19 in the EG. Two patients each in the CG (10%) and EG (10.5%) discontinued from the study; for all four, the primary reason was TEAEs.

The two study groups had similar baseline characteristics (Table 1). A slightly higher proportion of the EG had received prior dopaminergic agents.

Table 1
Patient demographics and baseline characteristics (Safety Set).

Variable	Control Group (n = 20)	Experimental Group (n = 19)
Age, mean (SD), y	69.76 (7.16)	67.62 (9.77)
Female, n (%)	12 (60.0)	10 (52.6)
BMI, mean (SD), kg/m^2	28.35 (7.20)	27.95 (5.06)
UPDRS Part II score, mean (SD)[a]	10.2 (4.3)	9.4 (3.4)
UPDRS Part III score, mean (SD)[a]	27.2 (8.5)	25.0 (11.5)
Prior dopaminergic agents, n (%)	14 (70.0)	16 (84.2)
Dopamine agonists	1 (5.0)	0
Levodopa	11 (55.0)	14 (73.7)
Monoamine oxidase B inhibitors	5 (25.0)	7 (36.8)
Amantadine	2 (10.0)	0
Other dopaminergic agents	1 (5.0)	1 (5.3)
Concomitant dopaminergic agents, n (%)[b]	20 (100)	19 (100)
Dopamine agonists	20 (100)	19 (100)
Levodopa	12 (60.0)	14 (73.7)
Monoamine oxidase B inhibitors	5 (25.0)	7 (36.8)
Amantadine	2 (10.0)	0
Other dopaminergic agents	1 (5.0)	1 (5.3)

Abbreviations: BMI = body mass index; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.
[a] Data for the Full Analysis Set, which included the same patients as the Safety Set.
[b] Includes rotigotine transdermal patch.

3.2. Primary outcome results

At Week 12, the least squares (LS) mean improvement (decrease) in UPDRS III was numerically greater in the EG versus the CG (−5.3 (standard error 2.0) vs −1.0 (2.1), EG vs CG $p = 0.134$; Fig. 1A). Small changes in the direction of improvement (decrease) were observed in most Kinesia ONE variables in both study groups (Table 2).

At Week 12, the EG had a numerically higher mean rotigotine dosage (4.8 (standard deviation 1.8) vs 3.9 (1.7) mg/24 h) and a greater mean dosage increase from baseline versus the CG (Table 3). The starting dosage was 2 mg/24 h for all patients (Table 3). The mean number of dosage changes during the study was numerically higher in the EG versus the CG (2.8 vs 1.8 changes; Table 3).

During the study, five patients each in the CG (25.0%) and EG (26.3%) discontinued rotigotine (odds ratio 1.14, 95% confidence interval 0.23–5.66, $p = 0.876$); of these patients, two in each study group withdrew from the study (all due to a TEAE). In the CG, the reason for discontinuing rotigotine was intolerance (three patients) and “other” (two patients); in the EG, the reason was intolerance (two patients), “other” (two patients), and lack of efficacy (one patient).

3.3. Other variables

At Week 12, an LS mean improvement (decrease) in UPDRS II was observed in the EG and no improvement or slight worsening (increase) in the CG (−2.1 (standard error 0.6) vs 0.5 (0.6), EG vs CG, $p = 0.004$; Fig. 1B).

Patients in the EG used Kinesia 360 on a mean of 29.2 days (standard deviation 20.3 days, median 26.0 days, range 4–74 days). Changes in Kinesia 360 scores during the study are shown in Table S1, supplementary materials.

In both study groups, there was no notable change in PDQ-39 sum score or individual domain scores at Week 12 (Table S2). For PAM-13, the CG showed a slight worsening while the EG showed no change (EG vs CG $p = 0.164$; Fig. 1C).

Both in patients with advanced and early PD (with and without concomitant levodopa at baseline, respectively), the EG showed a numerically greater LS mean improvement (decrease) in UPDRS III versus the CG at Week 12 (EG vs CG: advanced PD, $p = 0.463$; early PD, $p = 0.601$; Fig. S5A). With UPDRS II, an LS mean improvement (decrease) was observed in the EG and a slight worsening (increase) in the CG regardless of disease stage (EG vs CG: advanced PD, $p = 0.021$; early PD, $p = 0.040$; Fig. S5B).

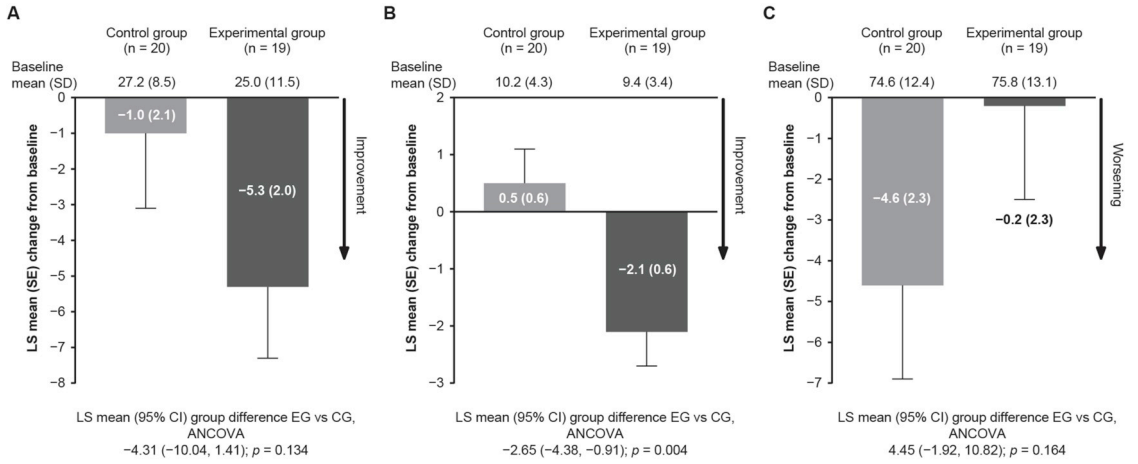

Fig. 1. Change from baseline to Week 12 in: (A) Unified Parkinson's Disease Rating Scale Part III score (on a scale of 0–108); (B) Unified Parkinson's Disease Rating Scale Part II score (on a scale of 0–52); (C) 13-Item Patient Activation Measure score (on a scale of 0–100) (Full Analysis Set).

Table 2
Change from baseline to Week 12 in Kinesia ONE variables (on a scale of 0–4, with a higher score indicating greater impairment; Full Analysis Set).

Kinesia ONE variable, LS mean (SE)	Control Group (n = 20 at baseline; n = 19 at Week 12)	Experimental Group (n = 19 at baseline; n = 18 at Week 12)	Difference EG vs CG (95% CI), *p*-value
Rest tremor score	−0.495 (0.231)	−0.674 (0.238)	−0.18 (−0.81, 0.45), 0.566
Postural tremor score	−0.489 (0.141)	−0.342 (0.143)	0.15 (−0.24, 0.53), 0.443
Finger tapping speed score	−0.394 (0.160)	−0.389 (0.167)	0.01 (−0.44, 0.45), 0.982
Averaged finger tapping speed and resting tremor scores	−0.450 (0.156)	−0.525 (0.156)	−0.07 (−0.50, 0.35), 0.720
Finger tapping amplitude score	0.083 (0.242)	−0.009 (0.238)	−0.09 (−0.75, 0.57), 0.777
Hand grasp speed score	−0.178 (0.115)	−0.188 (0.117)	−0.01 (−0.33, 0.31), 0.947
Hand grasp amplitude score	0.119 (0.190)	−0.147 (0.188)	−0.27 (−0.79, 0.26), 0.306
Rapid alternating movement speed score	−0.202 (0.102)	−0.171 (0.106)	0.03 (−0.25, 0.31), 0.819
Rapid alternating amplitude score	−0.240 (0.123)	−0.167 (0.122)	0.07 (−0.26, 0.41), 0.663
Dyskinesia score	0.125 (0.108)	−0.074 (0.112)	−0.20 (−0.51, 0.11), 0.197

Abbreviations: CG = Control Group; CI = confidence interval; EG = Experimental Group; LS = least squares; SE = standard error.

Table 3
Dosage of rotigotine transdermal patch at baseline and Week 12 and number of dosage changes (Safety Set).

	Control Group (n = 20)	Experimental Group (n = 19)
Starting dosage, n (%)		
2 mg/24 h	20 (100)	19 (100)
Dosage at Week 12		
Mean (SD), mg/24 h[a]	3.9 (1.7)	4.8 (1.8)
2 mg/24 h, n (%)	4 (20.0)	2 (10.5)
4 mg/24 h, n (%)	8 (40.0)	8 (42.1)
6 mg/24 h, n (%)	2 (10.0)	4 (21.1)
8 mg/24 h, n (%)	1 (5.0)	2 (10.5)
Other, n (%)	1 (5.0)	0
Change in dosage from baseline to Week 12, mean (SD), mg/24 h[a]	+1.9 (1.7)	+2.8 (1.8)
Number of dosage changes		
Mean (SD)	1.8 (1.2)	2.8 (1.7)
0–1, n (%)	9 (45.0)	6 (31.6)
2–3, n (%)	10 (50.0)	5 (26.3)
4–5, n (%)	1 (5.0)	8 (42.1)
≥6, n (%)	0	0

Abbreviation: SD = standard deviation.
[a] n = 16 for Control Group and n = 16 for Experimental Group at Week 12.

Long and short duration Kinesia 360 wear time subgroups had the same starting rotigotine dosage, but long duration patients showed a slightly greater increase in dosage at Week 12 (Table S3).

3.4. Safety variables

Safety profiles were similar in the two study groups (Table S4). The most common TEAEs (≥10% of patients in either group; CG vs EG) were somnolence (three (15.0%) vs four (21.1%) patients), fatigue (one (5.0%) vs three (15.8%) patients), nausea (three (15.0%) vs two (10.5%) patients), dizziness (one (5.0%) vs two (10.5%) patients), and asthenia (0 vs two (10.5%) patients).

One patient in each group (5.0% of CG, 5.3% of EG) experienced serious TEAEs (Table S5), none of which were considered related to rotigotine or use of the wearable sensor systems. The CG patient experienced dehydration and renal impairment; the EG patient experienced obstruction of the small intestine.

The proportion of patients who discontinued rotigotine because of TEAEs was similar in the two study groups (CG: two (10.0%) patients; EG: three (15.8%) patients; Table S6), despite more dosage changes in the EG.

4. Discussion

Patients using Kinesia 360 for ambulatory monitoring as an adjunct to clinical management had more rotigotine dosage changes (2.8 vs 1.8 changes) and a higher mean rotigotine dosage at Week 12 versus the CG (4.8 vs 3.9 mg/24 h), where investigators used only standard care to titrate the optimal dosage. Closer evaluation of the EG because of feedback from Kinesia 360 could explain the more frequent dosage adjustments. Greater motor symptom improvement was observed in the EG versus the CG, as reflected by UPDRS II and III. The 5.3-point improvement in UPDRS III in the EG is clinically meaningful (minimal

clinically important change: 5 points [11]). Moreover, the magnitude of change is similar to that in pivotal rotigotine trials, before and after rotigotine treatment (3.5–8.7 points [12,13]), but here the difference in scores is between two groups both receiving rotigotine, with the only dissimilarity being the use of Kinesia 360. Given the study was not powered to detect statistically significant differences between the two study sets, such numerical differences are encouraging. Although unblinded investigators and patients likely biased self-reporting and UPDRS II/III measurements, this reflects routine clinical evaluation. Our results suggest that medication dosage can be more frequently adjusted to optimal dose based on objective measures from wearable biosensors. This should be confirmed and further explored in larger, controlled, higher-powered studies.

The higher mean rotigotine dosage may help explain the greater efficacy on UPDRS II and III in the EG. Notably, there was no difference in the number of adverse events or the proportion of patients who discontinued rotigotine versus the CG, even though the EG had more dosage changes (both increase and decrease).

The greater reductions in UPDRS II and III in the EG versus the CG were observed in both the advanced and early PD subgroups, although these results should be interpreted with caution because of the small sample size. Wearable devices may have differential uses and importance depending on disease stage: In early PD, the focus is on improving motor symptoms; in later stages, it is on improving motor fluctuation.

Kinesia ONE motor scores have been shown to highly correlate with clinician ratings of individual tasks [14–16] and the device has shown greater reliability and responsiveness for bradykinesia than clinician ratings [17,18]; yet the improvements in UPDRS II (home ADL) and III (in-clinic motor examination) were not reflected in the at-home Kinesia 360 or in-clinic Kinesia ONE motor scores. There were small improvements in Kinesia ONE variables and no clear changes in Kinesia 360 variables during the study. This could be for various reasons. Kinesia ONE and Kinesia 360 measure specific motor tasks rather than an aggregate (as with UPDRS). Due to the low patient numbers, individual correlation between Kinesia ONE and UPDRS tasks was not assessed. Since the Kinesia devices measure a subset of UPDRS items, one or more unmeasured items may have driven the improvement in UPDRS scores. The magnitude of the scales is also different: 0–108 for UPDRS III overall versus 0–4 for individual Kinesia scores. The study was not powered to detect small changes in Kinesia variables. Furthermore, UPDRS II assessed ADL at home over the prior week, whereas with Kinesia 360, patients may have worn the device at home preferentially during times when they were experiencing “off” periods, and if so the data may not reflect overall function at home.

Patient activation (PAM-13) showed no change in the EG and a slight worsening in the CG. For quality of life (QoL), improvements in the PDQ-39 sum score were small in both groups (CG −3.5, EG −5.1), but nonetheless they approached or exceeded the minimally important difference (−4.72 [19] and −1.6 [20]).

Consistent with UPDRS II, the PDQ-39 ADL domain showed a potentially greater improvement in the EG versus the CG: the EG (−5.9) but not the CG (−1.7) showed an improvement that reached the minimally important difference for this domain (−4.4) [20]. The PDQ-39 cognition domain also showed a potential signal for improvement in the EG versus the CG, with improvement in the EG (−3.4) but worsening in the CG (6.6) that both exceeded the minimally important change for this domain (1.8) [20]. These results suggest possible QoL benefits when Kinesia 360 is added to standard care for patients with PD initiating transdermal rotigotine.

Patients in the EG appeared to like using Kinesia 360, using the device for a mean of 29.2 days (median: 26.0 days) despite being required to use it for only 10 days. Interestingly, the patients who used Kinesia 360 for a longer duration showed a slightly greater increase in rotigotine dosage during the study than the shorter-duration patients. The two study groups had similar numbers and types of TEAEs, which were consistent with the known rotigotine safety profile, and comparable proportions of patients who discontinued from the study.

Text S6 describes the study limitations and Text S7 potential future research.

5. Conclusion

This pilot study suggests using a wearable biosensor at home for continuous, objective, motor symptom monitoring as an adjunct to standard care enhances clinical decision-making, and may improve clinical outcomes of patients with PD newly prescribed rotigotine.

Author contributions

Babak Boroojerdi, Stan Carson, Dustin Heldman, Michael Markowitz, Maureen Phillips, Dolors Terricabras, and Franz Woltering designed the study. Babak Boroojerdi, Stan Carson, Kevin Klos, Maureen Phillips, Daniel Truong, Stuart H. Isaacson, David L. Kreitzman, Martha McGraw, Fredy J. Revilla, and Olga Waln were involved in data collection. Franz Woltering contributed to data analysis. All authors contributed to data interpretation. All authors were involved in the critical review/revision of manuscript drafts and approved the final version.

Declaration of interest

Stuart H. Isaacson has received research funding and/or honoraria for continuing medical education, consulting, and/or promotional speaker activities from AbbVie, Acorda, Adamas, Biogen, Global Kinetics, Impax, Intec Pharma, Kyowa, Lundbeck, Michael J. Fox Foundation, Neurocrine, Neuroderm, Parkinson Study Group, Pfizer, Pharma Two B, Roche, Sanofi, Sunovion, Teva, UCB Pharma, US WorldMeds, and Zambon. Babak Boroojerdi, Michael Markowitz, Franz Woltering, and Stan Carson are employees of UCB Pharma. Babak Boroojerdi has received UCB Pharma stock units and stock options from his employment. Michael Markowitz has received restricted stock units in UCB Pharma from his employment. Franz Woltering has received UCB Pharma stock awards from his employment. Stan Carson has received UCB Pharma stock units and stock options from his employment. Dolors Terricabras was an employee of UCB Pharma when the study was conducted and is currently employed by ADC Therapeutics (UK) Ltd. She has received stock units in UCB Pharma from her employment. Olga Waln has nothing to declare. Martha McGraw has received research funding and/or honoraria for consulting and speaker activities from TEVA, Lundbeck, Acadia, US WorldMeds, Sunovion/Cynapsus, AbbVie, and UCB Pharma. David L. Kreitzman has received honoraria for consulting from Acadia, Adamas, UCB Pharma, and US WorldMeds, honoraria for speaker bureau from Acadia, Adamas, UCB Pharma, US WorldMeds, Lundbeck, Impax, UCB Pharma, and Teva, and research funding from Acadia, Intec, Pharma Two B, and UCB Pharma. Kevin Klos has received honoraria from UCB Pharma for speaker bureau, and research funding from UCB Pharma. Fredy J. Revilla has received consulting honoraria from TEVA. Dustin Heldman is an employee of and owns stock in Great Lakes NeuroTechnologies. Maureen Phillips was an employee of Great Lakes NeuroTechnologies when the study was conducted and is currently employed by Intel IT. Daniel Truong has received research funding from Ipsen, Merz, Auspex, Daiichi Sankyo Pharma, AbbVie, National Institute of Neurological Disorders and Stroke, Kyowa, Neurocrine, Sunovion, Acadia, Acorda, Cynapsus, NeuroDerm, and Intec.

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Appendix A. Supplementary data

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