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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

Wearable sensor-based objective assessment of motor symptoms in Parkinson's disease

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Abstract Effective management and development of new treatment strategies of motor symptoms in Parkinson's disease (PD) largely depend on clinical rating instruments like the Unified PD rating scale (UPDRS) and the modified abnormal involuntary movement scale (mAIMS). Regarding inter-rater variability and continuous monitoring, clinical rating scales have various limitations. Patient-administered questionnaires such as the PD home diary to assess motor stages and fluctuations in late-stage PD are frequently used in clinical routine and as clinical trial endpoints, but diary/questionnaire are tiring, and recall bias impacts on data quality, particularly in patients with cognitive dysfunction or depression. Consequently, there is a strong need for continuous and objective monitoring of motor symptoms in PD for improving therapeutic regimen and for usage in clinical trials. Recent advances in battery technology, movement sensors such as gyroscopes, accelerometers and information technology boosted the field of objective measurement of movement in everyday life and medicine using wearable sensors allowing continuous (long-term) monitoring. This systematic review summarizes the current wearable sensor-based devices to objectively assess the various motor symptoms of PD.

Keywords Parkinson's disease (PD) · Clinical scores · Motor symptoms · Objective measurement · Accelerometer · Gyroscope

Introduction

Parkinson's disease (PD) is the second most frequent neurodegenerative disease and affects 0.1–0.2 of the general population (Dorsey et al. 2007; de Rijk et al. 2000). Since PD—as a neurodegenerative disease—is age-related the number of patients will significantly grow in the forthcoming decades due to the aging society (Checkoway

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and Nelson 1999). The disease is primarily characterized by motor symptoms such as bradykinesia, rigidity, tremor and postural instability. In later disease stages, motor complications such as motor fluctuations and levodopa-induced dyskinesia complicate the spectrum (Fahn et al. 2004). Not only disease management using drug therapy, surgical interventions and rehabilitation programs, but also clinical studies to develop new treatments for motor symptoms strongly rely on the quantitative measure of the target symptoms. To evaluate motor symptom severity itself as well as effects of motor treatments, various clinical scoring systems and tools have been developed (Ramaker et al. 2002). Among these, the Unified Parkinson's disease rating scale (UPDRS) assessing all motor symptoms (among various non-motor symptoms) has been extensively tested and its validity and reliability are well established (Fahn et al. 1987), but its use in clinical diagnosis and evaluation is limited by its subjective nature and depends on the patient's current status. Nevertheless, the UPDRS is an internationally accepted rating scale to assess efficacy in clinical routine and clinical trials. A revised version was introduced by the Movement Disorder Society (MDS-UPDRS) and subsequently validated to rate motor symptoms in PD (Goetz et al. 2008c). Besides the UPDRS estimating all motor symptoms of PD, there are specific clinical scoring systems for all motor conditions including tremor, bradykinesia, gait and postural instability, motor fluctuations and dyskinesia (see Table 1 for details). For motor fluctuations the PD home diary as a self-assessment tool was introduced and validated by Hauser and colleagues (Hauser et al. 2006). Most of the scales and scores are sufficiently validated and widely used in clinical practice and trials. However, each of these clinical ratings has limitations regarding inter-rater variability and continuous monitoring. In particular the use of self-administered scales such as the PD home diary heavily relies on the accuracy of completion and is thus associated with a large recall bias and diary fatigue, particularly in patients with cognitive dysfunction or depression (Papapetropoulos 2012; Stone et al. 2002). Consequently, there is a strong need for objectivity and continuous monitoring of motor performance in PD for improving therapeutic regimens in routine care and for assessments in clinical trials.

The advances during the recent decades in battery technology, movement sensors such as gyroscopes and accelerometers as well as innovations in the information

Table 1 Wearable sensor-based devices for objective measurement of motor symptoms in Parkinson's disease

Symptom	Clinical scoring systems (selection)	Wearable sensor-based devices/methods (selection)
Tremor	UPDRS (Fahn et al. 1987) MDS-UPDRS (Goetz et al. 2008c) Fahn–Tolosa–Marin Tremor Rating Scale (TRS) (Stacy et al. 2007)	Wearable accelerometers/gyrostats, SOMNOwatch TM plus, DigiTrac, ActiTrac, all from SomnoMedics GmbH, Randersacker, Germany (Bhidayasiri et al. 2014) Tremor apps for IOS and Android mobile phones, based on accelerometry (apps for medical applications are not regulated/controlled and are thus not approved by the FDA in most cases)
Bradykinesia	UPDRS (Fahn et al. 1987) MDS-UPDRS (Goetz et al. 2008c)	Gait analysis using wearable accelerometer/gyrostat sensors combined with Intelligent Technology, for example eGAIT, www.egait.de, Astrum IT GmbH, www.astrum-it.de, Erlangen, Germany (Klucken et al. 2013; Barth et al. 2011) Watch-like accelerometers, for example PKG, Global Kinetics Corporation, Melbourne, Australia (Griffiths et al. 2012)
Gait	UPDRS (Fahn et al. 1987) MDS-UPDRS (Goetz et al. 2008c) Timed "Up and Go" test (Morris et al. 2001)	Gait analysis using wearable accelerometer/gyrostat sensors (Tao et al. 2012; Muro-de-la-Herran et al. 2014), for example eGAIT, www.egait.de, Astrum IT GmbH, www.astrum-it.de, Erlangen, Germany (Klucken et al. 2013; Barth et al. 2011)
Dyskinesia	UPDRS (Fahn et al. 1987) MDS-UPDRS (Goetz et al. 2008c) Unified Dyskinesia Rating Scale (Goetz et al. 2008b) mAIMS (May et al. 1983)	Accelerometer and gyroscope-based systems, most using several sensors on various body parts (Keijsers et al. 2000, 2003; Patel et al. 2008; Tsipouras et al. 2011, 2012; Pulliam et al. 2014) Watch-like accelerometers, for example PKG, Global Kinetics Corporation, Melbourne, Australia (Griffiths et al. 2012)
Motor fluctuations	PD home diary (Hauser et al. 2000, 2006) Home video recording (Goetz et al. 2008a)	Accelerometer on various body parts (Patel et al. 2008, 2009) Watch-like accelerometers, for example PKG, Global Kinetics Corporation, Melbourne, Australia (Griffiths et al. 2012; Horne et al. 2015)

FDA Food and Drug Administration, *mAIMS* modified abnormal involuntary movement scale, *PD* Parkinson's disease, *UPDRS* Unified Parkinson's disease rating scale

technology boosted the field of objective assessment of movement not only in all facets of everyday life such as navigation and sports, but also in medicine with a particular focus on movement disorders due to obvious reasons. We performed a systematic PubMed search to discuss the relevant data on wearable sensor-based devices for the assessment of motor symptoms in PD focusing on accelerometer- and gyroscope-based systems. Stationary systems to measure motor function in PD such as the Gaitrite® device (Chien et al. 2006) or 3D camera-based systems are not included in our analyses. Home video recording or telemedicine are considered as clinical scoring systems (Achey et al. 2014), since there is a physician-based scoring behind the recordings, and are thus also not part of this review.

Literature search strategy

We performed a PubMed search to collect the literature and considered reports published between January 31, 1990 and April 30, 2015. The following terms were used: "gyroscope AND Parkinson's disease", "accelerometer AND Parkinson's disease" and "wearable sensor AND Parkinson's disease". The search term "gyrostat" did not reveal any results. The search term "gyroscope AND Parkinson's disease" revealed 16 results, but 1 article is categorized as a review article. The search term "gyroscope AND Parkinson's disease" revealed 110 results with five articles categorized as reviews and 11 were duplicate results with the previous search term. The search term "wearable sensor AND Parkinson's disease" revealed 13 results with two articles categorized as reviews and eight were duplicate results with the previous search terms. The remaining reference list containing 113 articles was reviewed and is provided as Supplementary Text.

General search results

Table 1 summarizes the technologies described in the literature to objectively assess motor function with respect to the various motor symptoms of PD. Most reports aimed to quantify the various motor symptoms or disease staging, but some studies goaled for using the devices in the diagnosis or differential diagnosis of PD or PD tremor (Jang et al. 2013; Bhidayasiri et al. 2014; Wile et al. 2014; Barth et al. 2011, 2012; Klucken et al. 2013; Louter et al. 2015). In general, the studies used cross-sectional designs and compare the devices with clinical parameters/ratings or clinical diagnosis not confirmed by neuropathology. We did not find prospective data for severity measurements, disease staging or treatment effects. The following sections discuss the utility data of wearable sensor-based systems for the major motor symptoms of PD including motor fluctuations and dyskinesia in details. Rigidity—defined as the resistance of a joint to a passive movement—is yet not measurable with wearable sensors based on gyroscopes and/or accelerometers and thus not included in this review.

Tremor

Tremor is defined as involuntary repetitive contractions of agonistic and antagonistic muscles leading to oscillatory movements of the extremities or the head. Tremor can be clinically evaluated by using the UPDRS or through the quantification of drawn spirals (Deuschl et al. 1998). The highest standard for evaluation of tremor through spiral drawings was defined by Bain and Findley who classified 37 representative spiral drawings with varying degrees of tremor into 11 stages (Bain et al. 1993). Another tremor scale—which is, however, not commonly used—is the Fahn–Tolosa–Marin tremor rating scale (TRS). This 5-point scale rates tremor severity based on tremor amplitude, from 0 (no tremor) to 4 (severe tremor) in each part of the body (Stacy et al. 2007; Fahn et al. 1993).

Automated tremor analysis assesses tremor frequency, amplitude and central oscillator by using accelerometry and electromyography (EMG) combined with Fast Fourier Transformation analysis. While reasonable criteria are available to distinguish between centrally and peripherally mediated tremors by using the automated tremor analysis, it is still challenging to differentiate between different types of central tremors (Deuschl et al. 1996). Consistently, automated tremor analysis is not routinely used in clinical practice for the differential diagnoses of central tremor syndrome. By using a digitizing tablet, tremor characteristics such as frequency, direction, and amplitude can be detected and quantified, as well as drawing speed and acceleration, loop-to-loop width tightness and drawing pressure over time (Pullman 1998).

Bhidayasiri and co-workers developed a 3-dimension inertial sensor to automatically assess tremor (Bhidayasiri et al. 2014). The tilting angle relative to the gravity, the linear acceleration and the angular velocity of the tremor affected body parts are measured by a 3-axis accelerometer and a 3-axis gyroscope. PD tremor and tremor due to essential tremor (ET) show specific features in the analysis, but cannot yet be consistently differentiated. The costs of the production of the system including the analysis software are estimated by $500 (Bhidayasiri et al. 2014). Similar results were reported for the differential diagnosis of resting tremor in PD versus drug-induced parkinsonism (Jang et al. 2013). In contrast to previous studies using conventional tremor analysis systems or wearable sensors

(Deuschl et al. 1996; Bhidayasiri et al. 2014), Wile and co-workers showed sufficient discrimination between postural tremor due to PD and ET using a smart watch-based tri-axial accelerometer (WIMM One, CA) tightly affixed to the dorsum of the predominantly affected (Wile et al. 2014). They compared data from short-time recording with a traditional analog accelerometer system. Data collection time was estimated as approx. 5 min in a clinical setting. The mean harmonic peak power was both highly sensitive and specific (both >90 %) for distinction of PD postural tremor from ET (Cohen's $\kappa = 0.91 \pm 0.08$). The reasons for this discrepancy remain unclear from the report and are not discussed in detail.

Together, several accelerometer-equipped watches or mobile medical apps are on the market to record tremor in home settings (Table 1). Notably, the Food and Drug Administration (FDA) has recently reported that it will apply the same risk-based approach the agency uses to assure safety and effectiveness for other medical devices, but does not necessarily regulate mobile medical apps or app stores or mobile phones or tablets. Therefore, caution must be exercised when applying any of these apps in professional patient care or clinical studies. Wearable devices do not provide accurate and diagnostically relevant information about various types of tremor [theoretically, orthostatic tremor can be distinguished from PD tremor by its higher tremor frequency (Deuschl et al. 1996), but no such data are available for wearable devices]. Although the determination of tremor severity (amplitude) needs careful (intraindividual) calibration, the portability and ease of use could help to translate these techniques into routine clinical use. Tremor analysis or devices does not reach clinical significance in daily routine yet and their suitability to improve patient care including health-related quality of live (hr-QoL) needs to be demonstrated in prospective clinical studies.

Gait

In PD, a bent forward, shuffling gait, reduced step length, and reduced gait speed is very common. In later stages also impaired gait initiation is observed. Postural instability is an axial symptom due to the loss of postural reflexes and rather typical for advanced PD. The pull-test is performed to rate postural instability (Morris et al. 2001). During this test, the clinician gives a moderately backward push on the standing patient and observes the reaction. The common response is a quick backward step to prevent falling. PD patients might tumble backwards and have to be caught in order to prevent falling. A clinical scoring tool for gait is the "Timed-Up-and-Go" Test (Podsiadlo and Richardson 1991). This test assesses the patient's mobility and balance. The time that is needed to rise from a chair, walk three meters, turn around, walk back to the chair, and sit down is recorded. Depending on the duration in seconds, the degree of immobility can be predicted. A strong inter-rater and retest variability particularly for PD patients has been shown (Morris et al. 2001). The functional ambulation performance (FAP) score is a quantitative tool for assessing gait based on specific spatial and temporal gait parameters and may distinguish between selected gait characteristics of patients with early PD and of non-impaired individuals (Gouelle 2014; Nelson et al. 2002).

Objective gait analysis was introduced by using high-speed camera-based 3D gait analysis systems to measure all gait parameters such as velocity, cadence (steps per minute), swing time, stride length, and step length. The GAITRite® gait analysis system is another stationary technology employing a pressure-sensitive walkway to record gait variations. We do not discuss these systems in this review [please refer to (Muro-de-la-Herran et al. 2014), (Nelson et al. 2002; van Uden and Besser 2004; McDonough et al. 2001) for details].

During the recent years, wearable accelerometer- and/or gyroscope-based gait analysis systems were developed to provide an easily accessible and a more continuous (long-term) gait monitoring. These new developments do not only allow to measure all standard gait parameters (Muro-de-la-Herran et al. 2014; Tao et al. 2012), but in combination with innovative intelligent technology (IT) also provide features classifying PD itself and its disease stages and motor impairment (Klucken et al. 2013; Barth et al. 2011; Del Din et al. 2015). Barth and colleagues reported high sensitivity and specificity (both >85 %) for the classification of PD patients and healthy control and, in addition, high accuracy in staging PD gait (Barth et al. 2011, 2012). In a follow-up study, the same research group reported mobile, biosensor based gait analysis using IT (Klucken et al. 2013). The system consists of both accelerometers and gyroscopes integrated into the shoes record motion signals during standardized gait sequence. Numerous features were extracted from the sensor signals (>650 features) and pattern recognition algorithms were applied to classify PD and its disease stage. The system showed a high rate of correct disease classification of 81–91 % depending on disease severity or stage and good agreement with clinical disease severity measures such as UPDRS part III motor score. The results were confirmed in a second and independent patient cohort. Del Din and colleagues went on this track by comparing a single triaxial accelerometer with the instrumented walkway GAITRite® for quantifying several gait characteristics in PD compared to healthy age-matched controls (Del Din et al. 2015). They were particularly interested in asymmetric features of PD gait problems. Agreement between the two methods was

excellent (ICCs >0.9) in only 30 %, but poor-to-moderate in 70 % of gait features. Interestingly, accelerometry seems to provide a higher sensitivity to detect motor problems, most likely due to its continuous measure characteristics.

Together, the new wearable devices are able to detect numerous gait characteristics in a continuous fashion (in real life), which might be useful not only to analyze gait disturbances but also as surrogate markers for motor impairment in general as well as disease progression. Whether this information is helpful as complementary information for the daily clinical workup to support therapeutic decisions throughout the course of the disease needs to be clarified in prospective studies.

Bradykinesia

Bradykinesia is defined as slowness of movement in initiation and execution (Yanagisawa et al. 1989). In PD bradykinesia is mainly presented as fatiguing and decrement in size of repetitive movement. The UPDRS and MDS-UPDRS are common clinical means to rate bradykinesia in PD patients (Fahn et al. 1987; Goetz et al. 2008c). There are several attempts to quantify bradykinesia in PD, most of them are based on accelerometry (in some cases combined with a gyrostat) or gait analysis. Most gait parameters as measured using the GAITRite® system showed significant correlations existing between Off–On improvement in gait parameters ("Timed-Up-and-Go" test) and in UPDRS III score (Chien et al. 2006). Among gait parameters, stride length seems to be the most effective indicator of bradykinesia.

Current approaches use various wearable inertial sensors (accelerometer with or without gyroscopes) integrated in shoes, watch-like devices or sensors placed on different body parts to measure movements including gait patterns (Tsipouras et al. 2012; Griffiths et al. 2012; Maetzler et al. 2013; Klucken et al. 2013; Barth et al. 2011; Patel et al. 2008, 2009). In most cases, the device is combined with the investigation of specific motor tasks: Palmerini and coworkers used the standard "Timed-Up-and-Go" test in combination with a single accelerometer fixed to the lower back (Palmerini et al. 2013). The authors calculated various features from all parts of the test, and found that a subset of three features (two from turning, one from the sit-to-stand component) combined with a classifier (linear discriminant analysis) have the best accuracy for the discrimination between healthy and mild PD patients. Recent studies showed that various gait parameters measured by wearable sensor-based devices strongly correlate not only with the disease state, but also with bradykinesia scores (Barth et al. 2011, 2012; Klucken et al. 2013; Del Din et al. 2015). Together, the data provided so far using wearable sensors and specific motor tasks suggest that these methods can characterize PD motor impairment and might be useful for prospective follow-up and monitoring of disease progression. Such prospective studies are warranted to confirm both their practicability and validity in long-term approaches.

As another example, the Parkinson's Kinetigraph (PKG) logger measures movement accelerations of the wrist and analyses the spectral power of the low frequencies of accelerometer data providing a continuous variable—namely the median bradykinesia and dyskinesia scores—as described by Griffiths and colleagues (Griffiths et al. 2012). In contrast to most other studies, the recordings were performed over several days during normal daily life. There are strong correlations of the PKG output not only with clinical scores of bradykinesia and dyskinesia, but also with levodopa effects. The use of only accelerometry (not combined with gyrostatic measurements) allows for wireless long-term recordings without the need of battery recharge potentially suitable to measure treatment effects. A similar approach was used by Louter and colleagues by using a triaxial accelerometer-based sensor during nighttime sleep (Louter et al. 2015). They found that mean acceleration of nocturnal movements was lower in patients with PD compared to controls, while frequency and speed of axial movements did not differ between patients with PD and controls. The authors did not report test characteristics such as sensitivity/specificity for the diagnosis of PD, but show that motor problems in sleep occur early in the disease course. Together, by reviewing the current data, bradykinesia and its severity are accurately detectable with wearable sensors (accelerometry) in specific motor tasks and during normal life.

Dyskinesia and motor fluctuations

Another approach using wearable sensors is to objectively measure dyskinesia and motor fluctuations in PD patients. Dyskinesia and motor fluctuation occur in advanced stages of PD and are considered as levodopa induced side effects. The UPDRS and MDS-UPDRS are common clinical means to rate dyskinesia and motor fluctuations in PD patients (Fahn et al. 1987; Goetz et al. 2008c). The Unified Dyskinesia Rating Scale and the modified abnormal involuntary movement scale (mAIMS) are further commonly used rating scales for clinical assessment of dyskinesia (Goetz et al. 2008b; May et al. 1983). For the estimation of motor fluctuations, the PD home diary (Hauser et al. 2000, 2006) as well as home video recording (Goetz et al. 2008a) are validated and frequently used in both clinical routine and clinical trials. Both techniques are based in subjective clinical rating, in the case of the PD home diary by the

patient itself (usually after a training session) or in the case of home video recording by the analyzing/treating neurologist.

There are several studies reported in the literature using wearable sensors to detect dyskinesia. As an example, Tsipouras and colleagues used signals from several accelerometers and gyroscopes, which are fixed to various parts of the subjects' body while they were performing a series of standardised motor tasks as well as voluntary movements, to measure levodopa-induced dyskinesia (Tsipouras et al. 2012). The recordings were analyzed to classify LID symptom severity in comparisons to clinical annotation of the signals. The sensitivity and positive predictive values were approx. 80 %. Pulliam and co-workers used the KinetiSense motion sensor units (Great Lakes NeuroTechnologies, Cleveland, OH) containing a triaxial gyroscope and triaxial accelerometer on three body parts and compared the results with mAIMS rating (Pulliam et al. 2014). The authors found that dyskinesia scores predicted by the model using all sensors were highly correlated with clinician scores (correlation coefficient of 0.86) and accurate predictions were maintained when two sensors on the most affected side of the body were used. Although it is difficult to compare the various approaches, because they used different technologies as well as recording modes (random voluntary movement, specific motor tasks, etc.), the accuracies of the approaches when compared to clinical estimation of dyskinesia (video rating, mAIMS, UPDRS) are high and around or above 90 % (Keijsers et al. 2000, 2003; Patel et al. 2008; Tsipouras et al. 2011, 2012; Griffiths et al. 2012; Pulliam et al. 2014).

In a series of reports, Patel and co-workers reported the use of data from multiple accelerometers fixed to various body parts to assess the severity motor complications (Patel et al. 2008, 2009). They implemented a support vector machine classifier by using various kernels to calculate severity of tremor, bradykinesia and dyskinesia and compared these data with clinical video-ratings by experienced neurologists. The optimal time window to derive data segments and extract features from the accelerometer time series was estimated as 5 s, while allowing the utilization of recordings of only 30 s. Although differences were observed among estimation error values for the different motor tasks performed during the recordings, several motor tasks performed equally well. This suggests that the proposed accelerometer features capture aspects of the movement patterns most likely not specific to a distinct motor task. Horne et al. recently introduced an objective fluctuation score calculated out of data from a watch-like accelerometer by summing the interquartile range of bradykinesia scores and dyskinesia scores (see above for details on algorithms for score calculations) produced over several days expressing it as an algorithm (Horne et al. 2015). The score distinguished between fluctuating and non-fluctuating patients with high sensitivity and selectivity (approx. 97 and 88 %, respectively). Deep brain stimulations reduced the score leading to values in a band just above the score separating fluctuators from non-fluctuators, suggesting that this score might be sensitive to treatment effects.

Together, current data strongly suggest that wearable sensor-based devices are able to accurately measure overall dyskinesia and motor fluctuations not only during specific motor tasks, but also during random voluntary movements in the context of daily life.

Discussion and outlook

We summarized here some of the recent advantages in estimating motor function deficits in PD by using objective wearable technologies, that use accelerometer and gyroscope data. It is very likely that further advantages in battery technology, movement sensors and information technology will help to translate these technologies further into the clinical routine and/or as endpoints in clinical trials. However, there are several open questions coming with these devices: (1) Although it was shown that some devices or technologies are helpful to distinguish between PD patients and healthy controls, their validity in the differential diagnosis of movement disorders and the predictive values for PD or other movement disorders in the premotor or very early disease stage remain enigmatic. Gait analysis or nocturnal motion tracking might serve as surrogate markers. (2) There is growing evidence that wearable sensors can aid in selection of candidates for specific therapies such as deep brain stimulation [see (Lieber et al. 2015) for review], but there are no controlled/randomized and prospective data confirming these evidences. (3) Which sensor fixed to which body part is best in detecting the various motor dysfunction. Most studies used triaxial accelerometry adjusted to extremities and/or the lower back, in some cases combined with gyroscope measures (mainly in gait analysis). There are no conclusive data, how many sensors are needed and which body part is best in detecting motor impairment. A survey in patients (in this case mainly patients with arthritis) revealed a high interest in wearable devices, but the system needs to be small, discreet, unobtrusive and preferably incorporated into everyday objects (like watches). The upper extremity was seen as the favoured position, while invasive placement yielded high levels of acceptance. The users are then willing to wear the device for more than 20 h a day (Bergmann et al. 2012). Of note, current battery technology does not allow long-term recordings from gyroscopes due to their high energy demand. (4) There are not controlled

data confirming the promising data from the rather small cross-sectional studies reported above that data from wearable sensor-based devices leads to better treatment decisions and better patient care and that these data are valid outcome measures in clinical trials. However, the introduction of wearable accelerometer and/or gyroscope-based sensors in conjunction with IT to measure movements will help to gain access to these quantification methods for both patient care and clinical trials and allow long-term continuous monitoring including motor fluctuations.

In conclusion, the suitability and/or practicability of data obtained from wearable sensor-based devices as endpoints in clinical trials as well as to improve routine clinical care of PD patients remain enigmatic and need confirmation from controlled and prospective studies.

Compliance with ethical standards

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