HHS Public Access

Author manuscript

Mov Disord. Author manuscript; available in PMC 2021 May 12.

Published in final edited form as:

Mov Disord. 2019 May ; 34(5): 676–681. doi:10.1002/mds.27673.

The Parkinson's Disease e-Diary: Developing a Clinical and Research Tool for the Digital Age

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Relevant conflicts of interest/financial disclosures: None of the authors have anything to declare.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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As a consequence of limitations in current pharmacotherapy, the symptoms of patients with Parkinson's disease (PD) may fluctuate throughout the day, impacting functional ability and quality of life.[1] A diary has been the most common method for assessing fluctuations in symptoms in research settings. Diaries enable patients to monitor daily symptoms at specified intervals and report their severity, frequency, and duration for a limited repertoire of predominantly motor symptoms dichotomized into "ON" (defined variably as "good" response to dopaminergic treatment) or "OFF" (poor response to dopaminergic treatment) states. Prioritizing simplicity, most diaries consider dyskinesia exclusively as an ON-state phenomenon, and divide it into whether it interferes with overall function (troublesome) or does not interfere (nontroublesome).[2,3] Emphasis on the development of treatments designed to "reduce OFF" or "increase ON" time has limited attention to common intermediate, transitional, and nonmotor states that may not squarely fall into 1 of these 2 states.

Current Gaps in PD Diaries and Strategies to Address Them in an e-Diary

PD diaries have provided valuable information often as primary end points in clinical trials of symptomatic therapies over the past 20 years. Two diaries (Parkinson Disease Home Diary and CAPSIT-PD Diary) have been designated as "recommended" by the MDS Task Force on Rating Scales. Nonetheless, these 2 diaries have the caveat that limited data exist regarding their validity, compliance, and completion,[4] and their assessment is implicitly linked to the presence of motor fluctuations.[5,6] A systematic literature search found a total of 12 published PD diaries, for which a narrative review (Supplementary material 1) and quality criteria (Supplementary material 2) are available online. The phenomenological, contextual, and clinimetric gaps identified in existing diaries as well as the potential strategies to correct them are listed in Table 1.

In recent years, the advent of new technologies has introduced the opportunity to redesign this diary tool. Current diaries are almost exclusively designed in paper format (or in an electronic format that resembles paper diaries). Newer digital methods should enable the capture of a wider range of individualized motor, nonmotor, and circadian complex fluctuations with greater accuracy as an electronic diary/tracker interface (e-Diary). With the aim of bringing the PD diary into the digital age, the MDS Technology Task Force and the MDS Rating Scales Program Electronic Development Ad-Hoc Committee elaborated a set of desirable characteristics and developmental steps for a technology-enhanced e-Diary,

usable in both clinical practice and treatment trials. At the request of *Movement Disorders* editors, a draft of this article was made available on the MDS website (movementdisorders.org/MDS/Resources/2018/PD-Diary.htm) to facilitate public comments on the proposed road map between October 7 and November 7, 2018. The MDS Secretariat sent an email invitation to MDS members and 2 reminders within that time frame. Supplementary material 3 contains a summary of the feedback, highlighting the suggestions that prompted changes into the final document contained in this article.

Desirable Characteristics of a PD e-Diary

1. *Phenomena recognition*. A diary must focus on capturing key symptoms and signs that correlate with clinically pertinent fluctuations in motor and nonmotor function. Two archetypal states have been defined in research settings, anchored on motor fluctuations (MFs) but also adaptable to nonmotor fluctuations (NMFs): "OFF," the clinical condition reflective of no treatment effect, and "ON," associated with full and effective treatment. However, patients often experience partial, transitional, or "gray-zone" states throughout the day that cannot be dichotomized into full ON or OFF states. Further, dyskinetic and dystonic behaviors can develop during ON, OFF, and transitional states, so that diaries that restrict them as subcategories of ON are conceptually and operationally inadequate. Another important metric with direct implications in therapeutic decisions is functional status, which can vary independently of the duration and severity of fluctuations. Finally, because the biological, pharmacological, and clinical relationships between MFs and NMFs have not been clarified, an ideal diary tool should not implicitly link them and must allow for independent registration of different symptoms.

2. *Patient language*. If the terms "OFF" and "ON" are to be used, definitions must be clearly outlined. The definitions should incorporate both motor and nonmotor symptoms. Testing patients' understanding of definitions must be conducted during the development phases to ensure adequacy of language, content, and health literacy.[7,8] This practice can lead to the modification of items to increase the precision of self-reported measures.[9,10] Video-based training sessions and standardized instructions can be developed for ensuring validation.[11] Following these steps should render the final diary intuitive for patients, minimizing the need for additional training in subsequent clinical or research uses.

3. *Administration and data collection*. The adequate frequency or duration of recording needed to capture MFs and NMFs to define a baseline pattern and to evaluate treatment response is still unknown. Regardless, frequency of assessments and method of state determination (averaged over a period or in real time) must be tailored to clinical or research settings. Current diaries predominantly use the "averaged over a period of time" method. Even with these efforts, however, studies using similar instructions stress the "peak-end rule" that dominates human behavior, judging an epoch for its worst or best point or its state at the moment of the assessment.[12] Such averaging can be cognitively

challenging and may increase measurement errors and recall bias, even in the absence of cognitive impairment.[13,14] Compliance of data recording and frequency of missing or erroneous data collection must be recorded. Accurate sleep and wakefulness detection is necessary. Medication — and possibly meal — intake tracking is required to recognize their influence on MFs and NMFs. One advance of electronic methods is that alerts and interactive involvement may enhance valid data collection. Finally, data should be protected and kept confidential.

4. *Diary format and data visualization*. An accessible interface would ideally include visual results and feedback to the patient in the form of percent completed and progress reports, independently tailored for clinical care and research settings. Visualization of the *evolution* of fluctuations over time could be an added value of such an e-Diary. An inviting interface, such as currently applied by wearable fitness technologies and exercise devices, may serve to stimulate long-term compliance with an e-Diary.[15] Flexibility in this capacity (on-off switch for "shared feedback") could help adaptability for research and clinical settings.

5. *Data and clinimetric properties*. Desirable measurement formats include active (requiring input by patients, eg, questions or tasks) and passive data collection (not requiring input by patients). Visual analog scales (VASs) are ideal to use for nondichotomous questions in active data collection, can be used by patients with cognitive impairment, and are very sensitive to small intrapersonal changes.[16–19] Wearable sensors (see below) may be ideal for passive MF and NMF assessments. Regardless of the methods employed, understanding the instruments' clinimetric properties is important. Validation methods may include internal consistency (Cronbach's alpha), construct validity (convergent, divergent, known groups), patient-clinician agreement, predictive validity calculations, cross-cultural validation, and factor analyses, among other methods. Reliability assessments with test-retest calculations are acceptable, but not desirable as a sole method because of the fluctuating nature of the latent variables. Above all, demonstration of how patients feel or function is of the utmost importance in defining utility and relevance.

6. *Technology-based objective measures*. An e-Diary/tracker would allow tools such as surveys and VASs to be administered regardless of time or place. Advanced hardware components, such as accelerometers, gyroscopes, microphones, radio signals, among other wearable sensors, can provide complementary action-dependent and action-independent objective measures.[20,21] Active data collection should be tailored for motor and nonmotor symptoms. Examples for motor symptoms include spiral drawing, finger tapping, and voice characteristics and for nonmotor symptoms, assessments of visual performance and short-term memory.[20,22–25] Passive measures should be obtained in an unsupervised and unobtrusive fashion,[26] recorded preferentially during patients' daily regular activities. One hope is that in the future, passive tracking should capture a subset of relevant MFs and NMFs.[27–30] Smartphones,

increasingly being used across all age groups, are ideally suited for the e-Diary development, allowing for an ever-present yet unobtrusive and ecologically valid data collection.[6,31,32] Challenges related to the technological development include the costs associated with software and hardware development and maintenance, patient/health provider interface configuration, and regulatory difficulties with data storage, confidentiality, and management. Challenges related to usability, on the other hand, include possible issues of long-term compliance with active measures and the requirement to navigate an application, which might be difficult in the setting of motor disability or poor literacy of digital health technologies.[33] Incorporation of artificial intelligence methods would be expected to minimize the need for active measures, as "learning" from their initial integration into passive data serves to eventually "predict," in their absence, the patient-relevant motor, nonmotor, and functional states.

Next steps: Milestones for the Development of the PD e-Diary

We propose a development plan to construct an e-Diary that harnesses the complementary role of diaries (eg, assessments of data meaningfulness based on patient feedback) and wearable sensors (eg, continuous, objective measures, independent of patient feedback). The scope and features of an e-Diary/tracker will require tight collaboration in all developmental phases between all stakeholders, including clinicians, technology developers, regulatory experts, scientists from industry, caregivers, patient advocacy groups, and especially patients. This tool development may benefit from guidelines from the Food and Drug Administration,[34] the Clinical Trials Transformation Initiative,[35] and the Electronic Patient-Reported Outcome Consortium,[36] among others. The new e-Diary should be built on an open-access data management concept, preferentially with the endorsement of the International Parkinson and Movement Disorders Society to standardize the mechanism for technology developers to gain regulatory approval, assist in improvements of the instrument over time, and contribute to its wide acceptance and adherence. Here, we outline the specific developmental milestones suggested by consensus.

- *First milestone: minimal viable product*. A fully functional "minimal viable product" would consist of a wireless-enabled, secured, web-based e-Diary of patient-reported outcomes. The elements to be considered for this first step will require the prioritization of patient-relevant outcomes, as outlined in a parallel ongoing effort by the MDS Task Force on Technology. Optimization of existing data-capturing methods and technologies could facilitate the assessment of partial medication states, NMF reporting, medication tracking, and functional assessments. Some existing instruments (eg, NMSQuest,[37] NoMoFa,[38] Wearing-Off Questionnaire[39]) and PROMIS (Patient-Reported Outcomes Measurement Information System) could assist this process by providing relevant items to the construction of the e-Diary. Verification and validation processes should start at this step and continue throughout the development.[35]
- *Second milestone: integration of action-dependent metrics*. Selection of hardware components (eg, accelerometers, gyroscopes, microphones, among

others) and development of software will be tailored to acquire action-dependent data. Individualized assessments for motor (eg, spiral drawing, finger tapping) and nonmotor (eg, visual performance, memory) symptoms could be selected according to patient-reported relevance and feasibility.

- *Third milestone: incorporation of action-independent metrics*. Hardware components selected in previous steps, potentially including available wearable devices, could be optimized for passive data gathering, enabling the "tracker" functionality.
- *Fourth milestone: algorithm development, improvement, and simplification*. A desired final step will be the analysis and integration of diary data and active and passive recordings with hypothesis-driven and machine learning algorithms. Such algorithms must control for the state and setting in which patients enter action-dependent measures into the diary (for instance, dyskinesia might be interpreted differently in a patient with versus without anxiety, the former possibly magnifying its severity). The end point is the transformation of patient data into individualized current and predictive feedback to patients themselves, providers, and caregivers for both self-guided behavioral changes and facilitation of personalized management decisions by clinicians.

The feasibility of an e-Diary has been demonstrated by recent smartphone-based "rating scores." A recently introduced mobile application combines active and passive data gathering,[40] whereas another mobile application uses active-only data.[25] In both cases, data were processed with machine-learning algorithms, yielding adequate reliability and validity metrics.[25,40] Major unknown variables include the heterogeneity of PD and the extent to which integration of an e-Diary, daily or intermittently, is capable of enhancing patient empowerment for long-term sustainability. Further, the use of a new tool will be different if applied in clinical research (limited time) or in "real life," both for patients and, through a separate interface, for their caregivers.

Conclusions

The highly dynamic and user-friendly technological advances of recent years enable the development and validation of an accepted e-Diary/tracker that simultaneously assesses MFs and NMFs and uses action-dependent and action-independent end points for clinical management and research efforts. An e-Diary can be patient-friendly and intuitive as well as capable of providing real-time feedback to the patient (empowered to influence any state) and clinician to ensure widespread use and long-term adherence. The time has come to move beyond the simplistic dualism of "ON" and "OFF" states of paper diaries and reconfigure this important source of clinical information for care and research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

We thank all MDS members who provided feedback during the public comment phase.

Funding agencies: Nothing to declare.

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TABLE 1.

Gaps in current (paper) diaries and strategies to address them in an e-Diary

	Gap in current diaries	Strategies for correction in an e-diary
Essential limitations	Absence of nonmotor fluctuations	Although separate nonmotor fluctuations tools are under development,[38] nonmotor fluctuation assessment within a diary is needed.
	Incomplete definitions of OFF and ON states	Expand the repertoire of motor behaviors and include nonmotor fluctuations. Combine real-time assessments with wearable sensors and e-Diary tracking.
	Underrepresentation of partial states	Partial states can be recognized by patients and add granularity to transitional states. OFF and ON states may be replaced with measurement of symptom and disability severity along a continuum.
	Inaccurate and partial reporting of motor complications	Allow for independent recognition of peak dose and diphasic dyskinesia and OFF-associated dystonia. Allow for separate/complementary input by spouse or other immediate caregiver.
	Lack of functional assessment	Allow for quantification of functioning that accounts for the wide nature, duration and severity of OFF periods at any “level” of fluctuation.
Contextual limitations	Absent cognitive debriefing	Conduct cognitive debriefing to improve items and increase the precision of self-reported measures.
	Heterogeneous frequency of assessments	Evaluate real-time assessments with or without variably spaced frequency of assessments.
	Data integrity limitations	Compliance assessment and improved patient interface can be implemented with electronic diaries.
	Absent medication tracking	Implement medication tracking to correlate with function and assist with management strategies.
	Absent meal type and sleep quality	Implement meal tracking and sleep quality recording to determine effect on response to medications.
Clinimetric limitations	Subjective information without objective measures (trackers)	Implement a smartphone-based application with integrated action-dependent and action-independent (wearable sensors) symptom measures.
	Heterogeneous measurement formats and validation methods	Adopt visual analog scales as measurement format and anchor metrics on patient-relevant outcomes.

Other limitations for all diaries include episodic and categorical assessment for continuous behaviors, lack of determination when assessment is completed, and undefined time to completion.

Mov Disord. Author manuscript; available in PMC 2021 May 12.