REVIEW

Wearing-Off Scales in Parkinson's Disease: Critique and Recommendations

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ABSTRACT: Wearing-off occurs in the majority of patients with Parkinson's disease after a few years of dopaminergic therapy. Because a variety of scales have been used to estimate wearing-off, the Movement Disorder Society commissioned a task force to assess their clinimetric properties. A systematic review was conducted to identify wearing-off scales that have either been validated or used in Parkinson's patients. A scale was designated "Recommended" if it had been used in clinical studies beyond the group that developed it, if it had been specifically used in Parkinson's disease reports, and if clinimetric studies had established that it is valid, reliable, and sensitive. "Suggested" scales met 2 of the above criteria, and those meeting 1 were "Listed." We identified 3 diagnostic and 4 severity rating scales for wearing-off quantification. Two questionnaires met the criteria to be Recommended for diagnostic screening (questionnaires for 19 and 9 items), and 1 was Suggested (questionnaire for 32 items). Only the patient diaries were Recommended to assess wearing-off severity, with the caveat of relatively limited knowledge of validity. Among the other severity assessment tools, the Unified Parkinson Disease Rating Scale version 3 and the version revised from the Movement Disorders Society were classified as Suggested, whereas the Treatment Response Scale was Listed. © 2011 *Movement* Disorder Society

Key Words: Parkinson's disease; wearing-off; clinimetrics; psychometrics; rating scales; validity; reliability

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Treatment of idiopathic Parkinson's disease (PD) with dopaminergic therapy in the early stages is usually associated with significant improvements in mobility and tremor suppression. However, within 2–5 years of therapy,[1] whether with levodopa alone or levodopa and a dopamine agonist, the majority of PD patients report a decline in the duration of benefit with each medication dosing cycle, a phenomenon commonly termed ''wearing-off.''

TABLE 1.

	Criteria			
	Used in PD	Used in PD beyond original developers	Successful clinimetric testing	Total number of required items
Recommended	X	X	X	3
Suggested	X	X	0	2
Listed	X	0	0	1

Wearing-off has been defined by some authors as a generally predictable recurrence of motor and nonmotor symptoms preceding scheduled doses of antiparkinsonian medication that usually improve postdosing.[2] Although no formal consensus definition of wearing-off exists, the predictability of wearing-off differentiates it from ON–OFF phenomena, which are often unpredictable. For some patients, wearing-off frequently also includes reappearance of nonmotor symptoms such as anxiety, fatigue, mood changes, difficulty in thinking, restlessness, sweating, or increased salivation.[3] Recent studies have reported that up to 50% of patients show the onset of motor fluctuations as early as 2 years after starting levodopa therapy[4] or even within 5–6 months.[5,6]

Because of the impact of wearing-off on the global disability, activities of daily living, and quality of life of PD patients, the Movement Disorder Society (MDS) organized a systematic review of the clinimetric properties of the scales used for its assessment.

Materials and Methods

Administrative Organization and Critique Process

The steering committee of the MDS Task Force on Rating Scales for PD invited the chairman (A.A.) to form a task force to critique existing motor wearing-off rating scales. This group followed the same working methods as the task forces that critiqued other rating scales like those for anxiety,[7] apathy,[8] depression,[9] psychosis,[10] dyskinesia,[11] and fatigue[12] in PD. The review used a pro forma that includes descriptive properties, availability, content, use, acceptability, clinimetric properties, and overall impression in patients with PD.[7–12]

The aim of this process was to identify all published scales that (1) could be used as diagnostic screening tools to establish the presence or absence of wearing-off and (2) could be used to assess the severity of the problem. Although many patients with wearing-off and other motor fluctuations often have coexistent dyskinesias during their ON time, this report does not focus on dyskinesias, which are the subject of another report in this series (Table 1).[11]

Each scale was reviewed by 2 task force members. The completed reviews were then assessed by all other members following terminology used in the development of the Appendix of ancillary scales to complement the MDS-sponsored revision of the UPDRS.[13]

The official definitions for the critiques are: ''Recommended'' if it has been applied to PD populations, if there are data on its use in studies beyond the group that developed the scale, and if it has been studied clinimetrically and found to be valid, reliable and sensitive to change; ''Suggested'' if it has been applied to PD populations, but only 1 of the other criteria applies; or ''Listed'' if it meets only 1 of the 3 criteria defined for Recommended scales. As an official MDS document, this report was submitted and approved by the Scientific Issues Committee of the MDS before submission to *Movement* Disorders.

Literature Search Strategy

All scales that have been designed to assess wearing-off or Off time and have been either validated or used in studies with PD patients were included in the review.

Medline on PubMed was systematically searched for relevant articles published until June 2010. Only published peer-reviewed articles were included in this review.

Results

Identified Questionnaires and Scales and Their Utilization in Clinical Practice and Research

We identified 3 diagnostic screening questionnaires[14–17] and 4 severity scales (UPDRS[18] and MDS-UPDRS, the Treatment Response Scale, and patient diaries used to quantify OFF time) (Table 2). The Florida Surgical Questionnaire for Parkinson Disease,[19] which includes a single item on the presence of

TABLE 2. Overview of scales assessed and their classification

	Applied in PD	Applied beyond original authors	Screening properties tested	Qualification
Screening Questionnaires				
Wearing-Off Quest (32 items)	Yes	Yes	Yes	Suggested
Wearing-Off Quest (19 items or Quick)	Yes	Yes	Yes	Recommended
Wearing-Off Quest (9 items)	Yes	Yes	Yes	Recommended
Scales				
UPDRS-III	Yes	Yes	Yes	Suggested
MDS-UPDRS-IV	Yes	Yes	Yes	Suggested
Treatment Response Scale (TRS)	Yes	Yes	No	Listed
Motor Fluctuation Diaries	Yes	Yes	Yes	Recommended[q]
CAPSIT-PD Diaries	Yes	Yes	Yes	Recommended[a]

[a]Recommended with certain caveats (refer to text for full description).

motor fluctuations, was not included as it also required the presence of dyskinesia within the same item.

Diagnostic Screening Scales for Wearing-Off: The Wearing-Off Questionnaires

The authors of this questionnaire developed 3 versions of a patient survey based on a review of the literature and a consensus view.[14] Thirty-two motor and nonmotor symptoms were incorporated into the survey (the WOQ-32). Nineteen of the 32 symptoms were subsequently found to be statistically relevant for inclusion into the WOQ-19 (also called ''QUICK''). Data were further reassessed to focus on the 9 symptoms (WOQ-9) believed to be the most ''important'' or significant of the original 32 symptoms in terms of wearing-off.[16]

Questionnaire Application in PD

The WOQ-32 was evaluated in 289 PD patients.[14] Two studies have evaluated translated versions of the WOQ-19.[20,21] The sensitivity and specificity of the WOQ-9 has been studied in the United States.[22]

Use in Studies by Groups Other Than Original Developers. The WOQ-19 has been used in a number of studies as a screening tool to try to identify patients in the early stages of wearing-off. The WOQ-9 has recently been used as a screening tool in an open-label 6-week study that evaluated the efficacy of entacapone formulations.[23] Because of the rapid recruitment rate for this study, it was suggested that the use of such tools aids in the more rapid identification of PD patients currently experiencing wearing-off.[23,24]

Clinimetric Properties. The sensitivity and specificity of the WOQ-9 as a screening tool for the recognition of wearing-off were compared with a standard neurologist assessment in 216 PD patients.[22] The WOQ-19 was evaluated in 222 patients.[17]

Strengths. The WOQ-32, WOQ-19, and WOQ-9 forms are in the public domain and have been specifically designed to screen for the presence/absence of motor and nonmotor symptoms related to wearing-off in PD. The WOQ-19 and WOQ-9 have been found to possess adequate screening properties for the detection of wearing-off. However, the specificity of the WOQ-9 has been reported to be low. Whether this reflects poor specificity or underrecognition of wearing-off needs further clarification.

Weaknesses. All 3 versions depend on the patient understanding wearing-off. The scales cannot be used as rating instruments of the severity of wearing-off.

Final Assessment. The WOQ-32 is a Suggested diagnostic screening tool for wearing-off because it has been used in PD and has been used by authors other than the developers, but there are insufficient clinimetric data on it. The WOQ-19 and WOQ-9 can be considered Recommended diagnostic screening tools for screening for the presence/absence of wearing-off in PD because they also have undergone at least some clinimetric testing. The task force members suggest that further clinimetric studies including further tests of specificity and sensitivity in a larger cohort be assessed with the WOQ-19 and WOQ-9.

Scales to Assess Severity of Wearing-Off

Assessment of the severity of wearing-off fluctuations can be challenging, as factors such as the amount of time spent OFF and the intensity of the difference between ON and OFF episodes should be taken into account. The group found that the following scales did not differentiate between wearing-off and other motor fluctuations.

Unified Parkinson's Disease Rating Scale (UPDRS)

Description of the Scale. The UPDRS version 3 is the most widely used clinical rating scale for PD.[18] The 4 questions related to motor fluctuations (section IV) refer to the past week and ask about patient or caregiver perception of the presence or absence of: predictable OFF periods, unpredictable OFF periods, OFF periods that come on suddenly, and the proportion of the waking day the patient is OFF on average.

Scale Application in PD. The UPDRS was designed specifically for PD patients. It has been applied across the spectrum of PD from very early patients with mild disease and no motor fluctuations to patients with advanced disease, motor fluctuations, and dyskinesias. The UPDRS Part IV has been included as a primary outcome in a DBS study.[25]

Use by Multiple Groups Outside the Original Developers. Since its introduction, the UPDRS has been the most used outcome measure in PD clinical trials.[26]

Clinimetric Properties. No clinimetric work has been performed on the wearing-off items.

Strengths. Because of its widespread use in clinical practice and research, the UPDRS offers excellent comparability among centers and studies.

Weaknesses. The 4 questions relating to motor fluctuations, 3 of which are simple yes/no options, represent a relatively crude measure. Moreover, section IV is structurally inconsistent in that it consists of

dichotomous (yes/no) and 5-point options, making this section itself, as well as the scale as a whole, difficult to analyze together.

Final Assessment. The UPDRS is formally considered a Suggested scale for the rating of severity of wearing-off.

MDS Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

Description of the Scale. Because of relevant limitations of the UPDRS scale,[26] an ad hoc Task Force of the Movement Disorder Society (MDS) developed a revision termed the revised MDS-UPDRS.[13] In this version, section IV contains three 5-point items covering wearing-off duration, functional impact, and complexity.

Scale Application in PD. The MDS-UPDRS was designed for PD patients and is currently used in several clinical trials covering early PD as well as more advanced subjects with motor complications.

Use in Studies Outside the Original Developers. The MDS-UPDRS is currently being used as an outcome measure in several studies organized by teams not directly related the MDS Task Force that developed the scale.

Clinimetric Properties. The MDS-UPDRS correlates highly with the original UPDRS ($r = 0.96$ for the entire scale; $r = 0.89$ for part IV). The MDS-UPDRS showed high internal consistency (Cronbach's alpha for part IV, 0.79). Part IV showed an expected floor but no ceiling effect.

Strengths. Compared with the UPDRS, the MDS-UPDRS is more clearly written, and the wearing-off items comprise an established factor structure.

Weaknesses. The main weakness is the current lack of experience with this new scale, as it was only recently introduced.

Final Assessment. The revised MDS-UPDRS has largely overcome the limitations associated with the UPDRS version 3, and further clinimetric testing of this version (including responsitivity to change) is ongoing. At present, it is considered a Suggested scale.

Treatment Response Scale (TRS)

Description of the Scale. The TRS was developed based on previous scales.[27,28] This scale has been used to grade motor status throughout the day from normal function to severe OFF (score 0–3/0–5) as well as dyskinesias from none to severe.

Scale Application in PD. To date, the TRS has only been used in studies with L-dopa/carbidopa gel infusion.[27,28]

Use by Authors Other Than the Developers. One small study in 9 patients with severe motor fluctuations and dyskinesia used the TRS to assess efficacy of continuous daily levodopa duodenal infusion.[29]

Clinimetric Testing. A validation study has not been published, but a validation process in ongoing.

Strengths. With respect to characterization of duration and severity of OFF-time, it is relatively simple to apply.

Weaknesses. The scale was not designed to assess specifically wearing-off but rather to grade changes in motor conditions (both occurrence of OFF periods and dyskinesia) in patients undergoing infusion therapies. Additional weaknesses are that there is no general agreement on which parts of the symptomatology should be included in the TRS score.

Final Assessment. The TRS is a Listed scale that was not intended primarily as a scale for wearing-off but rather as a tool for research purposes.

Motor Fluctuation Diaries

Description of the Diaries. The most commonly used evaluation of motor fluctuations in clinical trials today involves patient-completed "diaries," in which the patient denotes his/her status (OFF/ON/± nontroublesome or troublesome dyskinesia) during preset intervals. Ideally, the patient should complete the diary for each period at the end of that interval. The accuracy of this data is dependent on the patient being able to understand the definition of the various motor states and being able to correctly self-identify his/her status. Because of this, most clinical trials now incorporate an educational component for the patients and a check of their understanding and awareness of the state they are in through a response cycle.[30]

The most commonly used diary is the Parkinson's Disease Diary, developed by Hauser and colleagues, which includes the categories asleep, OFF, ON without dyskinesia, ON with nontroublesome dyskinesia, and ON with troublesome dyskinesia.[31,32] Also available and validated is the CAPSIT-PD (Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease) ON–OFF diary, which differentiates among 4 motor conditions: OFF, partial OFF, ON, and ON with dyskinesia.[33,34]

Application in PD. The Parkinson's Disease Diary was specifically developed for PD and has been the

source of multiple clinical trials reported by the developers of the scale as well as others.

Use by Authors Other Than the Scale Developers. - Since the Parkinson's Disease Diary was developed, it has been used in studies assessing the efficacy of new antiparkinsonian medications[35–38] in patients experiencing motor fluctuations.

Clinimetric Testing. Overall patient–clinician agreement in CAPSIT-PD diary entries during a 4-hour observation period was good ($\kappa = 0.62$; weighted $\kappa = 0.84$). Agreement for individual diary categories was good for OFF and ON with dyskinesias ($\kappa \geq 0.72$) but moderate for partial OFF and ON ($\kappa = 0.49$). The overall validity of patient-kept diaries was also supported by expected differences in motor assessment scores between diary categories during the 4-hour observation period.[33] One day's home diary data failed to predict outcomes from the full 4 weeks for all diary categories, and data from 3 days failed to yield good prediction for the time spent OFF and partially OFF. Data from 1 week yielded good prediction in all instances except partial OFF, which could not be well predicted, even when 2 weeks' home diary data were considered.

The Parkinson's Disease Home Diary has been assessed for reliability using test–retest calculations.[31] Overall, 83% of 302 patients completed 6 days of the diaries with no missing or duplicate entries, suggesting that the diary is simple and feasible.[32] The percentage of the awake day ON without dyskinesia or with nontroublesome dyskinesia was found to be reliable (intraclass correlation coefficient > 0.70). Diary results were not influenced by age, sex, and country. Predictive validity, as assessed by estimating the strength of association between results from patient diaries and responses to 5 VAS items, was moderate ($R = 0.36$–0.57).

There is no comparison with clinician ratings or objective scores during diary category times or data on predictive validity of diary entries.

Strengths. Diaries are presently the best way of following an outpatient throughout a full day over the course of a study. There is some support for the accuracy, reliability, and validity of the CAPSIT-PD and Parkinson's Disease Diary, and there is evidence that a brief standardized training session can yield good agreement between patients and clinicians in categorizing parkinsonian motor conditions.[30]

Weaknesses. Although 2 diaries have undergone formal validation, validity testing has been limited to the Hauser diary, suggesting moderate validity. The extent to which diary data can be extrapolated beyond the period during which they were collected requires further study. Delays in denoting motor status during an interval likely reduce the accuracy of those data. In addition, if a patient returns the diary with missing data, it cannot be recaptured. It is labor intensive for patients to keep the diaries with them and complete them every half hour, especially if diaries are to be completed several days in a row. The compliance rate appears to fall when patients are requested to complete a greater number of consecutive days of diaries. Electronic diaries that alarm when an entry has been missed have been shown to increase entry compliance, but such diaries are costly.[39] Another limitation of patient-reported OFF time is that there is usually no closely associated evaluation of patients' motor function during that OFF time and OFF-period quality may be differ from the practically defined OFF period during assessment.

Final Assessment. Both diaries are considered Recommended instruments with the caveat of limited knowledge of validity.

Discussion

Wearing-off is a common manifestation in treated PD patients. Its identification is now facilitated by the use in the clinic of dedicated questionnaires. However, the precise assessment of wearing-off in PD is more complex and in theory would require a continuous evaluation of a patient's motor function throughout the day. Because this is not possible outside of very laborious research techniques that require patients to be in a hospital or outpatient unit with continual monitoring, all current methods utilize shortcuts that make an assessment feasible, but do so at the cost of losing potentially important information.

Today, we commonly describe an amount (in hours) or a percentage (of the waking day) for OFF time, ON time, and ON time without troublesome dyskinesia. These terms are readily understood and their general meaning is clear, but by their very nature are imprecise. Many patients experience a transition over some time from their best to their worst motor state, and there is no uniform definition that captures all the nuances of ON and OFF. We define ON time as time when medication is providing (clear) benefit for motor signs of PD, and we define OFF time as time when medication has worn off and is no longer providing (substantial) benefit for motor signs. But there is an ambiguous zone covering the transition between these 2 states, thereby making any evaluation of ON and OFF times imprecise. A further problem is the current lack of a clear definition for wearing-off. We found that the scales currently used to assess the severity of wearing-off do not distinguish between types of motor fluctuations (eg, wearing-off, sudden ON–OFF fluctuations, or delayed ON).

In addition, severity of OFF varies between patients. Some patients may experience more OFF time but may have better overall function than another patient with a much smaller amount of OFF time but more dramatic worsening in mobility in the OFF state. In addition, the presence of disabling nonmotor features during OFF time such as pain, bladder dysfunction, or mood changes may worsen patient perception of severity of his or her motor condition.

Finally, explaining to patients and caregivers the terminology and significance of the assessment can be complex. This could be partially overcome by using available videotapes and dedicated sessions that may help patients and caregivers familiarize themselves with the scales or diaries used.

Future Directions

Technology will likely help to improve assessments of motor fluctuations in the future. An electronic device can potentially be carried on a belt holster or in a pocket (like a cell phone) to provide greater convenience for the patient in having access to the recording device. The device can be set to provide a signal at appropriate times to remind the patient to provide input.

Farther in the future, there may be electronic methods to monitor patient motor function at home throughout a normal day. However, the greatest difficulty is in creating algorithms and methods to truly understand patient motor function based on the input received. It will be important to consistently and accurately distinguish tremor and dyskinesia. Moreover, it is not yet clear how to judge motor function when patients are sitting still, for example. Despite these potential hurdles, technology can be expected to improve the assessment of motor function and fluctuations in the future.

In conclusion, the current scales to assess the severity of wearing-off are primarily focused on the extent of OFF time and do not gather extensive information on the severity of associated motor and nonmotor features as a critical factor in the assessment. It would be desirable for such a scale to capture the severity of wearing-off to allow a comprehensive evaluation of clinical benefit of specific therapeutic strategies. The MDS-UPDRS gathers the complexity, predictability, and severity of motor fluctuations as well as the time, but has not yet been sufficiently tested. Until that time, we do not recommend a new scale.

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