The Most Bothersome Aspects of Off Periods Reported by Individuals with Parkinson’s Disease

Lana M. Chahine, MD,1,* Briana Edison, MPH,2 Margaret Daeuschler, BA,3 Sneha Mantri, MD, MS,4 Steven Kahl, PhD,5 Robyn Rapoport, MA,6 Arina Goyle, PhD,6 Chelle Precht, BSBA,6 Catherine Kopil, PhD,7 and Connie Marras, MD, PhD8

ABSTRACT: Introduction: The off periods in Parkinson’s disease have a significantly negative impact on quality of life. What the most bothersome aspects of off periods are from the patient’s perspective are not well studied, nor is the degree to which screening tools for wearing off such as the Wearing Off Questionnaires (WOQs) capture what bothers patients most.

Methods: A questionnaire was deployed to eligible participants of Fox Insight, an online study of individuals with self-reported Parkinson’s disease. Inclusion criteria were the use of ≥1 dopaminergic medications and an affirmative response to a question on experiencing off periods. Participants provided free-text responses regarding the top 3 most bothersome symptoms they experience when off. A determination was made regarding whether each response would have been captured by the 32-item, 19-item, and 9-item WOQs.

Results: The final sample had 2106 participants, a mean age of 66.6 years, 52.3% were men, and had a disease duration of 4.9 years. The WOQ-32 items covered all of the most bothersome symptoms for 53.2% of respondents. Among bothersome aspects of off not captured by the WOQs, 597 (66.2%) were specific symptoms, with freezing of gait, apathy, and memory problems being the most common. The functional consequences of off periods were most bothersome to 232 (25.7%), with walking problems being the most common. The emotional response to off periods was the most bothersome aspect to 169 respondents (18.7%).

Discussion: This study emphasizes the value of narrative data in understanding patient experiences, and what bothers patients most about off periods. The WOQs, although of established utility in the screening for wearing off, may not capture those symptoms most bothersome to patients.

In Parkinson’s disease (PD), patients experience fluctuations in the clinical state intimately tied to the effects of treatment or the lack thereof. Within 2 to 3 years of starting levodopa therapy, 40% to 50% of patients develop motor fluctuations.1,2 These fluctuations include off periods, which manifest with an emergence of symptoms as the effects of medications wear off.3 The presence of off periods is associated with a reduced quality of life (QOL),2,4 but which aspects of off periods are most bothersome is not well understood. An understanding of what matters most to patients has been identified as a best practice to enhance physician–patient communication and the human connection between provider and patient.5 Understanding patient perspectives and priorities is also important to inform the development and testing of therapies to treat off periods.6

The Wearing Off Questionnaires (WOQs) were developed to detect wearing off. Initially developed as a 32-item questionnaire,7 the WOQ was shortened into 9 items for ease of use in clinical practice.8 A 19-item patient card for capturing...
wearing off has also been published.7 These questionnaires were developed based on expert consensus. A systematic review on behalf of the Movement Disorders Society published in 2011 found that, based on the available evidence, the WOQ-9 and WOQ-19 are recommended as scales for the assessment of wearing off;10 The WOQ-32 was qualified as “suggested” as a screening tool for wearing off. However, the WOQs have been used in several studies to quantify symptom burden and examine the relationship between off symptoms, disease severity, and QOL.2,4,11,12 There are few data on the utility of the WOQs for the purpose of assessing the frequency and impact of different off symptoms. The degree to which these scales capture the symptoms most bothersome to patients is also not clear. It is critical to understand the relative salience of WOQ-identified symptoms to interpret responses on the WOQ in the clinical and research settings and to determine the utility of the WOQs beyond screening for the general detection of the wearing-off phenomenon.13,14 The objectives of this analysis were to (1) identify what aspects of off periods are most bothersome to patients and (2) examine whether the WOQs, commonly used to screen for wearing off, can capture what bothers patients most.

Methods

Sample

A questionnaire was deployed to a subset of the Fox Insight (FI) cohort. As described,15 FI is a study in which individuals with and without self-reported PD participate in online assessments. Study information is available online at foxden.michaeljfox.org/. FI participants were considered eligible to participate in this survey if they met the following criteria: self-reported PD, reported taking ≥1 PD medications, and living in the United States. On November 26, 2018, the survey was deployed. Those who were eligible (n = 13,359) received a link by email that, when clicked, took them to the following screening question:

Many individuals with Parkinson’s disease fluctuate between periods in which their symptoms are better controlled and periods during which symptoms return. We refer to the periods during which symptoms are better controlled as ON, and periods during which symptoms return as OFF. Based on this definition of OFF, do you experience OFF periods?

Study participation was terminated for those responding “no.” This was instituted (along with the requirement of participants taking ≥1 PD medications) to increase the likelihood that respondents had some first-hand experiences with off periods. Those responding “yes” progressed to receive a questionnaire consisting of a series of open-ended (free text) and multiple-choice questions. This questionnaire was developed based on a 2-phase qualitative approach. First, a moderator-facilitated online journaling exercise was conducted for 1 to 2 hours/day for 3 days with a convenience sample of 12 individuals with self-reported PD. The exercise elicited detailed descriptions from the participant about the experience of wearing off, facilitated by questions, interactive graphics, and images. Next, in-depth, semistructured telephone interviews were administered to 14 additional participants. The results of the online journaling and telephone interviews were used to inform the development of a questionnaire regarding the experience of wearing off and off periods. The questionnaire was then pilot tested with 4 individuals (also with self-reported PD) via telephone interview and revised according to participant feedback to ensure optimal questionnaire wording.

Inclusion criteria for this analysis were self-reported PD at all FI study visits, available information for age at survey, age at PD diagnosis, gender, and provision of any response to the question on most bothersome symptoms of off (see Assessments section below). Of the 13,359 eligible FI cohort participants, 2684 started the survey in the 4-week period in which participation remained possible via the FI portal (20% response rate; Fig. 1). A total of 507 participants responded “no” to the question regarding the presence of off symptoms. Of the remaining 2177, 49 did not fill out any part of the survey, 12 had inconsistencies in self-reported diagnoses across FI study visits, 6 had missing or unexpected values for age of PD onset, and 4 did not respond to the question on most bothersome symptoms. The final sample size for this analysis was therefore 2106 respondents.

Assessments

The assessments administered as part of FI study participation included (1) demographics (gender, education) and (2) the following PD diagnosis information:

• At the time of initial enrollment, participants are asked about whether they have a PD diagnosis and are asked if their diagnosis has changed at each return visit.
• Month and year of diagnosis.
• Specialty of healthcare provider who diagnosed the PD. The query is stated as follows: “Please tell us who you received your diagnosis from.” Possible responses are the following: primary care physician (such as a general practitioner, family physician, or internist); a general neurologist; a neurologist specializing in movement disorders (ie, "movement disorder specialist"); other type of physician or health care professional. More than 1 selection is possible.

Assessments were administered as part of this study; throughout the questionnaire, the participants were able to view the definition of off as stated previously.

1. The question regarding most bothersome aspects of off, phrased as follows: “Thinking about all of the different types of symptoms you experience when OFF, including physical, emotional and intellectual/mental, what are the top three most bothersome for you?” This question is henceforth referred to as the “most bothersome symptoms” question (MBSQ). The responses are open ended, free text, with no character limit.
2. Time spent off, ascertained with the following 2 questions, which allowed free-text responses:
In a typical 24-hour period, for how many hours are you awake? Please include both the hours you are awake during the day and night. For example, if you are awake 14 hours a day, please enter 14 in the text box below.

And, in a typical day, how many hours are you OFF?

3. A series of multiple-choice questions querying the predictability/unpredictability of off symptoms and medication responsiveness of off symptoms, worded as shown in the following list. There were 5 possible responses to each: always, most of the time, sometimes, rarely, never.

- “How often does taking your PD medication resolve your OFF symptoms”?
- “How often does taking your PD medication NOT resolve your OFF symptoms”?
- “How often do your OFF periods have a predictable relationship with the timing of your medication? Some examples of predictable relationships would be: OFF periods that are more common just before you are due to take more medication, just after, or at a consistent time point in the middle of your medication cycle.”
- “How often are your OFF periods unpredictable? Unpredictable means they happen ‘out of nowhere’—even during a typical time your medication dose is usually effective.”

4. PD medications.

- Participants were presented with a list of available PD medications (generic and U.S. trade names) and were able to select 1 or more from that list.

    - A multiple-choice question was included regarding the frequency of PD medication intake, worded as follows: “How many times per day do you take medication(s) for your Parkinson’s disease? For example, if you take two pills in one day at the same time, please count that as ‘once a day’. If you take 1 pill in the morning and 1 pill in the evening, please count that as ‘2 times a day’.” Possible responses were once a day, 2 times a day, 3 times a day, 4 times a day, or 5 or more times a day.

This study was performed in accordance with the Declaration of Helsinki. This study and the FI study are approved by the New England Institutional Review Board, and online consent was obtained from each participant at enrollment.

**Analysis**

**Statistical Analysis**

Descriptive statistics were used to summarize demographics and the proportion responding to each answer on the multiple-choice questions. Where a response was not provided on a given question, that item was considered missing for a given respondent.

**Text Analysis**

Each response to the MBSQ was reviewed (by author B.E.). A determination was made as to whether all symptoms reported by each participant had a high likelihood of being captured on the WOQs. In some cases, this designation was straightforward,
### TABLE 1  WOQ listed symptoms and examples of patient responses considered to be likely to be captured by the symptom as listed on the WOQ

| WOQ Symptoms | Examples of Verbatim Patient Responses Classified as Being on WOQ |
|--------------|--------------------------------------------------------------------|
| **Motor**    |                                                                    |
| Tremor       | Tremor, shakiness, jitteriness                                     |
| Stiffness/stiffness during the night/stiffness in the early morning/stiffness in the afternoon | Rigidity, reduced range of motion or flexibility |
| Slow movement/slowness in the early morning/slowness at night | Worsening bradykinesia, slowness |
| Difficulty getting in and out of chair | Trying to stand from a recliner |
| Reduced dexterity | Typing, handwriting difficulty, clothes buttoning and unbuttoning, hand coordination, fine motor coordination |
| Balance problems | Unsteady, falling, fear of falling, looking/feeling drunk, disoriented, tipping over, gait unsteadiness, stumbling |
| Muscle cramping (arms, legs, or feet)/early-morning muscle cramps in the feet or legs | Tightening of muscles, dystonia, hand twisting, tense, clenching, toe curling, cramps from my clenching toes, toes turn in, foot turning in, dystopia, pulling sensation in my legs |
| **Speech/swallow** |                                                                    |
| Difficulty in speech | Speech, communication, can't talk, speech clarity, slurred speech, slower speech, loss of ability to speak clearly, hypophonia, change in tone and volume, hoarse voice |
| Difficulty swallowing | Choking, not being able to swallow |
| **Neuropsychiatric** |                                                                    |
| Depression | Sad, feeling useless |
| Mood changes/mood swings | Heightened emotional response, short-tempered, can’t control emotions, outbursts, agitation, agitated, grumpiness |
| Anxiety | Worrying, fear, not wanting to go in public, nervous, concern, feeling of insecurity, self-conscious, stressed, uneasy, not comfortable in public around other people |
| Panic attacks | Panic-y feeling, panic, panic at the inability to move |
| Cloudy mind/dullness of thinking/slowness of thinking/cloudy thinking | Can’t find words, confusion, decision-making difficult, spacey, drunk feeling, not sharp, can’t think straight, losing train of thought, brain is all jittery, cognitively weak, fog, concentration, lack of focus or concentration, inability to multitask, can’t finish tasks, lack of attention, distracted, I cannot do any tasks requiring concentration and patience, foggy thinking, mental fog, brain fog, foggy brain, foggy not thinking clearly, foggy brain–can’t think straight or focus, foggy head, fuzzy brained, blanking on words |
| **Tiredness/weakness** |                                                                    |
| Tiredness | Sluggish, fatigue, sleepy, exhaustion, drowsy, less energy, crashing, lethargy, stamina, I need to rest, low energy |
| Weakness | Feeling weak, weakness, muscle weakness, limp |
| **Sensory/pain** |                                                                    |
| Numbness/abnormal sensation of numbness | Tingling throughout body, tingling in face, numb lips, tingling/crawling creepy critters on my arms/face/legs, feels like electricity runs intermittently through my arms and leg |
| Restlessness | Urge to move, RLS, can’t stop moving, antsy |
| Pain/abnormal sensations of aching | Uncomfortable, hurting |
| Chest discomfort | Acid reflux, chest tightening, chest pressure |
| **Autonomic/gastrointestinal/gentourinary** |                                                                    |
| Bladder problems–problems passing urine | Bladder control, urinary incontinence, getting to the bathroom, urinary retention, bladder control, urinary frequency, urinary retention, urge to urinate, urgent urination, pressure against my bladder |
| Abdominal discomfort | Stomach pain, nausea, queasy, stomach upset |
| Hot flashes and chills/abnormal sensation of hot and cold/sweating | Dripping sweat from the hair onto the back of my neck, heat intolerance |

WOQ symptoms considered to be of a similar category are grouped together. WOQ, Wearing Off Questionnaires; RLS, restless legs syndrome.
when the patient listed a symptom just as it is listed on the WOQ (Table 1) or in similar enough terminology. Otherwise, judgments were made on a case-by-case basis as to whether the symptoms indicated would be captured by a given WOQ. In general, a liberal approach was taken. Table 1 presents examples of verbatim text given by participants that were considered to fall under corresponding WOQ items.

Some responses indicated a broad category and not a symptom per se, referred to a body part but did not describe a specific symptom, or were otherwise too vague to be classified (eg, “physical,” “emotional,” “legs,” “discomfort,” “my eyes”). These were considered not classifiable and were excluded from further analysis.

Each MBSQ response considered unlikely to be captured by the WOQs was reviewed and categorized (by B.E.) based on commonalities in the responses. One movement disorders specialist (L.M.C.) subsequently went through each response and confirmed classification or reclassified as fit. Then, a second movement disorders specialist (C.M.) reviewed the classifications and provided input. Through iteration, the categories and classifications were further refined.

Results

Cohort Characteristics

The final sample was 2106 participants, mean age 66.6 (standard deviation 8.5) years, 52.3% men. Level of education included at least a high school degree (or equivalent) in 1952 (92.7%) respondents; 654 (31.1%) had earned a bachelor’s degree and 523 (24.8%) had earned a master’s degree. Median disease duration at the time of survey was 4.9 years (25–75% interquartile range 2.5–8.5 years). The diagnosing physician was the primary care doctor for 191 respondents (9.1%), a general neurologist for 1080 (51.3%) respondents, a movement disorders specialist for 1092 (51.9%; 126 respondents selected both a neurologist and a movement disorders specialist), and “other” for 34 (1.6%) participants.

The median duration of off time was 3 hours (interquartile range 2–4 hours), and off time accounted for a median of 17.6% of awake hours (interquartile range 11.1%–27.8%; data missing for 23 participants). PD medications and the effects on off periods are shown in Table 2; 1768 (84%) of the sample reported both predictability of off periods and medication responsiveness (ie, that PD medications help their off periods) at least “sometimes,” with 1033 (50%) participants reporting both predictability and medication responsiveness “always” or “most of the time.”

Analysis of Most Bothersome Symptoms Text

Of the 2106 responses on the MBSQ, 180 were not classifiable; 79% of these consisted of nonspecific terms such as “physical and emotional” or “physical and mental” without describing a specific symptom, reaction, or consequence.

Of the remaining 1926 responses, the numbers considered likely to be captured on the WOQ32, WOQ19, and WOQ9, respectively (Table 1), were 1025 (53.2%), 756 (39.3%), and 478 (24.8%).

For 902 (46.7%) participants, ≥1 symptom reported in the MBSQ were considered unlikely to be captured by any of the WOQs. Responses were reviewed, and the categories generated are summarized in Table 3 and shown in detail in Supplementary Table 1 along with examples of verbatim wording given by respondents. The categories included (1) specific symptoms, (2) function related, (3) unpredictability, (4) emotional response to off—some symptoms described were considered a reaction to

| Variable                          | N (%)  |
|----------------------------------|--------|
| PD medications                   |        |
| Levodopa                         | 1909 (90.6) |
| Amantadine                       | 355 (16.9) |
| Pramipexole                      | 346 (16.4) |
| Rogluticole                      | 313 (14.9) |
| Selegiline or rasagiline          | 386 (18.5) |
| Entacapone or tasmar              | 189 (9.9) |
| Rotigotine                       | 122 (5.8) |
| Safranamide                      | 32 (1.5) |
| Apomorphine (subcutaneous)       | 23 (1.1) |
| Other                           | 121 (5.7) |
| None                             | 27 (1.3) |
| Frequency of PD medication intake |        |
| Once a day                       | 66 (3.13) |
| 2 times a day                    | 101 (4.80) |
| 3 times a day                    | 632 (30.81) |
| 4 times a day                    | 656 (31.15) |
| 5 or more times a day            | 620 (29.44) |
| Missing                          | 31 (1.5) |
| Predictability of off periods    |        |
| Always                           | 228 (10.83) |
| Most of the time                 | 981 (46.58) |
| Sometimes                        | 645 (30.63) |
| Rarely or never                  | 248 (11.8) |
| Missing                          | 4 (1.9) |
| Unpredictability of off periods  |        |
| Always                           | 68 (3.23) |
| Most of the time                 | 336 (15.95) |
| Sometimes                        | 1011 (48.81) |
| Rarely or never                  | 684 (32.5) |
| Missing                          | 7 (0.3) |
| PD medications help off symptoms |        |
| Always                           | 252 (11.97) |
| Most of the time                 | 1209 (57.41) |
| Sometimes                        | 452 (21.46) |
| Rarely or never                  | 182 (8.6) |
| Missing                          | 11 (0.5) |
| PD medications do not help off symptoms |        |
| Always                           | 44 (2.09) |
| Most of the time                 | 158 (7.50) |
| Sometimes                        | 909 (43.16) |
| Rarely or never                  | 992 (47.1) |
| Missing                          | 3 (0.1) |

1 Mainly nondopaminergic PD medications (eg, trihexyphenidyl, irsradapine) and non-PD medications (antidepressants, benzodiazepines, beta-blockers).

2 To be invited for the survey, Fox Insight participants had to have endorsed use of 1 PD medication during a Fox Insight study assessment. Responses in Table 2 are those provided to the questionnaire deployed on Fox Insight for this study. Therefore, it is possible for respondents to have been selected for the survey but not be on medication at the time of questionnaire response. PD, Parkinson’s disease.
**TABLE 3** Classification of patient responses considered unlikely for capture on the Wearing Off Questionnaires

| Category            | Class                        | Example of Text Classified Under Corresponding Class/Category | N   |
|---------------------|------------------------------|-------------------------------------------------------------|-----|
| Symptoms            | Freezing                     | Freezing, freezing of gait, frozen steps, getting stuck      | 106 |
|                     | Apathy                       | Lack of motivation or ambition, indifferent, withdrawn, don’t care, disinterest | 70  |
|                     | Memory                       | Can’t remember, poor recall, forgetful                      | 57  |
|                     | Dyskinesias                  | Dyskinesia, wiggly, involuntary body movements (sway back and forth), rocking back and forth | 51  |
|                     | Sleep                        | Insomnia, interrupted sleep, vivid dreams, nightmares       | 49  |
|                     | Dizzy                        | Light-headed, dizzy, vertigo, whoozy                        | 35  |
|                     | Lack of control              | Lacking control, feeling out of control                     | 29  |
|                     | Drooling                     | Excess saliva, drooling, slobbering                         | 26  |
|                     | Malaise                      | Feeling bad, malaise, feel like crap, feeling weird         | 24  |
|                     | Posture                      | Stooping, slouching, can’t straighten up                     | 21  |
|                     | Vision                       | Double vision, blurry vision, depth perception, bad sight   | 18  |
|                     | Internal tremor              | Internal vibration, internal shakiness, internal tremor, insides quiver | 16  |
|                     | Breathing                    | Panting, out of breath, hyperventilating, shortness of breath, difficulty breathing | 16  |
|                     | Facial control/hypomimia/other facial symptoms | Face twitch, fast blinking, facial expression/masking, the way my face feels, Emotional flattening of expression | 16  |
|                     | Heavy limbs/heavy nos        | My legs feel like cement is in them, leg feels heavy, when my arms feel heavy, heaviness in left arm and hand, feet feel like lead | 12  |
|                     | Headache                     | Headache, pressure in my head                               | 12  |
|                     | Bowel symptoms               | Constipation, bowel dysfunction                             | 10  |
|                     | Jerk/jerking                 | Jerk, jerking, jerky movements                              | 10  |
|                     | Dissociation                 | Feel like I am not in my body, emotional, intellectual/mental disconnect | 4   |
|                     | Appetite                     | Loss of appetite, no appetite                               | 4   |
|                     | Tongue symptoms              | My tongue feels swollen, involuntary movement of the tongue | 3   |
|                     | Ear/hearing symptoms         | Ringing in my ears, sensitive to loud noises                | 3   |
|                     | Psychosis                    | Have strong delusions, hallucinations                       | 3   |
|                     | Changes in sense of smell    | Lack of smell                                               | 2   |
| Function-related problems | Walking nos            | Shuffling, stutter stepping, gait disturbance, plodding gait, limping when walking, legs don't have any brakes on them | 193 |
|                     | Coordination problems nos    | Hand coordination, uncoordinated movements                  | 16  |
|                     | Task specific                | Difficulty reading Inability...to dance...I can’t hold a fork or spoon to eat Trouble cooking Trouble playing guitar | 12  |
|                     | Dragging limbs               | Dragging, leg dragging, drag feet                           | 11  |
| Miscellaneous        | See Supplementary Table 1    |                                                             | 26  |
| Unpredictability     | Unpredictability of the off periods |                                                             | 11  |
| Emotional response to off | Frustrated, embarrassed, scared, pissed off               | 169 |

Verbatim examples for text classified under each category are shown; for a more detailed list of examples, see Supplementary Table S1. N, number of participants with response classified under corresponding category/class.
off periods rather than an off symptom per se, and (5) miscellaneous, which was reserved for clear descriptions of an experience with off periods that could not be put into a specific category.

Specific symptoms accounted for 597 (66.2%) of the responses not captured by the WOQs, of which freezing (in 106), apathy (in 70), and memory problems (in 57) were most common. Function-related problems, the functional consequences of off symptoms, accounted for 232 (25.7%) responses not captured, with walking problems being the most common. The emotional response to off was reported as the most bothersome aspect for 169 (18.7%) respondents.

Discussion

In this analysis, we examined what aspects of off periods individuals with PD indicate as most bothersome and whether these would be captured by the WOQs, tools commonly used to screen for wearing off but also used to describe the spectrum of off symptoms in PD. In almost half of the responses, ≥1 most bothersome symptoms reported by patients would not be captured by the WOQs. Although the use of questionnaires to identify and communicate about off symptoms is seen as useful by PD patients, their care partners, and healthcare providers, our results highlight the limitations of using lists as tools in isolation to capture the patient experience in clinical practice. The results are also in keeping with the previous finding that patients with PD value the narrative interview as the most important facilitator of communication with their neurologist related to wearing off, and neurologists rate talking with their patients as the most important facilitator of discussions related to off periods. Our findings highlight the value of gathering unstructured, open-ended data from individuals with PD. Such information is useful in determining what bothers patients and what they value most. An understanding of this may in turn enhance physician–patient communication and connection.

Several findings emerged from the analysis of the free-text responses provided by participants. Our findings add to the extensive literature on the broad range of motor and nonmotor symptoms that PD patients experience. We found that many patients identify specific symptoms as most bothersome, and many of these were not captured by the WOQs. The 3 most common symptoms not captured by the WOQs were freezing of gait, memory complaints, and apathy. In other studies, a strong relationship between freezing of gait and lower QOL has been shown. Participants were typically explicit in describing these symptoms (eg, “freezing of gait,” “frozen steps”), and these reports were distinct from concerns about walking (considered a functional consequence of off) and balance (a symptom present on the WOQs). As for memory complaints, this was considered in our analysis as distinct from the cognitive symptoms included in the WOQs. The WOQ lists cloudy thinking/slow thinking, which we interpreted as encompassing bradyphrenia and difficulties in attention and concentration, whereas the often-cited complaints related specifically to forgetfulness were distinct and, in our view, not captured by the WOQ cognitive items. The frequent citing of apathy as the most bothersome symptom is consistent with other studies that have identified apathy as having a significant negative impact on QOL and points to the importance of considering this symptom in assessing off periods in PD. Our findings indicate that, despite the WOQs having demonstrated utility for the screening for wearing off in PD, changes would be needed to optimize their ability to quantify symptom burden and impact. The WOQs were developed based on expert opinion. Although experts’ clinical experience lends an invaluable perspective, our results illustrate that incorporating patient input into the development of patient-reported outcome measures may provide a useful perspective and could enhance the capture of information seen as being most relevant by patients—thus, not only patient reported but also patient centered. This is particularly relevant in efforts to ensure the representation of patient perspectives, experiences, and needs in prioritizing drug development.

We found that in a substantial proportion, the most bothersome aspects of being off were expressed as functional consequences, especially consequences on walking/gait. The only WOQ item that is a function (rather than a symptom) is “difficulty getting in and out of a chair.” The finding that several other functional consequences of off periods are what bothers patients most about being off is relevant to the clinical care of individuals with off periods. Probing for not only the symptoms of off periods but also their impact on function, especially activities of daily living, is an important consideration and could inform both treatment decisions (adjusting dopaminergic medications) as well as other possible interventions (such as the involvement of occupational therapy specialists). Our findings lend support to the proposed practical definition of wearing off, which includes the occurrence of functional disability during off periods. The results also indicate that when quantitative measures of off are being employed, the incorporation of items that measure not only symptom prevalence and severity but also functional consequences is critical for capturing the full experience of off periods. Future work to identify the optimal methods to assess the functional consequences of off periods in PD are needed but could include patient diaries or activities of daily living scales, among others.

In other participants, an emotional response to off was reported as most bothersome. Patients expressed frustration, anger, and embarrassment among many other emotions. These are of importance to explore further, and it would be of value to develop not only interventions to treat off symptoms but also strategies to help patients to emotionally cope with those that cannot be fully treated.

The strengths of this study include a large sample of individuals with a high prevalence of medication-responsive wearing off. Limitations of this study include the subjective nature of classifying patient free-text responses. To mitigate this concern, we involved 3 raters, including 2 movement disorders experts, in an iterative consensus process. In addition, a limitation of the FI study is the self-reported nature of PD diagnosis, the validity of which is not yet known. A high prevalence of diagnostic inaccuracy has been noted in individuals self-identified as having movement disorders online. However, during the past decade several other studies provide confidence in the diagnosis of PD...
among individuals self-identifying as having PD for purposes of participating in online research studies. In 1 study examining the accuracy of self-reported PD among 204 individuals self-identifying as having PD as part of seeking participation in research studies online, a neurologist assessed the patient virtually via a Webcam and agreed with the diagnosis of PD in 97% of cases. As for our sample, we drew from the FI cohort, which has been shown to be similar to other observational cohorts that have been assessed in person. In terms of indirect evidence from the data from this study, keeping in mind its self-reported nature, 90% of the sample reported being diagnosed by a neurologist and more than half by a movement disorders specialist. The diagnosis of PD is more accurate in the hands of a neurologist and especially a movement disorder specialist. Another limitation of our study relates to the inability to independently assess and confirm the occurrence of off periods/wearing off. However, the congruent responses to questions about the nature of wearing off, including medication responsiveness, provides face validity to the self-report in this analysis. Finally, the sample was drawn from a highly educated cohort of English-speaking individuals living in North America. Thus, our findings may not be generalizable to other PD populations.

Our findings illustrate the broad range of symptoms related to off periods that bother patients. The WOQs, established as being useful screening tools for wearing off, may not be useful in the clinical setting to capture symptom burden and what bothers patients most. Although questionnaires remain an integral part of assessments for clinical research, the incorporation of patient perspectives may improve patient-reported measures to ensure they capture outcomes relevant to patients. In particular, future questionnaires that may be developed to measure wearing-off symptom burden, impact, and other aspects of severity may need to include a broader array of symptoms as well as the functional and emotional consequences of off periods.

Acknowledgments

This work occurred as part of the Michael J. Fox Foundation’s Parkinson’s Disease Education Program Consortium 2018 project. The Parkinson’s Disease Education Program Consortium is sponsored by the following industry partners: ACADIA Pharmaceuticals, Adamas Pharmaceuticals, Intec Pharma, Lundbeck Inc., and Sunovion Pharmaceuticals. The Fox Insight study is funded by the Michael J Fox Foundation for Parkinson’s Research. We would like to thank the Parkinson’s community for participating in this study to make this research possible.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

References

1. Stacy M. The wearing-off phenomenon and the use of questionnaires to facilitate its recognition in Parkinson’s disease. J Neural Transm (Vienna) 2010;117(7):837–846.

Disclosures

Ethical Compliance Statement: This study was performed in accordance with the Declaration of Helsinki. This study is approved by the New England Institutional Review Board, and online consent is obtained from each participant at enrollment. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflict of Interest: This work was funded by the Michael J Fox Foundation for Parkinson’s Research. The authors declare that there are no conflicts of interest relevant to this work.

Financial Disclosures for the Previous 12 Months: Lana M. Chahine receives research support from the Michael J Fox Foundation (MJFF), has received travel payments from the MJFF to MJFF conferences, is a paid consultant to the MJFF, receives research support from the University of Pittsburgh Medical Center Competitive Medical Research Fund, is study site investigator for a study sponsored by Biogen, is a site subinvestigator for a study sponsored by Voyager, received payment from Elsevier for teaching, and receives royalties from Wolters Kluwer for teaching. Sneha Mantri receives research support from the MJFF, is a paid consultant to the MJFF, is a paid consultant to Cerevel Therapeutics, is a study site investigator for a study sponsored by Neuraly Rho, and is a study site subinvestigator for a study sponsored by Biogen. Margaret Daechler was an employee of the sponsor, the MJFF, at the time this work was done. Catherine Kopil is an employee of the MJFF. Connie Marras was a paid consultant for Acorda Therapeutics; is on the advisory board of Denali Therapeutics; received honoraria for teaching from EMD Serono; is a steering committee member for MJFF grants, the Canadian Institutes of Health Research, the Parkinson’s Foundation (US), the National Institutes of Health, and the International Parkinson and Movement Disorders Society; and is contracted with Grey Matter Technologies. Briana Edison, Steven Kahl, Robyn Rapoport, Anna Goyle, and Chelle Precht have no financial disclosures to report.
2. Stocchi F, Antonini A, Barone P, et al. Early Detection of wEating off in Parkinson disease: the DEEP study. Parkinsonism Relat Disord 2014;20 (2):204–211.
3. Wittig T, Kapfan E, Anzul JP, et al. Nonmotor fluctuations in Parkinson’s disease: frequent and disabling. Neurology 2002;59(3):408–413.
4. Rodriguez-Violante M, Ospina-Garcia N, Davila-Avila NM, Cruz-Fino D, Cruz-Landero A, Cervantes-Arriaga A. Motor and non-motor wearing-off and its impact in the quality of life of patients with Parkinson’s disease. *Ang Neuropsiquiatr* 2018;76(8):517–521.
5. Zulman DM, Haverfield MC, Shaw JG, et al. Practices to foster physician presence and connection with patients in the clinical encounter. *JAMA* 2020;323(1):70–81.
6. U.S. Food and Drug Administration. CDER patient-focused drug development. https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development. Published November 8, 2019. Accessed on December 14, 2019.
7. Stacy M, Bowron A, Gutman M, et al. Identification of motor and non-motor wearing-off in Parkinson’s disease: comparison of a patient questionnaire versus a clinician assessment. *Mov Disord* 2005;20(6):726–733.
8. Stacy M, Hauser R, Oertel W, et al. End-of-dose wearing off in Parkinson disease: a 9-question survey assessment. *Clin Neuropharmacol* 2006;29(6):312–321.
9. Martinez-Martín P, Tolosa E, Hernandez B, Badia X. The patient card questionnaire to identify wearing-off in Parkinson disease. *Clin Neuropharmacol* 2007;30(5):266–275.
10. Antonini A, Martinez-Martin P, Chaudhuri RK, et al. Wearing-off scales in parkinson’s disease: Critique and recommendations. *Mov Disord* 2011;26(12):2169–2175.
11. Pistacchi M, Gioulis M, Sanson F, Marsala SZ. Wearing off: a complex phenomenon often poorly recognized in Parkinson’s disease. A study with the WOQ-19 questionnaire. *Neurol India* 2017;65(6):1271–1279.
12. Melo LM, Chien HF, Barbosa ER. Identification of wearing-off manifestations (reduction of levodopa effect) in Parkinson’s disease using specific questionnaire and comparison of the results with routine ambulatory evaluations. *Ang Neuropsiquiatr* 2010;68(4):506–510.
13. Lach KE, Marquis P, Vigneux M, et al. PRO development: rigorous qualitative research as the crucial foundation. *Qual Life Res* 2010;19(8):1087–1096.
14. Storch A, Schneider CB, Klingelhofer L, et al. Quantitative assessment of non-motor fluctuations in Parkinson’s disease using the Non-Motor Symptoms Scale (NMSS). *J Neurol Transm (Vienna)* 2015;122(12):1673–1684.
15. Smolensky I, Anandikar N, Crawford K, et al. Fox Insight collects online, longitudinal patient-reported outcomes and genetic data on Parkinson’s disease. medRxiv. https://doi.org/10.1101/19002659
16. Armstrong MJ, Rastgardani T, Gagliardi AR, Marras C. Barriers and facilitators of communication about off periods in Parkinson’s disease: qualitative analysis of patient, carepartner, and physician interviews. *PLoS ONE* 2019;14(4):e0215384.
17. Rastgardani T, Armstrong MJ, Gagliardi AR, Grabovsky A, Marras C. Communication about OFF periods in Parkinson’s disease: a survey of physicians, patients, and carepartners. *Front Neurol* 2019;10:892.
18. Perez-Lloret S, Negre-Pages L, Danier P, et al. Prevalence, determinants, and effect on quality of life of freezing of gait in Parkinson disease. *JAMA Neurology* 2014;71(7):884–890.
19. Bruto-Leon J, Cubo E, Coronell C, ANIMO Study Group. Impact of apathy on health-related quality of life in recently diagnosed Parkinson’s disease: the ANIMO study. *Mov Disord* 2012;27(2):211–218.
20. Chou KL, Stacy M, Simuni T, et al. The spectrum of “off” in Parkinson’s disease: what have we learned over 40 years? *Parkinsonism Relat Disord* 2018;51:9–16.
21. Stamelou M, Edwards MJ, Espay AJ, et al. Movement disorders on YouTube—caveat spectator. *N Engl J Med* 2011;365(12):1160–1161.
22. Dorsey ER, Darwin KC, Mohammed S, et al. Virtual research visits and direct-to-consumer genetic testing in Parkinson’s disease. *Digit Health* 2015;1:2055207615592998. https://doi.org/10.1177/2055207615592998
23. Dorsey ER, Wagner JD, Bull MT, et al. Feasibility of virtual research visits in fox trial finder. *J Parkinsons Dis* 2015;5(3):505–515.
24. Chahine LM, Chin I, Caspell-Garcia C, et al. Comparison of an online-only Parkinson’s disease research cohort to cohorts assessed in person [published online ahead of print January 13, 2020]. *J Parkinsons Dis*. https://doi.org/10.3233/JPD-191808
25. Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. *Brain* 2002;125(4):861–870.

Supporting Information

Supporting information may be found in the online version of this article.

**Supplementary table 1.** Classification of responses considered to be unlikely to be captured by any of the Wearing Off Questionnaires with verbatim examples of responses provided by participants with PD.