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The experience of *off* periods: Qualitative analysis of interviews with persons with Parkinson's and carepartners

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ABSTRACT

Introduction: Off period research in Parkinson's disease commonly relies on questionnaires. We aimed to investigate the breadth of *off* period experiences by interviewing persons with Parkinson's disease (PwP) and carepartners.
Methods: Investigators performed PwP and carepartner dyad interviews using a semi-structured questionnaire to describe *off* period experiences. Investigators analyzed interview transcripts using a qualitative descriptive approach to identify and compare themes between groups.
Results: Twenty PwP and their carepartners participated in interviews. PwP were on average 65.1 years-old (SD 8.3) and 7.8 years (SD 4.7) after their Parkinson's disease diagnosis. PwP and carepartners identified 13 motor symptoms, 5 of which (immobility, gait changes, freezing, trouble swallowing, and having to concentrate on movements) were not in the wearing *off* questionnaires recommended by the International Parkinson and Movement Disorders Society. PwP and carepartners identified 15 non-motor symptoms, 8 of which (behavior changes, irritability, fatigue, language difficulties, dizziness, dry mouth, urinary symptoms, and swollen feet) were not in recommended questionnaires. Certain symptoms were reported only by PwP (e.g. dizziness, urinary symptoms) or carepartners (e.g. behavioral changes), or were reported by dyad members to different degrees (e.g. fatigue, anxiety).
Conclusion: Wearing *off* questionnaires capture the presence of fluctuations and can facilitate patient-physician communication regarding *off* periods. However, they may miss the breadth of individual PwP experiences. PwP and carepartners also report different PwP experiences during *off* periods. To fully appreciate an individual's *off* experiences, clinicians likely need to use multiple approaches to gathering information including questionnaires and both PwP and carepartner report.

1. Introduction

Off periods are defined as times when treatment-responsive Parkinson's disease (PD) symptoms reappear or worsen, usually at the end of a medication dose, and result in functional disability [1]. *Off* symptoms can include both motor (e.g., tremor, rigidity, bradykinesia) and non-motor (e.g., cognitive, mood) features [1], but non-motor symptoms remain under-recognized [1,2]. As many as half of persons with PD (PwP) experience motor *off* periods within 2 years of levodopa initiation [3–5], though their presence may be underestimated [5]. Non-motor *off* symptoms commonly emerge with or after motor *off* symptoms [6]. Presence of *off* periods is associated with poorer health-related quality of life [7,8].

Despite the fact that *off* periods were first described in 1976 [9] and are commonly encountered in PwP, the lack of a consensus definition until recently meant that physicians, PwP, and carepartners have different understandings of *off* periods [1]. Most PwP (87%) and carepartners (74%) indicated that they understood the concept of wearing *off* in one questionnaire. However, 53% of PwP and 36% of carepartners didn't answer a question querying the meaning of wearing *off* and 17% of patients and 47% of carepartners provided incorrect answers, often failing to recognize a relationship with medication timing [10]. Much existing research on the spectrum of *off* period symptoms uses wearing *off* questionnaires to identify experiences [5,11]. Questionnaires are important tools to understand the breadth of population experiences, but may miss un-queried symptoms. They also cannot explore the depth and unique nature of individual experiences. We thus aimed to investigate the experiences of *off* periods as reported by PwP and their carepartners through qualitative interviews.

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2. Methods

2.1. Study design

Investigators conducted telephone interviews with PwP and carepartners to thoroughly identify and describe *off* periods experiences. A qualitative descriptive approach, which aims to describe experiences without intending to generate or use theory [12], was employed to analyze interviews. The University Health Network Research Ethics Board provided study approval (file number 16-5880). Participants provided written informed consent to participate. Consolidated criteria for reporting qualitative research [13] guided study reporting (Esupp files Table S1).

2.2. Participants

Recruitment occurred via emails to the Parkinson Disease Foundation Care Partner 2016 Summit mailing list and posting of study information on Fox Trial Finder (2/13/17–10/16/17), a tool matching PwP to research studies (convenience sampling). Interested individuals responded by telephone, email, or via the Fox Trial Finder message system. PwP inclusion criteria were: U.S. residence, a PD diagnosis, experiencing *off* periods, and relationship with a carepartner also willing to be interviewed. There were no inclusion criteria relating to carepartner type or specifying minimum required contact. Consent forms were emailed to potential participants, who could discuss questions by telephone with an investigator. Participants and investigators had no pre-existing relationships.

2.3. Data collection

Investigators drafted semi-structured interview guides for PwPs and carepartners covering topics relating to *off* period experiences, knowledge, and communication. Guide development was reported previously [14,15]. The interview guide provided a description of *off* periods and asked PwP to "describe your *off* symptoms and episodes" with standardized prompts if needed. Carepartners received the same definition but were asked, "Please describe your experiences of when your loved one has *off* symptoms or episodes." The current analysis focuses only on the experience of *off* periods; additional interview details and results are presented elsewhere [14,15].

One investigator (TR), a neurologist and movement disorders fellow, completed all interviews under the guidance of a PhD with qualitative methodological expertise (ARG). PwP and carepartner interviews occurred separately. Target interview length was 30–60 min. Interviews were audio-recorded and professionally transcribed. Participants received a $100 prepaid cash card by mail after interview completion.

2.4. Qualitative analysis

Quotes were compiled and analyzed using Microsoft Word. One investigator (TR) independently created a log of codes reflecting emerging themes and sample quotes from interview transcripts (open coding). All investigators reviewed, revised, and discussed emerging themes to achieve consensus and expand or merge thematic codes (axial coding). Saturation was determined by discussion and consensus following completion of 40 interviews (20 dyads). Themes, subthemes, and exemplar quotes were tabulated and summarized. Given use of verbatim transcription, participant checking was not performed. Reported *off* period symptoms were compared to those included in the longer of two wearing off scales recommended by the International Parkinson and Movement Disorders Society [16]: the 19-item Wearing Off Questionnaire (WOQ-19) designed for clinical use [11]. The WOQ-19 includes 9 motor symptoms (tremor, decreased dexterity, stiffness, slowness, weakness, difficulty getting out of a chair, balance problems, muscle cramping, speech difficulty) and 10 non-motor symptoms (anxiety, panic attacks, mood changes, cloudy mind/dull thinking, sweating, abdominal discomfort, numbness, experience hot and cold, pain, aching).

3. Results

3.1. Demographic and clinical characteristics of participants

Twenty PwP-carepartner dyads participated (Table 1). All eligible PwP and carepartner volunteers were included. Interviews occurred between March and November 2017. Seventeen carepartners were spouses; the other three carepartners included a son, brother-in-law, and close friend. Mean interview duration was 39 min for PwP and 33 min for carepartners. Themes and select quotes are discussed here; additional quotes are summarized in Esupp file 2.

3.2. Symptoms occurring during off periods

Multiple PwP reported difficulty describing their *off* period symptoms:

> Generally, around two and a half hours in, I can start feeling a little, I don't know, goose-bumpily, I guess, is a good way of determining it, where I feel like the medication is starting to wear off a little.
>
> [(PwP3)]

> Well I start feeling strange about 4 hours after [medication]. You know I start feeling like it's wearing off and it's kind of a weird feeling, it's just I get kind of dizzy, but I can feel it coming on… I don't know how to describe it.
>
> [(PwP6)]

PwP and carepartners described a range of motor (Table 2) and non-motor (Table 3) symptoms.

3.3. Timing of off periods

Many PwP reported a temporal pattern to their symptoms. Several PwP described trouble getting started in the morning:

> Well they happen in the morning; upon arising - I don't feel it right away but within half an hour, as I start moving around I feel that my movements are slowing and then - then the tremors start. By the time I take my medication then it's about 20 minutes or half an hour before those recede a little bit and they get a little bit better, and then they pretty much go away, I guess, after about an hour. So right away in the morning I feel it.
>
> [(PwP9)]

Several PwP described afternoon *off* periods, whereas many described difficulties in the evening:

> My off periods usually happens like two o'clock in the afternoon, three o'clock in the afternoon, it's like my legs are weighted in cement, I can't lift them and I have a problem, you know I'm not very smooth on my feet walking.
>
> [(PwP5)]

> Generally, as far as time periods, they seem to happen more often between the time of 4 in the afternoon to 8 o'clock in the evening. That's,

Table 1
Demographic characteristics of interview participants.

	PwP	Carepartners
Total "n"	20	20
Gender (n, % male)	9 (45%)	9 (45%)
Age (years) (mean, SD)	65.1 (8.3)	
Years since diagnosis (mean, SD)	7.8 (4.7)	
Care from movement disorders specialist (n, %)	11 (55%)	

PwP: people with Parkinson's, SD: standard deviation.

Table 2
Motor symptoms reported during *off* periods.

Motor symptom	Exemplar quotes from persons with Parkinson's disease and carepartners
Tremor	Every two to two-and-a-half hours the tremor was severe enough that I couldn't operate much with my left hand - it was pretty useless, especially if I was under any kind of stress, and the stress could be as simple as talking to someone else. (PwP9) A tremor… mostly his right hand. And that's usually – sometimes when I see that and I will ask, you know, did he remember to take his meds? (CP17)
Decreased dexterity	I lose my hand dexterity. (PwP2)
Stiffness	Usually my off period is when I get up in the morning because I haven't taken any medicine for quite a while, and yeah, I'm stiff. (PwP17) If she gets a little low on medication then she gets some stiffness, especially like with walking. (CP9)
Slowness	I feel it more in movement, in lack of movement, slowness of movement, stiffness of movement probably. (PwP9) I can tell when it's time to take his medication just because everything slows. (CP18)
Immobility[a]	I feel like it's extremely difficult to move in general. (PwP7) The meds stop working and they manifest for her as almost complete immobility. She just can't move, so she becomes almost completely rigid. She will shuffle to a chair, kind of – she seems to feel them coming on, because she sometimes mentions them before they're obvious to me, but when they're at their peak, she is almost completely immobile. (CP2)
Difficulty getting out of a chair	And in the evening after supper it's really difficult getting up out of a chair, I think I'm beginning to [festinate] a little bit, when I do get moving I kind of go quickly. (PwP6) If he's in a chair he probably can't get up without assistance, and at other times he can get in and out of a chair by himself, but when he's in this state he just about always needs help. (CP1)
Balance problems	It's the imbalance that comes with it. I can't walk in a straight line and I just am completely unsteady and matter of fact, a couple of times within the last month, I've turned and fallen because of the unsteadiness. (PwP3) You can tell that she's having more problems with balance or she gets tired – [more] than she normally does. And that'll happen, you know, it sort of goes – ebbs and flows throughout the day. (CP6)
Gait changes[a]	It's like my legs are weighted in cement, I can't lift them and I have a problem, you know I'm not very smooth on my feet walking. (PwP5) The gait will go from almost a normal walk… it will slow down and slow down and slow down 'til it becomes that traditional shuffle. (PwP7) If she gets a little low on medication then she gets some stiffness, especially like with walking, you know its real short steps, kind of difficult to get going, slow walking if we got to go someplace… (CP9)
Freezing[a]	Well, they vary and during the course of the day the off periods are sometimes shown with freezing moments… (PwP3) He has what we call freezing periods, where he can't move. He's frozen where he is at that moment in time. And those seem to be coming more frequent with him as well. (CP3)
Muscle cramping or tension	During these periods… from the waist up tends to kind of seize up like a charlie horse, and it won't unseized… the foot will curl, the hand will curl…. (PwP7) She will have one side of her body tense up very significantly… her arm will come up such that her fist is closed and basically touching her opposite shoulder and it's just rigid like that; she has trouble walking and is sore, you know it ends up being sore all over because of the muscle tension. (CP7)
Speech changes	I have trouble pushing out enough air to speak louder and be heard during off periods. (PwP2) Well, they vary and during the course of the day the off periods are sometimes shown with… bad speech patterns or stuttering… (PwP3)
Trouble swallowing[a]	Oh, trouble swallowing. I have a lot of trouble swallowing, eating, at times. (PwP13)
Having to concentrate on movements[a]	And I have to like concentrate on, "Pick your foot up. Step out. Put your foot down." Like to walk across the room. My body says I'm going to move, but my feet don't move. And so I have to like seriously concentrate on it. I usually know it's medication and so I'll often get my medication and take that because that helps… Normal people, when they move don't think about when they're moving or, you know, the brain says move and you automatically move. With me, it's like I have to think about it. (PwP8) I just – I kind of have to orchestrate any kind of movement. I have to remind myself how to button my sleeves and all sorts of stuff like that. (PwP17)

[a] Themes not included in the 19-item Wearing Off Questionnaire.

> I'd say, 75% of the time, you know, regardless if I'm schedule, which I pretty much am, that's when they happen.
>
> [(PwP7)]

> In the early evenings, usually around between 8:30 and 9:00, the medication doesn't seem to do much of anything and I start the tremors pretty severely and I can't concentrate and I'll generally just wind up going to bed.
>
> [(PwP3)]

Some PwP reported that in addition to relating to medication and daily timing, off periods were triggered by stress, fatigue, poor sleep, and certain activities (Esupp file 2).

> I just feel anxious and I'm always a little afraid to reach out and shake someone's hand because it's the stress of – if they tell me something a little stressful or a little unusual, it could trigger kind of an off period. And then my posture changes… I don't think clearly. I'm thinking about how self-conscious I am and not thinking about how I'm presenting.
>
> [(PwP2)]

> I can't tell when it's going to happen, but I do know that when I get stressed it gets worse.
>
> [(PwP20)]

> I would say that at the end of the day, when I'm tired, I'm more likely to have an off period.
>
> [(PwP2)]

> On the nights where I do sleep well, I have much less of an off period when I get up in the morning.
>
> [(PwP17)]

4. Discussion

Interview participants described a wide range of motor and non-motor symptoms occurring during *off* periods. Most of the reported motor symptoms are in the WOQ-19 [11], but no PwP or carepartner reported weakness, one of the WOQ-19 items, as an *off* period symptom. PwP and carepartners described motor symptoms absent from the WOQ-19 including immobility, gait changes (in addition to imbalance), freezing, trouble swallowing, and having to concentrate on movements (Table 4). Having to concentrate on normally automatic movements overlaps with other wearing *off* symptoms, but multiple participants described the need to focus as a specific experience. Certain motor symptoms were described by PwP but not carepartners: decreased dexterity, speech changes, trouble swallowing, and having to concentrate on movements. No motor symptoms were described by carepartners alone.

Differences between PwP, carepartner, and WOQ-19 descriptions of non-motor *off* period experiences were more prominent than observed

Table 3
Non-motor symptoms reported during *off* periods.

Non-motor symptom	Exemplar quotes from persons with Parkinson's disease and carepartners
Anxiety	Depending on the pain level and how long it continues, the longer it continues and I'm not able to get out of it, the higher my anxiety level rises and I'd say about four times a year I do end up going to the emergency room for [anxiety]. (PwP7) Anxiety is my most common symptom when I'm off. (PwP11) I also sometimes I get very anxious… It's more of an antsy sort of anxious. So for instance if I wake up early in the morning and my medicines have sort of worn off overnight. I'll get very unsettled and so I'll toss and turn and get anxious about getting up… I get antsy is probably a better word… (PwP14) Definitely you know if we were out and about or doing anything that was different or there were things going on, you know, with the family or whatever, there would definitely be more anxiety. (CP12)
Panic attacks	Especially if there is freezing or my legs are bad, yes I have anxiety. As a matter of fact, I had a little attack shall we say, just about four nights ago… And my, I did have a problem with the breathing… [My son] heard me breathing… and he said; you have got to slow it down. And he talked with me and I felt very anxious and I was… trying to hyperventilate, and yeah, I think that felt like anxiety. (PwP16)
Mood changes	I get emotional for no reason… I mean for no reason, if anybody ask me how I'm doing you know I can cry. (PwP6) I mean it's just – you know it obviously affects you with your emotions and I think it was just sort of he'd be down, he'd be depressed, he'd be like, "Oh God here it comes again", you know, "When can I take my next pill, why aren't I getting more relief in between, why are the off periods so long", you know that sort of thing. (CP12)
Behavior changes[a]	When he is late taking his meds, or he's missed a time taking his meds, because they're the same thing, and his behavior absolutely changes; he is even quite dramatic, actually. (CP1) He just gets a different personality. He gets more quiet and sometimes he gets, he calls it nervous, jittery and that's how I know it's a, taking place. (CP4)
Irritability[a]	I can just feel the way my body starts feeling and I start getting irritable. And once I start getting irritable I just kind of try to hide it within myself and try to stay away from people so I don't get irritable with them. (PwP11) She's a little less patient, a little more irritable, but there's not been an outlandish development. Sometimes she's just a little less patient than usual and it's generally when it is an off period and what not. (CP14)
Fatigue[a]	Typically the first thing I notice is that I start to get tired… Not all the time but most of the time I get very fatigued and sort of, depending on where I am and what I'm doing, almost to the point where I feel like I need a nap. (PwP14) Well, the fluctuations in her mobility, her balance, her fatigability, energy levels come and go. (CP6) I think sometimes, periods, and almost like a major fatigue type thing (CP17)
Cloudy mind/dull thinking	I have a lot of brain fog -- what me and my husband describe as brain fog -- you know, difficulty concentrating, thinking. I get very forgetful. (PwP13) I can't think clear. (PwP20) Cognitive for sure. She kind of freezes. So for example, we'll be preparing dinner, and when she starts to freeze up, she can't even think about looking up to read the recipe, let alone follow the recipe. So yeah, the cognitive kind of freezes up as well. (CP2) And then in situations where we're not say at home, he tends to be… less able to go with the flow if something changes… He's not as flexible in his thinking processes as he would be if he was, you know, on. (CP12)
Language difficulties[a]	This is one of the things that I experience when I'm off… I keep grasping for words and they're not there, they don't come. (PwP1) Getting the right words in the proper sequence clearly and in some strength is what I – not having that is what I call the down period, and those are the symptoms that tell me that it's time to get back and get your medicines. (PwP18)
Dizziness[a]	Well I start feeling strange about 4 hours after [medication]. You know I start feeling like it's wearing off and it's kind of a weird feeling, it's just I get kind of dizzy, but I can feel it coming on. (PwP6) I guess an off period is when you don't function well, and I have dizzy spells and I tire very, very quickly. (PwP15)
Abdominal discomfort	Oh gee, it's probably the leg not wanting to go, the nausea, the cramping. She has told me about some loose bowels. (CP16)
Pain	Sometimes pain, stiffness of joints. (PwP8) … I can barely, I've got very, very sore muscles and I barely move. (PwP11) Aside from the tremor, there was pain involved… It was as if I had just stressed a muscle or strained a muscle. (PwP12) I get extremely stiff on my right side and it's very painful also. (PwP13) From our experience it is, the off periods involve a fair amount of pain, what we call brain fog. (CP13)
Experience hot and cold	Sometimes I get very warm, like a hot flash. (PwP2)
Dry mouth[a]	I worry about even being able to manage communion, because my mouth is dry. (PwP6) On occasion lately my mouth will start to get very dry which is sort of weird. You would almost think it would be the opposite. But my mouth is dry… It lasts a pretty decent amount of time, you know. (PwP14)
Urinary symptoms[a]	The urgency to use the bathroom and the accidents which I have, happen in the evening [during off periods]. (PwP6) Just feeling like I have to go a lot and I feel like I'm not able to empty my bladder. You know, I'm not sure if I am or not. It feels like I'm not able to empty my bladder. It's just that feeling of discomfort and feeling like I have to pee all the time… That's definitely an off period thing because if I've been real good about taking my medications, you know, and I've been hitting the schedule real close, then that's much relieved. (PwP13)
Swollen feet[a]	The feet swell up and it winds up feeling like you're walking on, do you know Bubble Wrap? It feels like you're walking on Bubble Wrap… It'll stay swollen for as long as I'm in the episode, whether it's 15 minutes or 5 hours. (PwP19) He is more cognizant of that than myself. He – his legs are naturally swollen and he wears an elastic stocking, so I just can't say that I've ever noticed you know them swelling. I have noticed times when his legs are more swollen than other times, but I can't really say that that's related to these off period episodes. (CP19, friend)

[a] Themes not included in the 19-item Wearing Off Questionnaire.

with motor symptoms (Table 4). Either PwP or carepartners reported 7 of the 10 non-motor symptoms on the WOQ-19. No participant described numbness, aching, or sweating as part of a PwP's *off* period. Only one carepartner (no PwP) referenced abdominal discomfort. Additionally, PwP commonly reported anxiety, but none used the term panic attack (Table 3). Multiple PwP and carepartners described pain as part of the PwP experience and one PwP reported hot flashes, but these fit into WOQ-19 categories ("pain," "experience hot and cold") distinct from "aches" and "sweating." Eight themes reflected non-motor symptoms not included in the WOQ-19: behavior changes, irritability, fatigue, language difficulties (separate from other cognitive changes), dizziness, dry mouth, urinary symptoms, and swollen feet (Table 3). Fatigue was a particularly common non-motor wearing *off* symptom; 8 PwP and 6 carepartners representing 12 dyads described fatigue as part of the PwP's *off* period experience. Multiple participants reported irritability and language difficulties, whereas a few PwP described dry mouth and urinary symptoms. One PwP reported *off* period leg swelling, but his carepartner, a friend, reported uncertainty regarding whether this was *off*-related (Table 3).

The International Parkinson and Movement Disorders Society (MDS) identified the original 32-item WOQ as "suggested" and the subsequent WOQ-19 and WOQ-9 as "recommended" scales for diagnostic screening for *off* periods [16]. The original WOQ was developed via a literature review and expert consensus regarding the most common *off* period symptoms. This 32-item scale identified *off* periods symptoms more frequently

Table 4
Comparison of *off* symptoms between interviews and published scales.

Symptom	Current study (interviews)	WOQ-32	WOQ-19	WOQ-9	Q10
Tremor	X	X	X	X	X
Decreased dexterity	X	X	X	X	X
Stiffness	X	X	X	X	X
Stiffness in the early morning	X	X			
Stiffness in the afternoon	X	X			
Stiffness during the night time		X			
Slowness	X	X		X	X
Slowness in the early morning	X	X			
Slowness of movement	X	X	X		
Slowness during the night time	X	X			
Weakness		X	X		X
Immobility	X				
Difficulty getting out of a chair	X	X	X		X
Balance problems	X	X	X		X
Gait changes	X				
Freezing	X				
Restlessness		X			
Muscle cramping	X	X	X	X	
Early morning muscle cramps in feet, legs		X			
Speech changes	X	X	X		X
Difficulty swallowing	X	X			
Having to concentrate on movements	X				
Anxiety	X	X	X	X	X
Panic attacks	[a]	X	X		
Mood changes	X	X	X	X	X
Behavior changes	X				
Irritability	X				
Fatigue	X	X			
Cloudy mind/dull thinking	X	X	X	X	
Slowness of thinking	X	X			
Language difficulties	X				
Dizziness	X				
Abdominal discomfort	X	X	X		
Chest discomfort		X			
Pain	X	X	X	X	
Aching		X	X		
Numbness		X	X		
Experience hot and cold	X	X	X		
Sweating		X	X		
Dry mouth	X				
Urinary symptoms	X	X			
Swollen feet	X				

[a] One patient reported symptoms consistent with a panic attack but did not use that terminology.

than a clinical assessment question or Unified Parkinson's Disease Rating Scale (UPDRS) Question 36 [17]. A retrospective data analysis resulted in the WOQ-19 ("QUICK"), a questionnaire felt more suitable for routine clinical use [11]. Developers based revisions on statistical analyses and an assessment of which symptoms were most bothersome or most useful to identify individuals with wearing *off* in the initial 300 person cohort. Sixteen of the original 32 symptoms were needed to capture all PwP reporting *off* periods; four symptoms (sweating, hot and cold, panic attacks, aching) were added because of their effect on quality of life or treatment decisions [11]. A Spanish version of the WOQ-19 identified more PwP with *off* periods than other screening methods [18]. Similarly, in a large study using an Italian version of the WOQ-19, the scale identified more PwP with wearing *off* than neurologists (67.3% vs. 56.9%), particularly in the cohort with <2.5 years disease duration (41.8% vs. 21.8%) [5].

The WOQ-9 includes tremor, slowness, stiffness, muscle cramping, reduced dexterity, anxiety/panic attacks, mood changes, cognitive changes, and pain/aching (Table 4), collapsing two pairs of previously included symptoms. It identified 96% of subjects with wearing off in the development cohort, missing 7 subjects reporting only balance difficulties (n = 3), numbness (n = 2), difficulty standing (n = 1), and abdominal discomfort (n = 1) [19]. Compared to a physician assessment, the WOQ-9 had 96% sensitivity and 41% specificity in a validation study [20]. Subsequent to the MDS review, developers proposed a 10-item questionnaire version (Q10) (Table 4). Compared to the WOQ-9, the Q10 added speech difficulties, weakness, balance problems, and difficulty getting out of a chair and removed pain/aching, cognitive changes, and muscle cramping [21]. The Q10 had 96% sensitivity for wearing *off* defined as one positive response and 90% sensitivity defined as two positive responses [21].

These publications highlight that various WOQ versions can help clinicians identify *off* periods. Indeed, other results from our study [14] suggest that patient questionnaires can be a facilitator of PwP, carepartner, and clinician discussions regarding *off* periods. Our interview results highlight, however, that while questionnaires may be useful for screening for the presence of *off* periods, they do not capture the breadth of PwP wearing *off* experiences. WOQ versions were validated by assessing if they correctly identified an individual as having *off* periods, not whether they identified the spectrum of symptoms experienced by a PwP. Our study identified *off* period symptoms included in the WOQ-32 but not its derivative forms (e.g. fatigue, urinary symptoms) and symptoms missing from the WOQs altogether (e.g. immobility, having to concentrate on movements, behavior changes, irritability, language difficulties, dizziness). In addition, the WOQ include some symptoms not represented in our small group of participants. These discrepancies emphasize the screening nature of the WOQ versions and the individual nature of wearing *off* symptoms and underscore that physicians should not rely on questionnaires to identify the breadth of *off* symptoms in an individual.

Two published scales attempt to specifically identify and assess the presence of non-motor fluctuations. The Non-Motor Fluctuation Assessment Instrument (NoMoFA) assesses 28 non-motor symptoms relating to cognition, difficulty word-finding, anxiety, mood, hallucinations, impulsivity, difficulty handling stress, fatigue/sleepiness, sensation (e.g. pain), shortness of breath, blurry vision, sweating, heart racing, urinary frequency, and constipation [22]. The Neuropsychiatric Fluctuations Scale (NFS) includes 20 (10 *off*, 10 *on*) items with *off* period symptoms including lethargy, fatigue, lack of energy, trouble planning, low mood, anxiety, lack of confidence, and trouble relaxing [23]. Using these scales could help identify some non-motor *off* period symptoms missed by the WOQs (e.g. fatigue, language difficulties), but other symptoms reported in the current interviews would still be missed, such as behavior changes and irritability.

In addition to the differences between interview responses and available scales, PwP and carepartners differed in the non-motor symptoms described. Many more PwP than carepartners reported anxiety and pain as part of *off* periods, suggesting that PwP may experience these symptoms more prominently than their carepartners recognize. Other symptoms reported by multiple PwP but not carepartners included dizziness, dry mouth, and urinary symptoms. Given that such symptoms may be more difficult for observers to appreciate, these differences are not surprising. In contrast, multiple carepartners reported behavioral changes in the person with PwP that alerted the carepartners to late medication; such changes were unreported by the PwP themselves. These results suggest that *off* symptoms may be missed if clinicians only query one member of the PwP-carepartner dyad, whether verbally or through questionnaire reporting.

This study's strength is that it evaluated *off* period experiences as described in PwP and carepartner interviews without relying on expert opinion or published scales, thus allowing participants to report experiences that could be unrecognized if assessed through other methods. Study limitations include the fact that subjects were U.S.-based, limiting generalizability to other medical contexts. PwP had to recognize the presence of *off* periods to participate, so the study lacks the views of PwP who have *off* periods but don't recognize them. The requirement for PwP and caregivers to enroll as dyads limits knowledge regarding the experiences of PwP living alone or carepartners of PwP who were uninterested (e.g. due to apathy) or unable to participate. Three PwP enrolled with non-spouse carepartners and these individuals may have less or different insight into PwP experiences. The study likely enrolled highly engaged PwP and carepartners, who may be particularly insightful regarding symptoms. Saturation of themes was reached, but it is possible that interviewing more individuals could identify additional

off period symptoms. Finally, additional demographic details were not collected, such as medications and levodopa equivalent doses for PwP and carepartner details other than gender.

Our findings show that PwP experience a broad range of motor and nonmotor *off* period symptoms. Existing questionnaires capture the existence of fluctuations more frequently than neurologist query alone and facilitate patient-physician communication about *off* periods, but they may miss the breadth of experiences. PwP and carepartners also appreciate different *off* period experiences. To fully appreciate an individual's *off* experiences and guide management decisions, clinicians likely need to use multiple approaches to gathering information including questionnaires and both PwP and carepartner report and will also need to probe the impact of *off* periods on daily function.

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Author roles

MJA: conception and design of the study, analysis and interpretation of data, drafting and revising the article, final approval; TR: acquisition of data, analysis and interpretation of data, revising the article critically for important intellectual content, final approval; ARG: acquisition of data, analysis and interpretation of data, revising manuscript critically for important intellectual content, final approval; CM: conception and design of the study, acquisition of data, analysis and interpretation of data, revising article critically for important intellectual content, final approval.

Declaration of competing interest

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References

[1] K.L. Chou, M. Stacy, T. Simuni, J. Miyasaki, W.H. Oertel, K. Sethi, H.H. Fernandez, F. Stocchi, The spectrum of "off" in Parkinson's disease: what have we learned over 40 years? Parkinsomism Relat. Disord. 51 (2018) 9–16, https://doi.org/10.1016/j.parkreldis.2018.02.001.

[2] K.R. Chaudhuri, C. Prieto-Jurcynska, Y. Naidu, T. Mitra, B. Frades-Payo, S. Tluk, A. Ruessmann, P. Odin, G. Macphee, F. Stocchi, W. Ondo, K. Sethi, A.H. Schapira, J.C. Martinez Castrillo, P. Martinez-Martin, The nondeclaration of nonmotor symptoms of Parkinson's disease to health care professionals: an international study using the nonmotor symptoms questionnaire, Mov. Disord. 25 (6) (2010) 704–709, https://doi.org/10.1002/mds.22868.

[3] Parkinson Study Group, Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP patients requiring levodopa, Ann. Neurol. 39 (1) (1996) 37–45.

[4] Parkinson Study Group, Pramipexole versus levodopa in early Parkinson disease: a randomized controlled trial, JAMA 284 (15) (2000) 1931–1938.

[5] F. Stocchi, A. Antonini, P. Barone, M. Tinazzi, M. Zappia, M. Onofrj, S. Ruggieri, L. Morgante, U. Bonuccelli, L. Lopiano, P. Pramstaller, A. Albanese, M. Attar, V. Posocco, D. Colombo, G. Abbruzzese, DEEP study group, Early DEtection of wEaring off in Parkinson disease: the DEEP study, Parkinsonism Relat. Disord. 20 (2) (2014) 204–211, https://doi.org/10.1016/j.parkreldis.2013.10.027.

[6] A. Kim, H.J. Kim, C.W. Shin, A. Kim, Y. Kim, M. Jang, Y.J. Jung, W.W. Lee, H. Park, B. Jeon, Emergence of non-motor fluctuations with reference to motor fluctuations in Parkinson's disease, Parkinsonism Relat. Disord. 54 (2018) 79–83, https://doi.org/10.1016/j.parkreldis.2018.04.020.

[7] S.E. Soh, M.E. Morris, J.L. McGinley, Determinants of health-related quality of life in Parkinson's disease: a systematic review, Parkinsonism Relat. Disord. 17 (1) (2011) 1–9, https://doi.org/10.1016/j.parkreldis.2010.08.012.

[8] M.C. Hechtner, T. Vogt, Y. Zöllner, S. Schröder, J.B. Sauer, H. Binder, S. Singer, R. Mikolajczyk, Quality of life in Parkinson's disease patients with motor fluctuations and dyskinesias in five European countries, Parkinsonism Relat. Disord. 20 (9) (2014) 969–974, https://doi.org/10.1016/j.parkreldis.2014.06.001.

[9] C.D. Marsden, J.D. Parkes, "On-off" effects in patients with Parkinson's disease on chronic levodopa therapy, Lancet 1 (7954) (1976) 292–296.

[10] H. Matthews, J. Stamford, R. Saha, A. Martin, Off-Park survey steering group, Exploring issues around wearing-off and quality of life: the OFF-PARK survey of people with Parkinson's disease and their care partners, J. Park. Dis. 5 (3) (2015) 533–539, https://doi.org/10.3233/JPD-150547.

[11] M. Stacy, R. Hauser, Development of a Patient Questionnaire to facilitate recognition of motor and non-motor wearing-off in Parkinson's disease, J. Neural Transm. (Vienna) 114 (2) (2007) 211–217.

[12] K.J. Colorafi, B. Evans, Qualitative descriptive methods in health science research, HERD 9 (4) (2016) 16–25, https://doi.org/10.1177/1937586715614171.

[13] A. Tong, P. Sainsbury, J. Craig, Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups, Int. J. Qual. Health Care 19 (6) (2007) 349–357.

[14] M.J. Armstrong, T. Rastgardani, A.R. Gagliardi, C. Marras, Barriers and facilitators of communication about off periods in Parkinson's disease: qualitative analysis of patient, carepartner, and physician interviews, PLoS ONE In press, 2019.

[15] T. Rastgardani, M.J. Armstrong, C. Marras, A.R. Gagliardi, Improving patient-centered care for persons with Parkinson's: qualitative interviews with care partners about their engagement in discussions of "off" periods, Health Expect. epub ahead of print, 2019https://doi.org/10.1111/hex.12884.

[16] A. Antonini, P. Martinez-Martin, R.K. Chaudhuri, M. Merello, R. Hauser, R. Katzenschlager, P. Odin, M. Stacy, F. Stocchi, W. Poewe, O. Rascol, C. Sampaio, A. Schrag, G.T. Stebbins, C.G. Goetz, Wearing-off scales in Parkinson's disease: critique and recommendations, Mov. Disord. 26 (12) (2011) 2169–2175, https://doi.org/10.1002/mds.23875.

[17] M. Stacy, A. Bowron, M. Guttman, R. Hauser, K. Hughes, J.P. Larsen, P. LeWitt, W. Oertel, N. Quinn, K. Sethi, F. Stocchi, Identification of motor and nonmotor wearing-off in Parkinson's disease: comparison of a patient questionnaire versus a clinician assessment, Mov. Disord. 20 (6) (2005) 726–733.

[18] P. Martinez-Martin, E. Tolosa, B. Hernandez, X. Badia, The Patient Card questionnaire to identify wearing-off in Parkinson disease, Clin. Neuropharmacol. 30 (5) (2007) 266–275.

[19] M. Stacy, R. Hauser, W. Oertel, A. Schapira, K. Sethi, F. Stocchi, E. Tolosa, End-of-dose wearing off in Parkinson disease: a 9-question survey assessment, Clin. Neuropharmacol. 29 (6) (2006) 312–321.

[20] M.A. Stacy, J.M. Murphy, D.R. Greeley, R.M. Stewart, H. Murck, X. Meng, COMPASS-I Study Investigators, The sensitivity and specificity of the 9-item Wearing-off Questionnaire, Parkinsonism Relat. Disord. 14 (3) (2008) 205–212.

[21] P. Martinez-Martin, B. Hernandez, Q10 Study Group, The Q10 questionnaire for detection of wearing-off phenomena in Parkinson's disease, Parkinsonism Relat. Disord. 18 (4) (2012) 382–385, https://doi.org/10.1016/j.parkreldis.2011.12.011.

[22] G. Kleiner-Fisman, R. Martine, A.E. Lang, M.B. Stern, Development of a non-motor fluctuation assessment instrument for Parkinson disease, Parkinsons Dis. 2011 (2011) 292719, https://doi.org/10.4061/2011/292719.

[23] E. Schmitt, P. Krack, A. Castrioto, H. Klinger, A. Bichon, E. Lhommee, P. Pelissier, V. Fraix, S. Thobois, E. Moro, P. Martinez-Martin, The neuropsychiatric fluctuations scale for Parkinson's disease: a pilot study, Mov. Disord. Clin. Pract. 5 (3) (2018) 265–272, https://doi.org/10.1002/mdc3.12607.