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Real-World Experiences of Parkinson's Disease OFF Time and Role of Demographics

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Purpose	OFF periods are episodes when Parkinson's disease (PD) medications work suboptimally, with symptoms returning and impacting quality of life. We aimed to characterize OFF periods using patient-reported frequency, severity, and duration, as well as determine these characteristics' associations with demographics.
Methods	A retrospective cohort study using Fox Insight Data Exploration Network (Fox DEN) database was conducted. Eligible patients had PD and were >18 years. The experience of OFF periods was characterized by frequency (number of episodes/day), duration (duration/episode), and severity (impact on activities). Significance level was Bonferroni-corrected for multivariate analyses.
Results	From a population of 6,757 persons with PD, 88% were non-Hispanic Whites (mean age: 66 ± 8.8 years); 52.7% were males versus 47.3% females; mean PD duration was 5.7 ± 5.2; and 51% experienced OFF periods. Subsequent analyses were limited to non-Hispanic Whites, as they constituted a large majority of the participants and were the subgroup that had the sample size to derive reliable inferences. The analyses showed that 67% experienced 1–2 episodes/day, 90% experienced >15-minute episodes, and 55% reported slight–mild severity/episode. Lower age was associated with a higher frequency (incidence rate ratio [IRR]: 0.992; P<0.001) and severity (odds ratio [OR]: 0.985; P=0.001) of OFF episodes. Income of <\$35,000 was associated with 15.1% more episodes/day (IRR: 1.15, p<0.001) and 66.5% higher odds of a severe episode (OR: 1.66; P<0.001). Females experienced 7.5% more episodes compared to males (IRR: 1.075; P=0.003). Longer PD duration was associated with 1.3% more episodes/day (IRR: 1.013; P<0.001) and 10% higher odds of a severe episode (OR: 1.10; P<0.001).
Conclusions	Lower age, income <\$35,000, longer PD duration, female gender, and being unemployed are associated with a higher frequency and severity of OFF periods with no associations for duration/episode among non-Hispanic Whites with PD. In time-constrained clinic environments, clinicians should tailor OFF periods management counseling to vulnerable demographic groups to enhance care delivery. (<i>J Patient Cent Res Rev.</i> 2024;11:8-17.)
Keywords	OFF periods; Parkinson's disease; risk factors; demographics; associations

OFF periods are a major source of disability for patients with advanced Parkinson's disease (PD). The prevalence of OFF periods is approximately 40%–50% within as early as 2–3 years of therapy¹ and increases with disease progression, with reports of 87.8% prevalence of wearing off within 9–15 years.² Thus, until a disease modifying therapy exists for PD, almost every patient with Parkinson's disease (PwP) will eventually

develop disabling OFF time. OFF periods occur due to a combination of disease progression and reduction in drug effect³ and are defined as “a change in the clinical state of a PD patient where motor and/or nonmotor symptoms appear or worsen and result in functional disability.”⁴ During OFF periods, patients suffer from debilitating motor symptoms such as rigidity, worsening tremors, bradykinesia, significant gait problems, and poorly recognized nonmotor symptoms such as pain, depression, anxiety, and agitation, which can significantly affect quality of life.² Symptom manifestations during OFF periods can vary between individuals,^{2,5} further complicating the recognition of OFF periods by patients and providers.

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Studies on OFF periods have examined ways to measure OFF periods using surveys,⁵⁻⁹ described communication about OFF periods,^{4,10-12} determined the impact of OFF periods on patients' quality of life,^{1,4,13} and, more recently, explored triggers and coping mechanisms to manage OFF periods.¹⁴ This literature has established that poor communication about OFF periods exists between patients and providers. This coupled with the inherent time constraints of clinical practice can minimize the efficiency of provider-patient interactions about OFF time. A targeted approach that enables providers to, at minimum, focus on patient subgroups that may be more severely impacted by OFF periods is needed. It is not known whether characteristics of OFF periods differ based on sociodemographic characteristics. This knowledge would enable clinicians to direct greater attention to sociodemographic groups more significantly impacted by OFF periods, thereby optimizing their limited time during office visits and enhancing provider effectiveness in care delivery. While previous research has identified some demographic characteristics such as younger age at onset, longer disease duration, and longer duration of antiparkinsonian therapy^{2,15-17} as risk factors, these have been based on two studies with smaller sample sizes and were not based on the US population. In addition, one of these studies did not account for patient-reported measurement of wearing off. Recent efforts to build databases of patients' experiences with PD, such as the Fox foundation database¹⁸ or the Parkinson's Outcomes Project database sponsored by the Parkinson's Foundation,¹⁹ while constrained by being available to those with access to technology (internet), offer rich opportunities to use real-world patient experiences to better understand this disabling and pervasive problem that impacts most patients with PD during their lifetime.

We used data obtained from Fox Insight, an online study comprising regularly administered questionnaires, to gather information on the lived experiences of patients with PD.¹⁸ Building on previous work, the objectives of our study were as follows: 1) describe OFF periods based on frequency, duration per episode, and severity; 2) determine demographic predictors of OFF periods with respect to frequency, duration per episode, and severity.

METHODS

Data Source

The data for this retrospective cross-sectional cohort study were obtained from Fox Insight, an anonymous online longitudinal data collection platform that tracks participants aged 18 or older who report a diagnosis of PD and those who do not.¹⁸ It is a convenience sample comprising volunteers who were recruited via digital or in-person methods across 131 countries. The majority

(85%) of registered participants were located in the US. Participants with PD responded to a battery of regularly administered longitudinal questionnaires that assessed, among other things, demographics, motor/non-motor experiences, health, and quality of life. Non-PD participants responded to a different set of health and lifestyle questionnaires. Patient-reported data for this study were compiled from three questionnaires, namely Users/Registration, "About You," "Impact of OFF episodes," and "Your Medications (PD)." See Smolensky et al for further details regarding the collection, storage, and validation of data, as well as the protection of patient confidentiality.¹⁸ For up-to-date information on the study, visit <https://foxinsight-info.michaeljfox.org/insight/explore/insight.jsp>.²⁰

Study Population

Survey respondents were included if they were in the US with an initial diagnosis for PD at the time of Fox Insight registration and had responded to the "Impact of OFF episodes" questionnaire in their first round of longitudinal assessments (N=6,757).

Study Variables

Dependent Variables. The dependent variables included 3 key variables characterizing OFF episodes in terms of:

- a) Frequency, determined by the average number of episodes per day ("Over the last week, on average, how many OFF episodes do you experience in a typical day?"). Response options for frequency of OFF episodes were: 0 = No episodes, 1 = 1 episode per day, 2 = 2 episodes per day, 3 = 3 episodes per day, 4 = 4 episodes per day, 5 = greater than 4 episodes per day.
- b) Duration, determined as the average duration (in minutes) of an episode ("Over the last week, on average, what is the typical duration of each OFF episode?"). Response options for the duration of each off episode were: Less than 15 minutes, Between 15 and 30 minutes, Between 30 and 45 minutes, Between 45 minutes and 1 hour, Between 1 hour and 2 hours, and Greater than 2 hours.
- c) Severity, determined by the extent that episodes prevented an individual from doing things ("Over the last week, on average, when you experience an OFF episode, did it stop you from doing things?"). Response options were: 0 = Neutral: when you have off time, you can do everything that you can do during on time; 1 = Slight: OFF time slows you down on a few activities, but you can do everything that you can do during on time; 2 = Mild: OFF time slows you down on many activities, but you can do everything that you can do during on time; 3 = Moderate: OFF time causes you to avoid or stop

doing a few activities that you can do during on time;
4 = Severe: OFF time causes you to avoid or stop
most activities that you can do during ON time.

Independent Variables. Demographic data were collected at the time of registration from 3 questionnaires: Users/Registration, “About You,” and “Your Medications (PD).” These data included age, gender (male/female), body mass index (BMI) (calculated from height and weight), race (White, African American, American Indian or Alaskan native, Native Hawaiian or other pacific islander, Asian, Prefer not to answer), ethnicity (Hispanic or Latino, Mexican, Mexican American or Chicano, Puerto Rican, Cuban, another Hispanic/Latino/a or Spanish origin), education level (the 8 categories in the questionnaire were combined to form four categories: ≤high school, some college/no bachelors, bachelor’s degree [BA, BS, AB, etc.], advanced degree [Masters, Professional school degree, Doctorate degree]), yearly household income (the 6 categories were combined into 4 categories: <\$35,000, \$35,000–\$75,000, ≥\$75,000, missing), and employment status (employed [part-time or fulltime], unemployed, retired, and whether they were a veteran). Another PD-related factor included the clinician who initially diagnosed the participant (primary care practitioner [PCP], such as a general practitioner, family physician, or internist; general neurologist; movement disorders specialist; or other physician or healthcare professional). The duration of PD was not directly available in the dataset. It was computed as the difference between age-at-diagnosis and age at time of completing the “Impact of OFF episodes” survey. Respondents were also asked to indicate the type of PD medication that they were currently taking from a list of approximately 41 medications typically given to treat symptoms of PD. Participants were asked to choose all the medications that applied to them from the list. This study was reviewed and deemed not human subjects research by the local institutional review board (IRB #1600), given the de-identified nature of the dataset.

Statistical Analyses

The top 10 frequently used medications by patients with PD were identified and used for further analyses. The categories of three demographic variables (education, income, and employment status) were combined for better data representation and ease of reporting. To avoid estimation biases due to underrepresentation of other races and ethnic groups in the database, multivariate analyses focused only on non-Hispanic Whites. Only about 2% of non-Hispanic Whites had missing values on at least one variable (except income) and were thus listwise deleted in multivariate analyses. While income was missing for 19% of the study population, a missing value indicator

was created and included in all regressions, rather than dropping those observations. Descriptive statistics were used to determine sample characteristics and the frequency, duration, and severity of OFF episodes. Chi-squared tests for categorical variables and independent t-tests for continuous variables were used to compare demographic characteristics and the top ten frequently used medications between those who experienced OFF episodes and those who did not. A censored Poisson regression was used to determine the relationship of demographic factors with the frequency of OFF episodes. Estimates from this model are interpreted as an incidence rate ratio with 95% confidence intervals. Ordered logistic regression was used to determine the relationship between the severity of OFF episodes and demographic characteristics. The estimates are reported as odds ratios, with 95% confidence intervals. Interval regression was used to model the relationship between the duration of OFF episodes and demographic characteristics. The coefficients and their 95% confidence intervals (CI) are reported. Bonferroni correction was applied to the 0.05 level of significance to account for multiple comparisons. All tests were performed at a corrected significance level of 0.003 and were 2-sided. All analyses were performed using Stata 15.²¹

RESULTS

In total, 6,757 persons with Parkinson’s Disease completed the “Impact of OFF episodes” questionnaire. Table 1 shows the demographics of the study population. The overall population reported having PD for an average of 6 years (standard deviation: 5.2) since their diagnosis. A large majority of the participants were non-Hispanic White (88%, n=5,971); thus, in the next subsections, analyses are based on non-Hispanic Whites, the subgroup that had the sample size to derive reliable inferences. Table 1 further shows that more than 60% of the population had a bachelor’s degree or higher. Almost 50% of the population had incomes ≥\$75,000. There was approximately equal distribution of participants who were diagnosed by general neurologists or by movement disorder specialists. Approximately 50% of the participants (51.35%, n=3,470) reported experiencing OFF episodes. Except for gender, BMI status, veteran status, and provider type that diagnosed PD, all other demographic variables showed significant differences in bivariate analyses.

Table 2 lists the top 10 frequently used medications to treat PD. The majority (62.7%) of respondents were on carbidopa/levodopa immediate release (Sinemet). In all cases, except for MAO-B inhibitors (rasagiline [Azilect], selegiline [Derived]) and one of the dopamine agonists (pramipexole [Mirapex]), there was a significant

Table 1. Demographic Characteristics by Percentage

Demographic variable	All, N=6,757 (100%)	Any episodes		P
		Yes, n=3,470 (51.3%)	No, n=3,287 (48.6%)	
Age in years ^a (N=6,757)	66.0 (8.8)	65.2 (8.8)	66.9 (8.6)	<0.001
Gender (n=6,381)				0.108
Female	47.3	48.3	46.3	
Male	52.7	51.7	53.7	
Race (n=6,371)				<0.001
Non-Hispanic White	88.4	46.3	13 (13.0%)	
African American	0.6	53.7	7 (7.0%)	
Asian	1.0			
American Indian	0.8	34 (17.8%)	16 (16.0%)	
Hispanic	3.9	64 (33.5%)	32 (32.0%)	
Other	0.2	69 (36.1%)	38 (38.0%)	
Body mass index (n=6,297)				0.004
Underweight/Normal	39.0	38.2	39.8	
Overweight	37.9	37.0	38.9	
Obese	23.1	24.8	21.3	
Education (n=6,371)				<0.001
High school or less	6.6	7.5	5.7	
Some college/No Bachelor's	24.4	26.9	21.7	
Bachelor's degree	30.3	30.2	30.5	
Advanced degree	38.7	35.4	42.1	
Income (N=6,757)				<0.001
Income <\$35,000	10.6	12.5	8.6	
Income \$35,000–<\$75,000	24.6	25.6	23.6	
Income ≥\$75,000	45.9	42.6	49.3	
Income missing	19.0	19.4	18.6	
Employment status (n=6,353)				<0.001
Employed	26.2	25.4	26.9	
Retired	68.8	67.4	70.3	
Unemployed	5.0	7.1	2.8	
Veteran (n=6,373)				0.034
Yes	17.0	16.0	18.0	
No	83.0	84.0	82.0	
Provider type who diagnosed (N=6,757)				
Diagnosed by General Neuro	51.1	51.8	50.4	0.239
Diagnosed by Neuro Specialist	50.8	50.4	51.3	0.480
Diagnosed by PCP	8.9	9.7	8.1	0.018
Diagnosed by other	1.4	1.5	1.3	0.376
Years since diagnosis ^a (n=6,723)	5.72 (5.2)	6.71 (5.4)	4.68 (4.6)	<0.001

^aReported as mean (standard deviation).

difference ($P < 0.001$) in the proportion of patients reporting OFF episodes compared to those who did not.

Duration, Frequency, and Severity of OFF Episodes

Figure 1 depicts the frequency, duration, and severity of

OFF episodes. As shown in Figure 1, the majority (67%) of the respondents experienced either 1–2 OFF episodes in a typical day, while approximately 5% experienced 5 or more OFF episodes in a typical day. The duration of each OFF episode when examined showed that approximately 90%

Table 2. Top 10 Frequently Used Medications for Parkinson's Disease by Percentage

Drug class/Medication	All, N=6,735	Yes, n=3,458	No, n=3,277	P
Decarboxylase inhibitors				
Carbidopa/Levodopa Immediate Release (Sinemet)	62.7	71.3	53.6	<0.001
Carbidopa/Levodopa Controlled Release (Sinemet CR)	15.6	20.8	10.2	<0.001
Carbidopa/Levodopa Extended Release (Rytary or Numient)	8.3	12.1	4.3	<0.001
MAO-B inhibitors				
Rasagiline (Azilect)	25.7	25.7	25.7	0.966
Selegiline [Derived]	4.1	3.9	4.3	0.409
Dopamine agonists				
Pramipexole (Mirapex)	11.3	12.0	10.6	0.068
Ropinirole [Derived]	9.2	10.6	7.8	<0.001
Requip (Ropinirole)	8.6	9.9	7.3	<0.001
Rotigotine Transdermal Patch (Neupro Patch)	4.5	5.4	3.5	<0.001
Adamantanes				
Amantadine (Symmetrel)	10.1	12.0	8.1	<0.001

P value describes whether there was a significant difference between those who experienced OFF periods and those who did not.

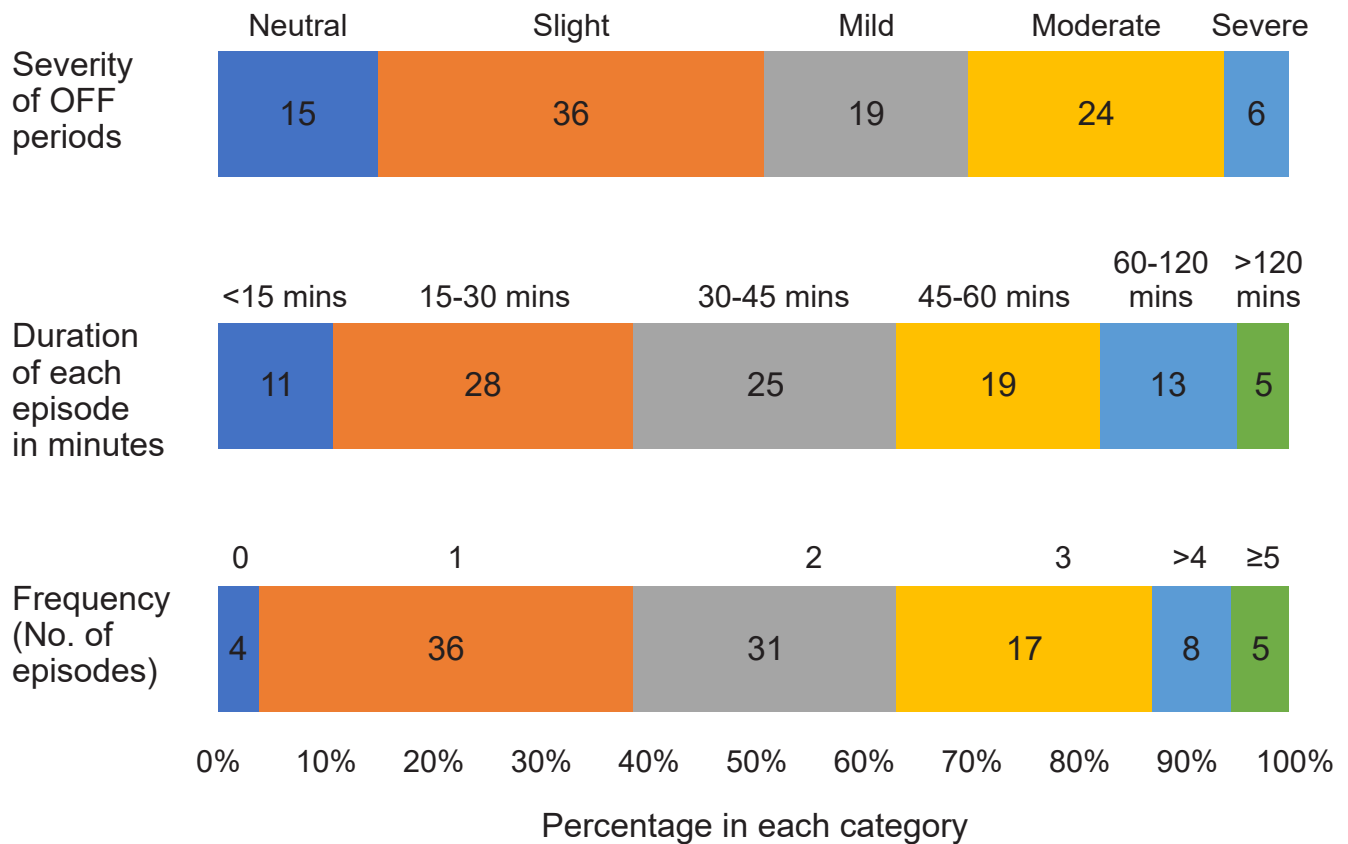


Figure 1. Patients' experiences of frequency, duration/episode, and severity of OFF periods.

of respondents experienced OFF episodes for more than 15 minutes. Approximately 18% of respondents reported that their OFF episodes lasted one hour or more. Figure 1 also shows the severity of each OFF episode based on the extent to which OFF episodes stopped patients with PD from doing things. There was a broad distribution of the severity of OFF episodes with 55% of respondents reporting slight–mild severity/episode. Only 6% indicated that OFF episodes severely impacted their activities.

Factors Associated with OFF Periods

Tables 3–5 show the demographic factors related to the frequency, duration, and severity of OFF periods for the majority of the non-Hispanic White patient population. No demographic factors were associated with the duration of OFF episodes when using the Bonferroni-corrected alpha value of 0.003 for significance testing. Age had a significant inverse association with the frequency (incidence rate ratio: 0.992, 95% CI: 0.989–0.995; $P<0.001$) and severity (odds ratio: 0.985, 95% CI: 0.976–0.994; $P=0.001$) of OFF periods. Older participants had fewer OFF episodes with lower severity. The estimates suggest that being 10 years older is associated with 8% fewer episodes per day and 15% lower odds of a more severe episode. Gender was significantly associated with frequency (incidence rate ratio: 1.075, 95% CI: 1.024–1.128; $P=0.003$) but not duration or severity of OFF episodes. Females were expected to have approximately 7.5% more OFF episodes daily than males. Income below \$35,000 was a significant predictor of the frequency (incidence rate ratio: 1.151, 95% CI: 1.072–1.236; $P<0.001$) and severity of OFF episodes (odds ratio: 1.665, 95% CI: 1.351–2.055; $P<0.001$). A low-income level (less than \$35,000) was associated with 15.1% more episodes per day and 66.5% higher odds of experiencing a more severe episode. Additionally, those who were unemployed experienced OFF episodes differently than those who were employed in terms of severity. The odds of a greater severity in episodes were approximately two times higher for unemployed respondents (odds ratio: 2.229, 95% CI: 1.670–2.975; $P<0.001$) relative to those who were employed. Years since diagnosis with PD was another factor that was significantly associated with the frequency (incidence rate ratio: 1.013, 95% CI: 1.009–1.018; $P<0.001$) and severity (odds ratio: 1.100, 95% CI: 1.083–1.118; $P<0.001$) of OFF episodes. Specifically, having PD for a year longer was associated with 1.3% more episodes per day and 10% higher odds of experiencing a more severe episode.

DISCUSSION

Our analysis of Fox DEN database of patient-reported descriptions of OFF periods for the non-Hispanic White (majority) patients with PD indicated that approximately

50% of the population experienced OFF periods, with the majority of respondents reportedly experiencing 1–2 episodes per day in frequency, having OFF episodes lasting more than 15 minutes in duration, and having slight–mild impact on their activities (severity). We focused on the majority White population to avoid the potential for estimation bias resulting from small samples of other races/ethnic groups. However, approximately 30% of the respondents indicated that OFF periods had a moderate to severe impact. The key demographic factors that influenced OFF episodes were older age, income less than \$35,000, female gender, being unemployed, and years since diagnosis of PD, with gender influencing only the frequency of OFF episodes.

In this study, the prevalence of OFF periods based on disease duration is consistent with the literature. OFF periods are known to occur in 40% of patients within 4–6 years of starting treatment.³ Our study population had PD for an average of 6 years, and approximately 50% of the population experienced OFF periods. A higher percentage of responses indicating “Yes” were present among those who were on medications such as Carbidopa/Levodopa, the controlled release version, Pramipexole, and Amantadine. This finding is expected given that the average duration of PD in the population was approximately six years and that wearing off is a typical complication expected with long-term use (more than 4 years) of PD medications such as carbidopa/levodopa.^{2,3} While the literature points to the debilitating effects of OFF periods resulting in considerable functional burden,²² the patients in our study did not seem to feel much impact from their OFF periods. As the majority of our population had only 1–2 episodes per day and the duration of each episode was not more than 45 minutes for the majority of the population, one reason may be that the patients might not have perceived the debilitating effects of the OFF periods just yet. However, after controlling for other demographics in our multivariate analyses, there were certain demographic groups that experienced significantly more severe or frequent OFF episodes than others and are described below.

Our study contributes valuable new knowledge by examining the association between the frequency and impact of OFF episodes by gender and other demographic characteristics. We found that females had 7.5% greater frequency of OFF episodes than males. This finding is consistent with the literature.^{16,18} However, the duration per episode and the impact of OFF episodes did not differ significantly between males and females in our study. While some authors have speculated about a higher frequency of wearing off in women to be due to their lower body weight, resulting in higher levodopa dose

Table 3. Association of Demographics to Frequency of OFF Episodes (n=2,940)

Demographic variable	IRR	95% CI	P
Age	0.992	[0.989, 0.995]	<0.001
Female	1.075	[1.024, 1.128]	0.003
Overweight	1.011	[0.960, 1.065]	0.680
Obese	0.949	[0.898, 1.003]	0.065
High school or less	1.014	[0.922, 1.115]	0.777
Some college/No Bachelor's	0.969	[0.914, 1.028]	0.300
Bachelor's degree	0.996	[0.943, 1.051]	0.871
Income of <\$35,000	1.151	[1.072, 1.236]	<0.001
Income of \$35,000–<\$75,000	1.067	[1.011, 1.126]	0.018
Income missing	1.089	[1.015, 1.168]	0.018
Retired	0.988	[0.932, 1.048]	0.697
Unemployed	0.986	[0.896, 1.085]	0.771
Veteran	1.003	[0.939, 1.072]	0.923
Diagnosed by neuro specialist	0.969	[0.907, 1.035]	0.349
Diagnosed by general neuro	0.968	[0.906, 1.034]	0.331
Years since diagnosis	1.013	[1.009, 1.018]	<0.001

Reference categories are: underweight/normal for body mass index; income of ≥\$75,000; employed for employment status; advanced degree for education; and diagnosed by PCP/other for provider type.

IRR, incidence rate ratio.

Table 4. Association of Demographics to Duration of OFF episodes (n=2,940)

Demographic variable	Coefficient	95% CI	P
Age	-0.178	[-0.325, -0.031]	0.018
Female	-0.684	[-2.969, 1.601]	0.557
Overweight	-0.739	[-3.232, 1.753]	0.561
Obese	-1.533	[-4.180, 1.114]	0.256
High school or less	3.118	[-1.924, 8.160]	0.225
Some college/No Bachelor's	-1.667	[-4.363, 1.029]	0.226
Bachelor's degree	-0.577	[-3.124, 1.970]	0.657
Income of <\$35,000	3.771	[0.037, 7.505]	0.048
Income of \$35,000–<\$75,000	0.759	[-1.787, 3.304]	0.559
Income missing	1.862	[-1.424, 5.149]	0.267
Retired	-2.987	[-5.888, -0.085]	0.044
Unemployed	2.785	[-2.179, 7.750]	0.272
Veteran	2.052	[-1.160, 5.264]	0.210
Diagnosed by neuro specialist	0.197	[-3.114, 3.509]	0.907
Diagnosed by general neuro	-1.631	[-4.925, 1.664]	0.332
Years since diagnosis	-0.022	[-0.235, 0.191]	0.842

Reference categories are: underweight/normal for body mass index; income of ≥\$75,000; employed for employment status; advanced degree for education; and diagnosed by PCP/other for provider type.

Table 5. Association of Demographics to Severity of OFF Episodes (n=2,940)

Demographic variable	Coefficient	95% CI	P
Age	0.985	[0.976, 0.994]	0.001
Female	1.009	[0.874, 1.164]	0.905
Overweight	0.948	[0.812, 1.107]	0.500
Obese	1.153	[0.971, 1.368]	0.104
High school or less	1.153	[0.844, 1.576]	0.370
Some college/No Bachelor's	1.070	[0.896, 1.278]	0.454
Bachelor's degree	0.926	[0.785, 1.091]	0.357
Income of <\$35,000	1.665	[1.351, 2.055]	<0.001
Income of \$35,000–<\$75,000	1.250	[1.056, 1.481]	0.010
Income missing	1.100	[0.888, 1.363]	0.381
Retired	1.254	[1.045, 1.504]	0.015
Unemployed	2.229	[1.670, 2.975]	<0.001
Veteran	1.123	[0.917, 1.375]	0.261
Diagnosed by neuro specialist	0.942	[0.772, 1.148]	0.553
Diagnosed by general neuro	0.930	[0.763, 1.133]	0.471
Years since diagnosis	1.100	[1.083, 1.118]	<0.001

Reference categories are: underweight/normal for body mass index; income of ≥\$75,000; employed for employment status; advanced degree for education; and diagnosed by PCP/other for provider type.

concentrations,^{16,23} our study did not find any relationships between bodyweight and frequency of wearing off.

Income was another demographic factor that was associated with the frequency and severity of OFF episodes. Lower-income (<\$35,000) individuals had a worse experience with OFF episodes, having more frequent, more severe episodes. The reasons for lower-income individuals having worse OFF episodes might be multifactorial with factors such as lower affordability of PD medications, potentially leading to lower medication adherence and consequent worsening of symptoms and OFF periods. Another explanation is the health literacy level of individuals with lower incomes. Limited health literacy has been shown in studies to be significantly associated with lower income²⁴ and may also contribute to poor self-management behaviors,^{25,26} with consequent worsening of disease and more severe OFF periods.

Employment status affected only the severity of OFF periods. Being unemployed was associated with more severe episodes. The greater severity for those who were unemployed may again be explained by the influence of multiple factors, such as limited incomes, possibly leading to lower affordability of newer, more expensive medications and resulting in few treatment options to address OFF time, lower medication adherence, limited health literacy, and higher stress levels.²⁷ As only 5% of the population were unemployed in our study, the role of this factor in serving as a predictor of severe OFF episodes needs further investigation in future studies. As the database had only limited categorical information about income and employment, we were unable to explore the interactions between income and employment using multifactorial analyses. While income <\$35,000 appears to significantly affect OFF time based on our analysis of Fox DEN database, the authors recognize the challenges that clinicians may face to target patients with PD based on income and recommend interpreting this finding cautiously and in the appropriate context.

An interesting finding of this study was that the frequency and severity of OFF periods were inversely associated with age; that is, older individuals tended to have a better experience with OFF episodes compared to younger individuals. It is unclear why this might have occurred, as the anticipated effect was that older individuals would experience worse OFF periods than younger individuals possibly due to differential sensitivities to dopaminergic medications. One explanation is that elderly patients may not be as active compared to younger PD patients and hence do not experience an impact on their activities to the same extent. Another explanation for this could be that age may have less of an impact on wearing off than

disease duration. Our analyses revealed this finding as discussed below. While discussion about OFF periods and their impact should be directed to all PD patients during patient visits, providers may want to offer more guidance about handling OFF periods to younger PD patients who might have a more negative perception of their severity and impact.

Years since diagnosis was also another factor contributing to the frequency and severity of OFF episodes. It is well known that OFF symptoms and severity increase with longer duration of disease^{2,16,23} or, in other words, greater number of years since diagnosis. This can be explained by the fact that PD is a progressive neurodegenerative disease with symptoms worsening with increased duration of PD. Worsening symptoms would necessitate more levodopa medication, which in turn increases the risk of levodopa-induced dyskinesias and worse OFF periods.²² An interesting finding of this study is the determination of age and duration of disease influencing OFF periods in opposite ways. While clinicians may be aware of the association of duration with PD and worsening wearing off experiences, they may not be aware of its differential influence based on different age ranges. Our analyses also determined that the duration of disease has a higher magnitude of impact than age on the frequency and severity of OFF episodes. In other words, patients who are elderly with shorter duration of disease experience less negative impact of wearing off than patients with a similar age but who have had PD for a longer time (longer disease duration). Given that there is evidence of poor communication about OFF periods between patients and providers,¹⁰⁻¹² clinicians can use the results of this study to initiate focused discussion about ways to better manage OFF periods with key demographic groups during their time-sensitive clinic visits. It would also be helpful to share informational brochures about OFF periods with all patients with PD as they reach the 4–6-year mark in their journey with PD.

The strengths of this study include a larger sample size for studying OFF periods, access to the patient's perspective on OFF periods, and having a sample consisting of nearly 50% women, a group that is less researched in PD studies.¹⁴ However, there are several limitations of this study. As the analysis focused on the majority White population in the database, generalizability of the results to other races cannot be made. Limited representation of minorities is a recognized universal challenge in PD research.²⁸ Significant racial and ethnic disparities exist in the diagnosis of PD, as well as in neurologic healthcare access and utilization.²⁹ Dahodwala et al determined that African Americans were half as likely to be diagnosed with PD compared to Whites.³⁰ While racial and ethnic diversity in Fox Insight database was

limited, a comparison of Fox Insight database to other databases such as Parkinson's Progression Markers Initiative (PPMI) and Parkinson's Disease Biomarkers Project (PDBP) shows similar results with respect to racial composition, in that these databases include more than 95% White participants.³¹ However, attention and efforts to increase the diversity in Fox Insight database via digital marketing efforts are underway.³² Other limitations include the use of a convenience sample of volunteers who participated in the Fox DEN study and the small percentage of missing data that could impact the results. Convenience sampling presents the potential for sampling bias and limits the generalizability. The use of internet to build Fox Insight database suggests that the convenience sample may be limited to individuals with PD that had internet access and the digital health literacy to provide essential data to complete the database. The data are also limited by recall bias, as respondents were asked to indicate the frequency, duration, and severity of OFF periods based on their recall over the previous week. As this was a retrospective database study involving patient questionnaires, we did not have direct access to the patients. Hence, we were unable to interview the patients or their care partners to gain a richer understanding of the subjective symptomatic experience of OFF periods. Another limitation was that our study did not examine other important factors such as geographic location and access to a tertiary care Parkinson's center or movement disorder specialist where advanced therapies for PD can be accessed and that may influence OFF periods. Additionally, as these are survey data, the quality of the data is limited by the accuracy of patient reporting and other common limitations of survey research.

CONCLUSIONS

OFF episodes are common and occur with disease progression and a wide variety of medications used in PD. The frequency, duration/episode, and severity of OFF periods varied among patients experiencing them. While duration/episode was not associated with demographics, frequency and severity were associated with different demographic risk factors. While duration of disease is a well-known risk factor associated with the development of OFF episodes, our study found that age, gender, being unemployed, and having an income <\$35,000 were also associated with varying patient perceptions of OFF periods' frequency and severity. In busy clinical practice environments, our findings can help clinicians tailor OFF periods management counseling to vulnerable demographic groups, thus enhancing care delivery. Future research should focus on the social determinants of health and examine their impact on OFF periods. In addition, further analysis of patient-specific factors is recommended, as it can guide clinicians to more fruitfully

tailor their clinic interactions with targeted population groups that might be impacted to a greater extent by OFF periods. This could contribute to better quality of life, equity, and access for patients with PD in the long term.

Patient-Friendly Recap

- Patients with Parkinson's disease (PD) experience OFF periods that significantly impact their quality of life. It is unknown whether OFF periods from PD differ based on sociodemographics.
- This study analyzed patient-reported data collected from the Fox Foundation to examine the relationship between sociodemographic factors and OFF period characteristics, specifically their frequency, duration, and severity.
- The key sociodemographic factors that influenced OFF episodes were age, income less than \$35,000, female gender, being unemployed, and years since diagnosis of PD, with gender influencing only the frequency of OFF episodes.
- In time-constrained clinic environments, this knowledge can enable clinicians to tailor OFF periods management counseling to vulnerable demographic groups to enhance care delivery.

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Author Contributions

Study design: Devraj. Data acquisition or analysis: Tracey. Manuscript drafting: Devraj, Elkouzi. Critical revision: all authors.

Conflicts of Interest

Ahmad Elkouzi serves on the advisory board of Duopa (AbbVie Inc.). All authors have no potential conflicts relevant to the manuscript to disclose.

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