# OFF PERIODS: ARE WE ASSESSING WHAT



#### **Are We Assessing What Matters?**

- Asking the right questions
- Understanding the impact of OFF
- Considering motor and non-motor OFF period symptoms
- Ensure to discuss the impact—How to enhance the dialogue?

"...OFF is in the ON of the beholder."

AJ Espay and AE Lang

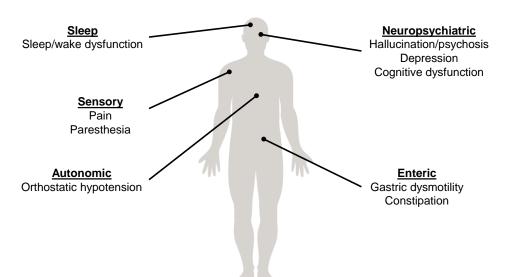
Espay AJ et al. *JAMA Neurol.* 2017; doi:10.1001/jamaneurol.2017.0348.

NOTES:		

### **SECTION 1:**

OFF Periods and Their Impact

# Non-motor Symptoms of PD Are Common and May Involve Many Body Systems



Hou JG et al. Int J Gerontol. 2007;1(2):53-64.

NOTES:

# Motor Features of PD Are Associated With Degeneration of Dopaminergic Neurons<sup>1</sup>

- Cardinal motor features are<sup>1</sup>:
  - Bradykinesia
  - Resting tremor
  - Rigidity
  - Postural instability
- Rate of progression may vary from person to person<sup>2</sup>
- 30% of individuals do not have tremor at presentation;
   15% never develop tremor<sup>1,3</sup>
- Postural instability usually occurs later in the disease course<sup>4</sup>



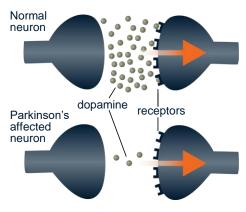
1. Olanow CW et al. Neurology. 2009;72(21 suppl 4):S1-S136. 2. Progression. http://www.pdf.org/en/progression\_parkinsons. Accessed October 2016. 3. Jankovic J. Handbook of Parkinson's Disease, 4th ed. 2007;49-76. 4. Jankovic J. J Neurol Neurosurg Psychiatry. 2008;79(4):368-376.

NOTES:		

#### **Impact of PD Progression**

- The progression of PD reduces the brain's ability to store and release dopamine when it is needed<sup>1,2</sup>
- Symptoms increase in frequency and severity due to continuing neurodegeneration<sup>1,3</sup>

## Dopamine levels in a normal and a Parkinson's affected neuron



1. Olanow CW et al. Neurology. 2009;72(21 suppl 4):S1-S136. 2. Stacy M et al. Mov Disord. 2005;20(6):726-733. 3. Hametner E et al. J Neurol. 2010;257(suppl 2):S268-S275.

NOTES:	

#### **Motor and Non-motor symptoms of PD**

#### **Motor Symptoms**<sup>1,2</sup>

- Tremor
- · Balance difficulties
- · Slowness of movement
- Stiffness
- · Reduced dexterity
- · Handwriting difficulties
- Dystonia

#### Non-motor Symptoms<sup>1,3,4</sup>

- · Depression
- Cognitive dysfunction
- · Anxiety
- · Cloudy mind/slowness of thinking
- Drooling (maybe)
- · Fatigue
- Mood changes
- Pain
- Orthostatic hypotension
- · Gastric dysmotility
- · Constipation

#### OFF periods are the reemergence of PD symptoms<sup>5</sup>

1. Stacy M et al. Mov Disord. 2005;20(6):726-733. 2. Jankovic J. J Neurol Neurosurg Psychiatry. 2008 Apr;79(4):368-76. 3. Witjas T et al. Neurology. 2002;59(3):408-413. 4. Hou JG et al. Int J Gerontol. 2007;1(2):53-64. 5. Hametner E et al. J Neurol. 2010;257(Suppl 2):S268-75.

NOTES:
NOTES:

#### **Burden of OFF Periods**

- In the US, approximately 350,000 people with PD experience OFF periods<sup>1-3</sup>
- In a survey of more than 3000 people with PD, most experienced at least 2 OFF periods daily, each with an average duration of 30 to 60 minutes<sup>4</sup>
- OFF periods can have a negative impact on health-related quality of life (HR-QOL)<sup>5</sup>
- Impact of OFF periods is physical and emotional<sup>5,6</sup>
  - Interrupt ability to function throughout the day
  - Prevent participating in work as well as social and leisure activities
  - Contribute to disability

1. Statistics on Parkinson's. http://www.pdf.org/en/parkinson\_statistics. Accessed February 2017. 2. Ahlskog JE et al. *Mov Disord*. 2001;16(3):448-458.
3. Decision Resources. Parkinson's Disease (Report: January 2015). 4. The Michael J. Fox Foundation Survey of Parkinson's Patients' Off Time Experience; July 2014. 5. Hechtner MC et al. *Parkinsonism Relat Disord*. 2014;20(9):969-974. 6. Brown RG et al. *J Psychosom Res*. 2015;78(2):143-148.

NOTES:	

# OFF Time Significantly Impacts Patient Quality of Life and Caregiver Burden

- Comparing PD patients who experienced OFF with those who did not experience OFF:
  - PD patients who experience OFF had significantly worse ADL, emotional well-being, stigma, and bodily discomfort
  - The number of OFF hours correlated with mobility, ADL, emotional wellbeing, stigma, communication, and bodily discomfort on the PDQ-39
  - Caregiver Interpersonal Strain was significantly impacted in patients who experienced OFF
  - Number of OFF hours increased caregiver burden as assessed by physical strain and time constraints on the MCSI

394 patients assessed at KUMC were included in this analyses. KUMC is part of the National Parkinson Foundation Quality Improvement Initiative (NPF-QII)

Dowell P et al. Neurology. 2017;88(16):suppl P6.007.

NOTES:	

#### Michael J. Fox Foundation (MJFF) Survey on OFF Time

- Online survey conducted between 16 July and 7 August 2014
- Nine questions covering:
  - OFF-time frequency
  - OFF-time duration
  - OFF-time impact on ADL
  - OFF-time impact on QOL
  - Perceived disability from OFF time
- Sample size: >3000
- Data reported include:
  - Number of OFF periods per day
  - Duration of an OFF period
  - Symptoms during OFF periods



\*There are no demographics from which to compare the survey responses by groups. For example, we do not know the duration of disease, age, sex, or medication history. For more information on this study, see <a href="https://www.michaelifox.org">https://www.michaelifox.org</a>.

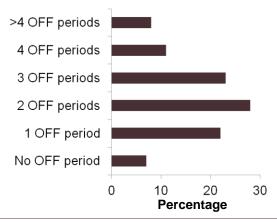
ADL indicates activities of daily living.

The Michael J. Fox Foundation Survey of Parkinson's Patients' Off Time Experience; July 2014.

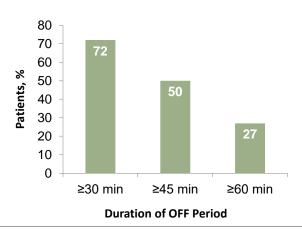
NOTES:			

# MJFF Survey on OFF Time: Number of OFF Periods per Day and Duration of an OFF Period

## Most patients experienced 2 OFF periods per day



## OFF period lasted ≥ 30 minutes in majority of patients



The Michael J. Fox Foundation Survey of Parkinson's Patients' Off Time Experience; July 2014.

NOTES:		

#### MJFF Survey on OFF Time: Most Patients Experience Both Motor and Non-motor Symptoms During OFF Periods

The most frequent difficulties experienced during an OFF period over the course of a week as selected from a predefined list:

- Anxiety
- Depression
- Difficulty walking safely
- · Difficulty getting around in public
- Difficulty with work tasks such as typing

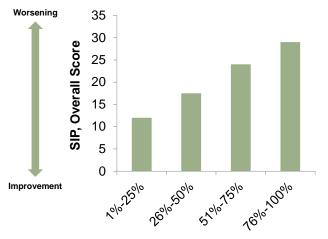
The Michael J. Fox Foundation Survey of Parkinson's Patients' Off Time Experience; July 2014.

Difficulty with housework or cooking

NOTES:			
NOTES			

#### **HR-QOL May Worsen As OFF Periods Increase**

- Prospective assessment of OFF time over 3 months (July-September 1995) and it's effects on patients' HR-QOL in a small study of 40 PD patients<sup>1</sup>
- OFF time was determined via the Unified Parkinson's Disease Rating Scale Part IVB<sup>2</sup>
- As OFF time increased, there was a stepwise decrease in QOL, as reported by the SIP instrument<sup>2</sup>



Percentage of Day in OFF Period<sup>2</sup>

HR-QOL indicates health-related quality of life; SIP, sickness impact profile.

1. Dodel RC et al. *Pharmacoeconomics*. 1998;14(3):299-312. 2. Dodel RC et al. *Pharmacoeconomics*. 2001;19(10):1013-1038. Figure adapted from Dodel RC et al. *Pharmacoeconomics*. Health-related quality of life and healthcare utilisation in patients with Parkinson's disease: impact of motor fluctuations and dyskinesias. 2001;19(10)1013-1038. © 2001 Adis International Limited. All rights reserved. With permission of Springer.

NOTES:	

## Motor Fluctuations (OFF) Impact Health Care Utilization

- PD is associated with significant health care utilization<sup>1</sup>
- The number of motor fluctuations (OFF) have been shown to have the most significant impact on PD-associated health care utilization<sup>2</sup>
- Both direct and indirect medical costs increase in patients experiencing greater than 25% OFF time per day compared to those patients with less than 25% of OFF time per day<sup>3</sup>
  - Average Costs by OFF Time/day were obtained over 6 Months (\$US)
  - Total 6 month costs increased more than 3 times in patients with >25% OFF Time/day

1. Boland DF et al. *Am J Manag Care*. 2012;18(7 suppl):S168-S175. 2. Dodel RC et al. *Pharmacoeconomics*. 2001;19(10):1013-1038. 3. Palmer CS et al. *Pharmacoeconomics*. 2002;20(9):617-628.

NOTES:		

#### PD Symptoms Impact All Aspects of Patients' Lives

 The FDA held a public meeting for individuals with PD and their care providers/representatives to hear their perspectives on the most significant effects of the disease

"The various OFF and ON states is what makes this disease so hard to live with."

- Participants emphasized the difficulty of living with the unexpected onset and progression of symptoms
- Many described living with both daily motor and non-motor symptoms
- · Symptoms impact all aspects of patients' lives
  - Limitations in performing at work, caring for self and family, and maintaining relationships
- Complexities of disease management include:
  - Time of day
  - Unpredictability of symptoms

"Symptoms can vary not only from day to day, but from hour to hour."

This includes a range of experiences and may not completely represent all individuals with PD.

FDA indicates the US Food and Drug Administration.

The Voice of the Patient. May 2016. http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM498266.pdf. Accessed October 2016.

NOTES:	

#### **Summary**

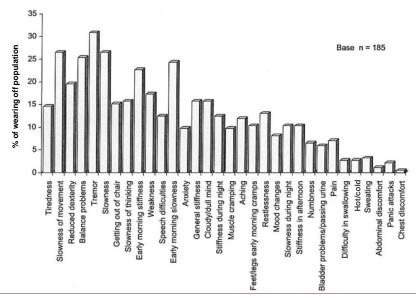
- PD is defined by a progressive loss of dopaminergic neurons in the brain, leading to a spectrum of symptoms
- PD symptoms become increasingly difficult to control owing to inadequate and variable levels of dopamine as the disease progresses
- OFF periods, defined as re-emergence of PD symptoms, can occur throughout the day and be unexpected
- Re-emergence of PD symptoms:
  - Are a major concern to people with PD
  - Can be physically and emotionally troublesome
  - Worsens patient QOL and increases caregiver burden
  - Impact PD-associated health care utilization
  - Can be challenging owing to symptom variability and a lack of communication between patients and their clinicians

NOTEC.			
NOTES:			

#### **SECTION 2:**

OFF Periods
The Patient/Health Care Provider Dialogue:
What We Know and What We Don't Know

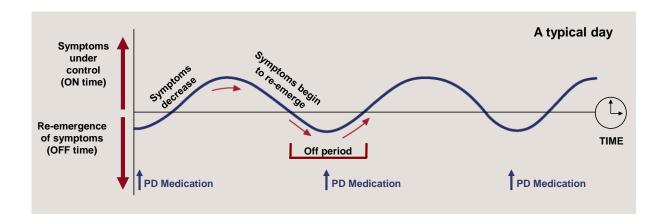
### **Symptoms During OFF Periods Are Highly Variable**



Stacy M et al. Mov Disord. 2005;20(6):726-733

NOTES:		

### OFF Periods Can Occur During Treatment<sup>1,2</sup>



1. Stacy M et al. Mov Disord. 2005;20(6):726-733. 2. Stacy M et al. 2009. www.medscape.org/viewarticle/701955. Accessed October 2016. Permission for use of adapted figure granted by John Wiley & Sons, Inc., for Stacy M et al. Mov Disord. 2005;20(6):726-733. © 2005 Movement Disorder Society.

NOTES:		

#### What are the options for assessing the situation?

- Medical history<sup>1</sup>
  - Review medication regimen, assess compliance, narrative history of day
  - Unstandardized
- Standardized tools, e.g., Wearing OFF questionnaire (WOQ)<sup>1</sup>
  - WOQ-9 contains 5 motor and 4 non-motor symptoms
- · Medication challenge
  - May be useful in complex cases and is time intensive
  - Does not replicate patient's usual situations
- Wearable devices/body sensors<sup>2</sup>

1. Pah	wa R et al.	. Curr Med R	es Opin	. 2009;25(4):84′	1-849. 2.	Mirelman A et a	I. JAMA.	2015;31	4(9):873	3-874	
--------	-------------	--------------	---------	------------------	-----------	-----------------	----------	---------	----------	-------	--

NOTES:		

## Impact of Motor and Non-motor Fluctuations: A Mixed-Methods Study

- To identify barriers and facilitators to communication about OFF periods between health care professionals, PwP, and care partners
- Step 1: Systematic review to summarize the existing literature on communication
- **Step 2:** Qualitative interviews with health care professionals, PwP, and care partners, to understand:
  - Experiences of OFF periods, their impact, and implications
  - How they communicate about OFF periods
  - The barriers and facilitators to communication about OFF periods
- Step 3: Survey ~200 health care professionals, PwPs, and care partners about communication around OFF periods

NOTES:			
NOTES:			

#### Impact and Communication of OFF Periods in PD

Scoping review 2006 to 2017

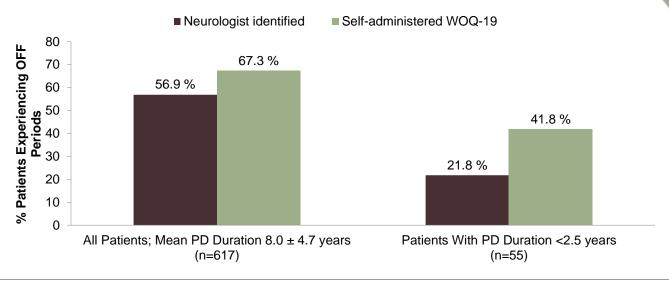
- 2021 abstracts identified, 51 full texts screened, and 14 papers met eligibility criteria
  - -7 studies showed an association between OFF periods and poorer HR-QoL
  - -2 qualitative studies highlighted **significant burden of OFF**, especially:
    - · unpredictability of functioning
    - reliance on others for administration of medications
  - 1 study addressed communication
  - 0 studies addressed strategies, barriers, or facilitators of communication about OFF periods between physicians and PwP or care partners

Quantitative and qualitative studies examining impact of OFF periods on PwP or care partners, or communication about OFF periods between health care providers and PwP or carepartners were eligible

Rastgardani T et al. Poster Presented At: International Congress Of Parkinson's Disease And Movement Disorders. June 4-8, 2017. Vancouver, BC.

NOTES:	

# **OFF Periods Are More Accurately Estimated Using Self-Administered Questionnaires**



Stocchi F et al. Parkinsonism Relat Disord. 2014;20(2):204-211.

NOTES:		

# **Medical Linguistic Analysis: Differences in OFF-Period Lexicon**

Physicians	Patients/Caregivers
Episodic language Time, days, morning, when, sometimes, commonly, frequently, periods, episodes	Symptom reports "I started off, it was just a little pain."
Motion metaphors	Unpredictability
Up/down, freeze, frozen, hold, stop/go, move stuck, on/off	"I like to walk, but I'm afraid to get too far from the houseI won't get back, you know."
Patterns	Personal narratives and comparative language
"So, it wears off?"	"I was standing at the kitchen sink doing something. I
"The effect of [medication] goes down more in the morning and in the afternoon, 3 PM?"	feel all of the sudden very, very weak, so I, I can walk over to the chair, and I sitI'm really out of it."
Had a defined lexicon drawing on patterns and episodic language	Relied on personal anecdotes and did not rely on an OFF-time lexicon

n = 30 dialogues recorded from 29 patients

Squillacote D et al. Neurology. 2017;88(16):suppl P6.015.

NOTES:		

# Medical Linguistic Analysis: Misunderstanding of Physicians' Questions

Physicians	Patients/Caregivers
<ul> <li>Physicians combined discussion on OFF periods with overall treatment assessment by asking:</li> <li>What medications are you taking?</li> <li>What dose are you taking, how often, and at what time(s)?</li> <li>Do the symptoms recur before the next dose is due?</li> </ul>	<ul> <li>Most patients did not understand why physicians asked these questions</li> <li>Some misinterpreted that these questions were about medication compliance</li> </ul>
quillacote D et al. <i>Neurology</i> . 2017;88(16):suppl P6.015.	
TES:	

# **Medical Linguistic Analysis: Differences in OFF-Period Assessment**

### **Physician Perspective** Patients/Caregiver Perspective · They ask patients about their symptoms and relate · Physicians did not ask about specific symptoms in them to the dosing schedule relation to dosing schedule Dialogue analysis: physicians were incomplete The lack of specific terminology to describe OFF in discussing symptoms in relation to dosing periods constitutes a barrier schedule · Patients did not realize the importance of They provide clear education about OFF periods communicating OFF periods Patients are too embarrassed or possibly in denial Dialogue analysis: indicated that few physicians gave detailed OFF-period of OFF periods as they realize symptom reinformation or discussed activity logs or emergence may indicate disease progression trackers Squillacote D et al. Neurology. 2017;88(16):suppl P6.015. NOTES:

#### **Conclusions and Recommendations**

- RE: Doctor-patient communication about OFF periods
  - Existing literature provides little guidance
- Current practice may not be identifying the issues of greatest concern to patients
  - Need a common lexicon between doctors and patients
  - Focus on the *impact* of OFF periods is important
  - Some patients do not understand the relevance of medication timing to OFF periods
  - Failure of physicians to explain the relationship may pose a barrier to communication
- NEXT STEPS: educational tools for physicians and patients to improve communication

NOTES:			