touchROUNDTABLE

The impact of delayed ON: Treating OFF episodes in patients with Parkinson's disease

An expert panel discussion

An expert panel discussion recorded in October 2022

This activity has been sponsored by Sunovion Pharmaceuticals Inc.
Sunovion Pharmaceuticals Inc. provided financial support and has had input into the selection of faculty and the detailed project scope.

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Expert panel

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After watching this touchROUNDTABLE activity, you should better be able to:

- ✓ Outline the impact of delayed ON in the context of the total daily OFF time experienced by a patient.
- ✓ Discuss potential changes in treatment approach based on the type of OFF experienced by patients.
- ✓ Identify patients who may benefit from an on-demand therapy for OFF based on the findings of an expert consensus panel.

Disclosures

Dr Stuart Isaacson

Honoraria for CME, consultant, research grants, and/or promotional speaker on behalf of: Abbvie, Acadia, Acorda, Adamas, Addex, Affiris, Alexza, Allergan, Amarantus, Amneal, Aptinyx, Axial, Axovant, Benevolent, Bial, Biogen, Biovie, Britannia, Cadent, Cala, Cerecor, Cerevel, Cipla, Eli Lilly, Enterin, GE Healthcare, Global Kinetics, Impax, Impel, Intec Pharma, Ipsen, Jazz, Kyowa Kirin, Lundbeck, Merz, Michael J. Fox Foundation, Mitsubishi Tanabe, Neuralys, Neurocrine, Neuroderm, Novartis, Parkinson Study Group, Pharma2B, Praxis, Prilenia, Promentis, Revance, Roche, Sage, Sanofi, Scion, Stoparkinson, Sunovion, Sun Pharma, Supernus, Teva, Theravance and Transposon.

Dr Yasar Torres-Yaghi

Honoraria from Sunovion.

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Agenda

	Discussion open and introduction	**5 mins**	**Stuart Isaacson**
1	**PRESENTATION:** The impact of OFF episodes including delayed ON	**10 mins**	**Yasar Torres-Yaghi**
2	**PRESENTATION:** The current treatment approach to OFF	**10 mins**	**Rajesh Pahwa**
3	**PANEL DISCUSSION:** How to identify the type of OFF and select an intervention	**10 mins**	**All faculty**
4	**PRESENTATION:** Selecting patients: the Delphi panel findings	**10 mins**	**Stuart Isaacson**
5	**PANEL DISCUSSION:** How to select patients	**10 mins**	**All faculty**
	Close		

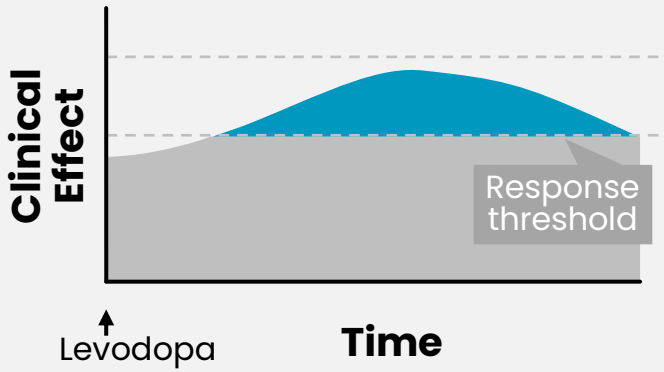
Introduction to OFF episodes

Dr Stuart Isaacson

Change in levodopa response over time[1,a]

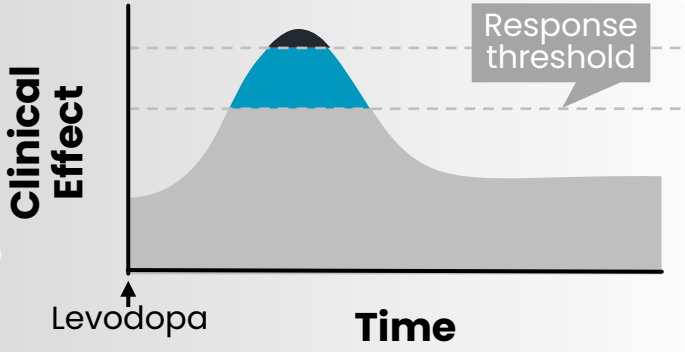
As the disease progresses, there are fewer healthy neurons to release dopamine, or to convert levodopa to dopamine and release it properly[2]

EARLY PD



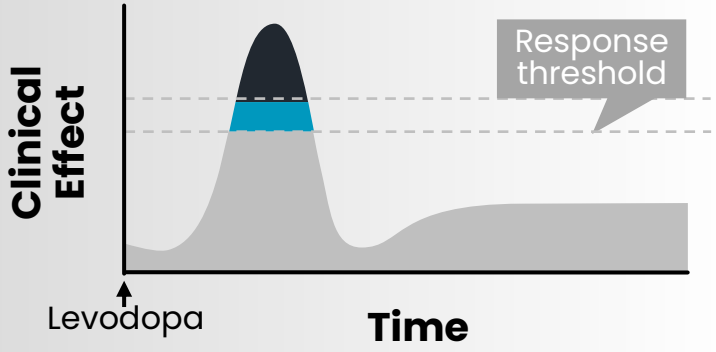
- Smooth, extended duration of target clinical response
- Low incidence of dyskinesia

MODERATE PD



- Diminished duration of target clinical response
- Increased incidence of dyskinesia

ADVANCED PD



- Diminished duration of target clinical response
- ON time is frequently associated with dyskinesia

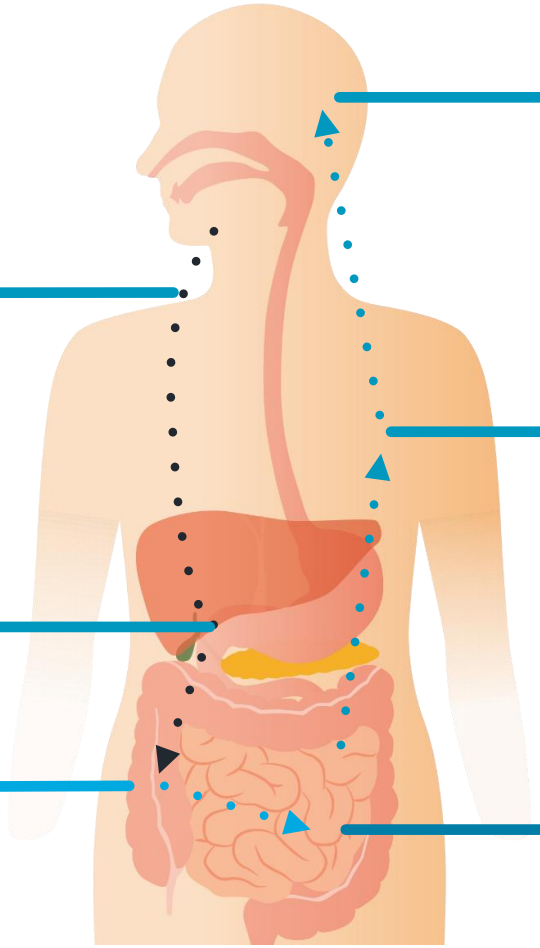
ON ON with dyskinesia OFF

[a]Mean time to ON following a typical carbidopa/levodopa dose may be 46 ± 21 minutes[3]; however, the duration of time spent ON declines with disease progression.[2]

1. Obeso JA, et al. *Neurology*. 2000;55(suppl 4):S13-S20; 2. Olanow CW, et al. *Mov Disord.* 2021;36:2244-2253; 3. Merims D, et al. *Clin Neuropharmacol*. 2003;26:196-198.

PD, Parkinson's disease.

Challenges that may impact optimal delivery of levodopa and other oral dopaminergic medications



Competition with amino acids for levodopa transport across the BBB[1,5]

Esophageal dysmotility[1]

Extensive peripheral breakdown of levodopa by AADC and COMT[1]

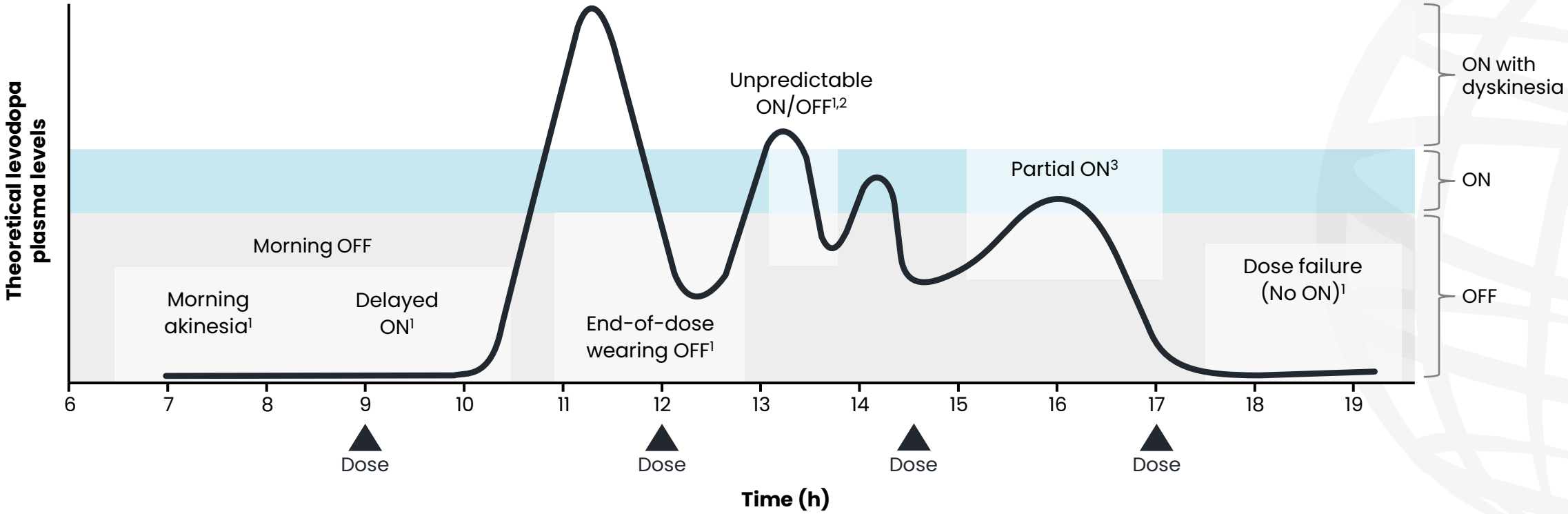
Gastroparesis leading to variable absorption[2,3]

Small intestine bacterial overgrowth[4]

Competition with amino acids for levodopa transport across the intestinal wall[1]

1. Suttrup I, et al. *Neurogastroenterol Motil.* 2017;29(1); 2. Müller T, et al. *Clin Neuropharmacol.* 2006;29:61-67; 3. Fasano A, et al. *Lancet Neurol.* 2015;14:625-639; 4. Tan AH, et al. *Parkinsonism Relat Disord.* 2014;20:535-540; 5. Leenders KL, et al. *Ann Neurol.* 1986;20:258-262.
AADC, aromatic L-amino acid decarboxylase; BBB, blood-brain barrier; COMT, catechol-O-methyltransferase.

Examples of OFF episodes[a]



[a]Graphical representation of response to treatment with levodopa in a hypothetical patient with Parkinson's disease.

1. Chou KL, et al. *Parkinsonism Relat Disord*. 2018;51:9-16; 2. Adler CH. *Neurology*. 2002;58(4 suppl 1):S51-S56; 3. Reimer J, et al. *J Neurol Neurosurg Psychiatry*. 2004;75:396-400; 4. Magrinelli F, et al. *Parkinsons Dis*. 2016;2016:9832839; 5. Olanow CW, et al. *Neurology*. 2009;72(21 suppl 4):S1-S136.

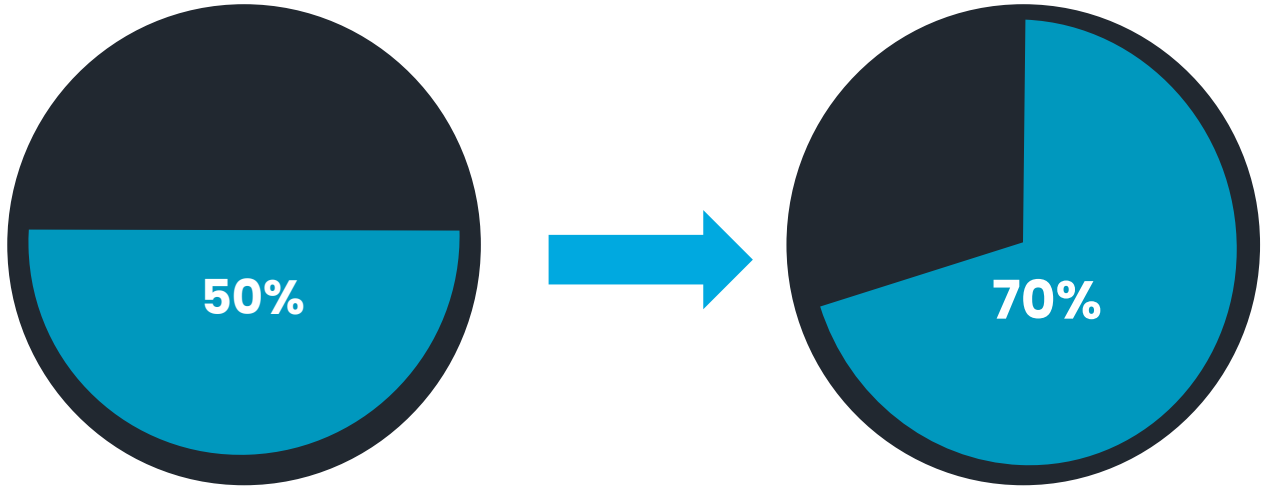
The impact of OFF episodes including delayed ON

Dr Yasar Torres-Yaghi

The incidence of OFF episodes

Most patients will experience OFF episodes with disease progression[1]

After **5 years** of oral levodopa treatment, nearly **50%** of patients with PD develop OFF episodes[1]

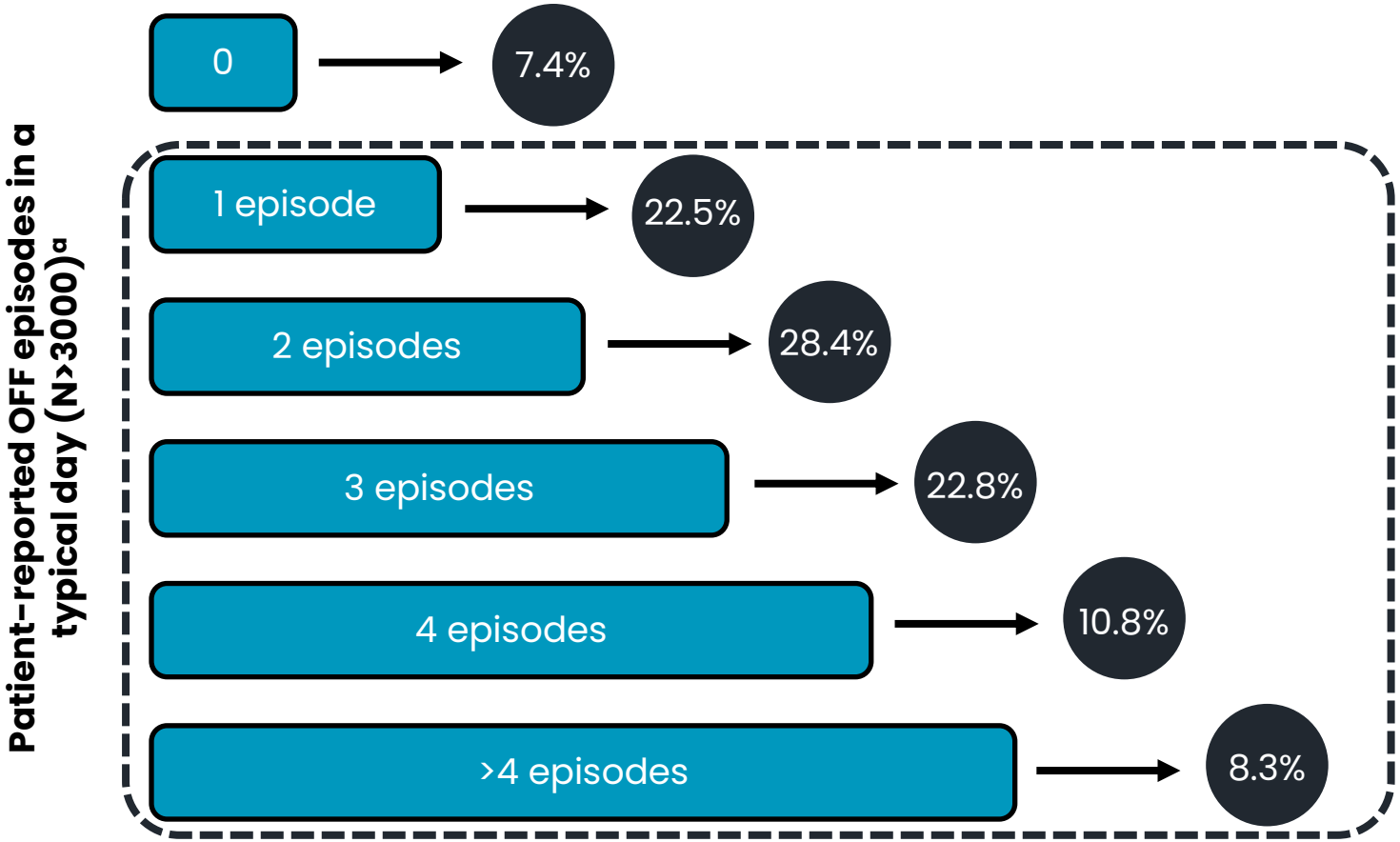


Beyond **9 years** of oral levodopa treatment, **70%** of patients with PD develop OFF episodes[2]

Patients with PD often experience OFF episodes in the morning; this particularly affects mobility and activities of daily living[3]

1. Thanvi BR, et al. *Postgrad Med J*. 2004;80:452-458; 2. Ahlskog JE, et al. *Mov Disord*. 2001;16(3):448-458; 3. Chapuis S, et al. *Mov Disord*. 2005;20:224-230.
PD, Parkinson's disease.

OFF episodes are commonly experienced multiple times per day



>90% of patients with PD reported ≥1 OFF episode each day

[a]Michael J. Fox Foundation for Parkinson's Research survey (N=~3000); patients' responses were self-reported online, treatment regimens were unknown and the survey did not specify the patients' levels of PD severity.

1. The Michael J. Fox Foundation. Executive summary: survey of Parkinson's patients and their OFF time experience; 2014.

PD, Parkinson's disease.

Relationship between Parkinson's Disease Questionnaire (PDQ-39)[a] scores and presence/absence of OFF episodes

PDQ-39 Dimensions	Coefficient (95% CI)[b]	P Value
Summary index	+5.2 (2.8, 6.5)	**<0.001**
Mobility	+7.9 (4.4, 11.4)	**<0.001**
Activities of daily living	+6.7 (3.2, 10.1)	**<0.001**
Emotional well-being	+4.5 (0.7, 8.3)	**0.019**
Stigma	+3.0 (−0.1, 6.1)	0.057
Social support	+2.3 (−0.7, 5.3)	0.134
Cognitions	+6.5 (3.5, 9.4)	**<0.001**
Communication	+9.0 (6.0, 11.9)	**<0.001**
Bodily discomfort	+1.7 (−3.0, 6.5)	0.470

When patients with PD who were receiving CD/LD (N=722) self-completed the PDQ-39, those with OFF episodes (n=321) reported poorer HRQoL per the PDQ-39 than those without OFF episodes (n=401)

[a]PDQ-39 is a 39-item questionnaire that measures health status and quality of life by assessing how often people with Parkinson's disease experience difficulty across 8 dimensions of daily living.

[b]Effect coefficient for difference between patients with/without OFF episodes from linear regression; + indicates a higher score on the PDQ-39 dimension or summary index, indicating poorer HRQoL, in patients with OFF episodes compared with patients without OFF episodes.

Thach A, et al. *BMC Neurol.* 2021;21:46.

CD, carbidopa; CI, confidence interval; HRQoL, health-related quality of life; LD, levodopa; PD, Parkinson's disease; PDQ-39, 39-item Parkinson's Disease Questionnaire.

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Examples of the specific impact of OFF episodes on mobility and activities of daily living

PDQ-39 Items, Mobility	OR (95% CI)[a]	*P* Value
Had difficulty doing the leisure activities which you would like to do	2.2 (1.5, 3.0)	**<0.001**
Had difficulty looking after your home	1.9 (1.4, 2.6)	**<0.001**
Had problems walking 100 yards	2.0 (1.5, 2.7)	**<0.001**

PDQ-39 Items, Activities of Daily Living	OR (95% CI)[a]	*P* Value
Had difficulty washing yourself	1.8 (1.3, 2.4)	**<0.001**
Had difficulty dressing yourself	1.8 (1.3, 2.4)	**<0.001**
Had problems doing up buttons or shoelaces	1.7 (1.3, 2.3)	**0.001**
Had problems writing clearly	2.2 (1.6, 2.9)	**<0.001**

[a]OR for difference between patients with/without OFF episodes from ordered logistic regression; an OR >1 indicates higher likelihood of problems in a PDQ-39 item, indicating poorer HRQoL, in patients with OFF episodes compared with patients without OFF episodes.
Thach A, et al. *BMC Neurol.* 2021;21:46.
CI, confidence interval; HRQoL, health-related quality of life; OR, odds ratio; PDQ-39, 39-item Parkinson's Disease Questionnaire.

Morning bradykinesia is underrecognized

Morning bradykinesia is underrecognized, as most individuals with PD experienced prolonged morning bradykinesia after their first daily dose of levodopa

Based on a retrospective evaluation of data collected with continuous objective monitoring devices in patients with early- through late-stage PD in the United States (n=1,524):

85%

Experienced morning bradykinesia

64%

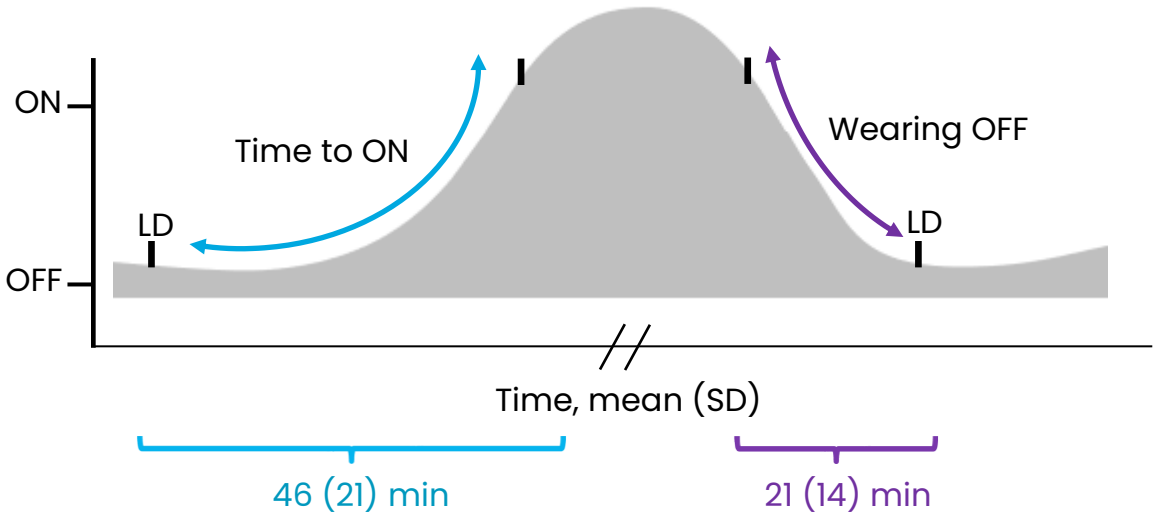
of those with morning bradykinesia experienced continued bradykinesia after the first daily levodopa dose

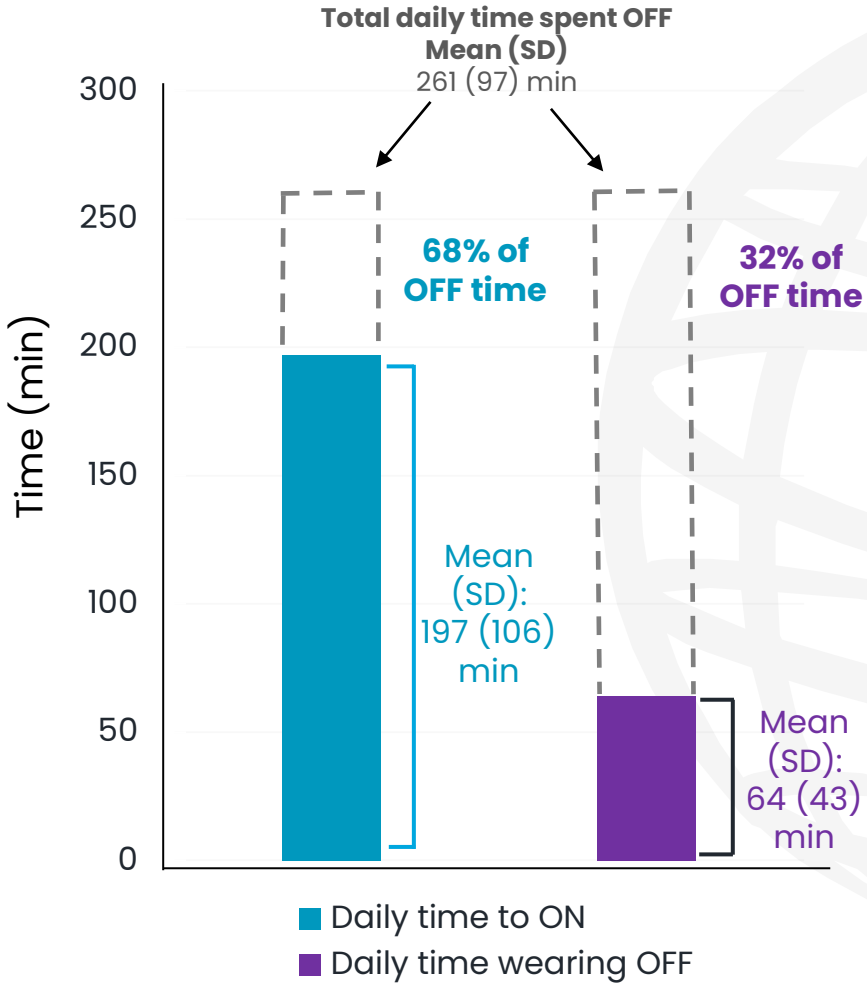
48%

of those with morning bradykinesia spent ≥75% of their daytime (9am–6pm) in bradykinesia

1. Isaacson SH, et al. *Clin Park Relat Disord*. 2022;6:100145.
PD, Parkinson's disease

The contribution of time to ON and wearing OFF to daily OFF time[a]





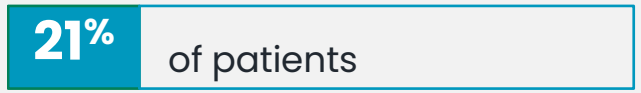
[a]Based on a study of 20 patients (H&Y 3–4) with advanced PD receiving levodopa (mean total daily dose of 821 mg, in 5–9 divided daily doses). Patient diaries were completed for 5 consecutive days.
Merims D, et al. *Clin Neuropsychopharm.* 2003;25(4):196-198.
H&Y, Modified Hoehn and Yahr Scale; LD, levodopa; mg, milligrams.

Delayed ON and no ON are common as part of morning off[a]

Delayed ON

Delayed ON ≥1 mornings in the past week

Delayed ON every morning in the past week



35–40 minutes

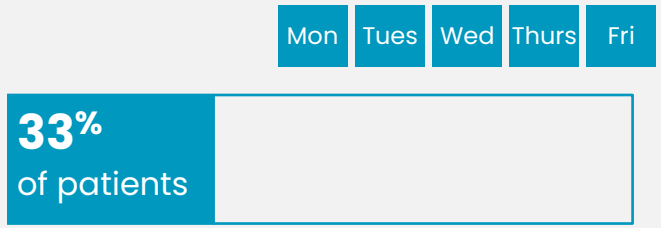
Mean time to ON after morning dose

56% **>30 minutes to turn ON**

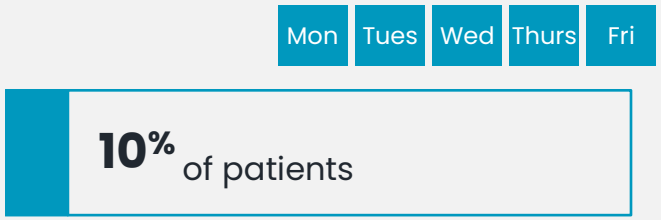
after morning dose

No ON

≥1 morning dose failure per week



≥4 morning dose failures per week



[a]An observational study in 97 fluctuating patients with PD; patients were Hoehn and Yahr stage 2–3 when ON, and had a mean PD duration of 8.1 years.
Stocchi F, et al. *Eur J Neurol*. 2019;26:821-826.
PD, Parkinson's disease.

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Time to ON with morning dose of carbidopa/levodopa baseline therapy[a]

A study of 88 patients with motor fluctuations[b] required patients to complete a 7-day baseline period, during which they recorded their time-to-ON following each morning dose of levodopa.

Mean (SD) time to ON: 60.9 (18.1) min

Dose failures: 46% of completed diary entries

[a]Patients in this study were required to have a minimum of a 45 minute latency to ON following morning administration of carbidopa/levodopa.
[b]Average age 65.6 years with average duration of PD of 11.6 yrs.
Isaacson S, et al. *Mov Disord Clin Pract*. 2017;4:78-83.
SD, standard deviation.

The current treatment approach to OFF

Dr Rajesh Pahwa

Goals and considerations of treatment with on-extenders for patients with PD

Treatment Considerations

- Over time, patients with PD often require more frequent and higher LD doses in order to manage their symptoms
- ON-extenders are available that help to improve OFF and may allow for reduction in daily LD dosing
- ON-extenders do not usually address the acute conversion from OFF to ON

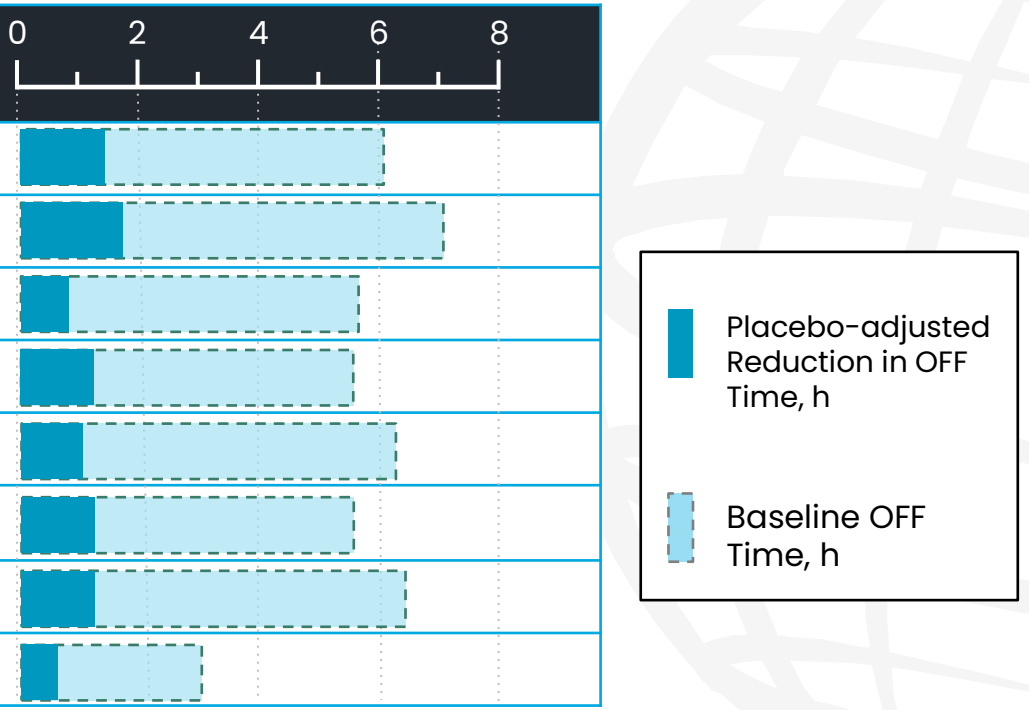
Treatment Goals

- ON-extenders are intended to provide additional symptom management when co-administered with CD/LD
- ON-extenders prolong time spent in the ON state

1. Armstrong MJ and Okun MS. *JAMA*. 2020;323:548-560. 2. Thach A, et al. Systematic literature review of key outcomes used to assess adjunctive treatments for Parkinson's disease. Presented at: International Parkinson's Disease and Movement Disorder Society Congress (MDS); 2022; Madrid, Spain. Poster 783.
CD, carbidopa; LD, levodopa; PD, Parkinson's disease.

Despite adjustments to CD/LD therapy and addition of adjunctive medications, patients may still spend ~4 hours of their day experiencing OFF episodes[a]

Drug	Baseline OFF Time, h	CFB in OFF Time, h[b]
Pramipexole[1]	6.0	−1.4
Ropinirole 24-h[2]	7.0	−1.7
Rasagiline[3]	5.6	−0.8
Entacapone[4]	5.5	−1.2
Opicapone[6]	6.2	−1.0
CD/LD/entacapone[4]	5.5	−1.2
Istradefylline[7]	6.4	−1.2
Amantadine ER[8]	3.0	−1.0

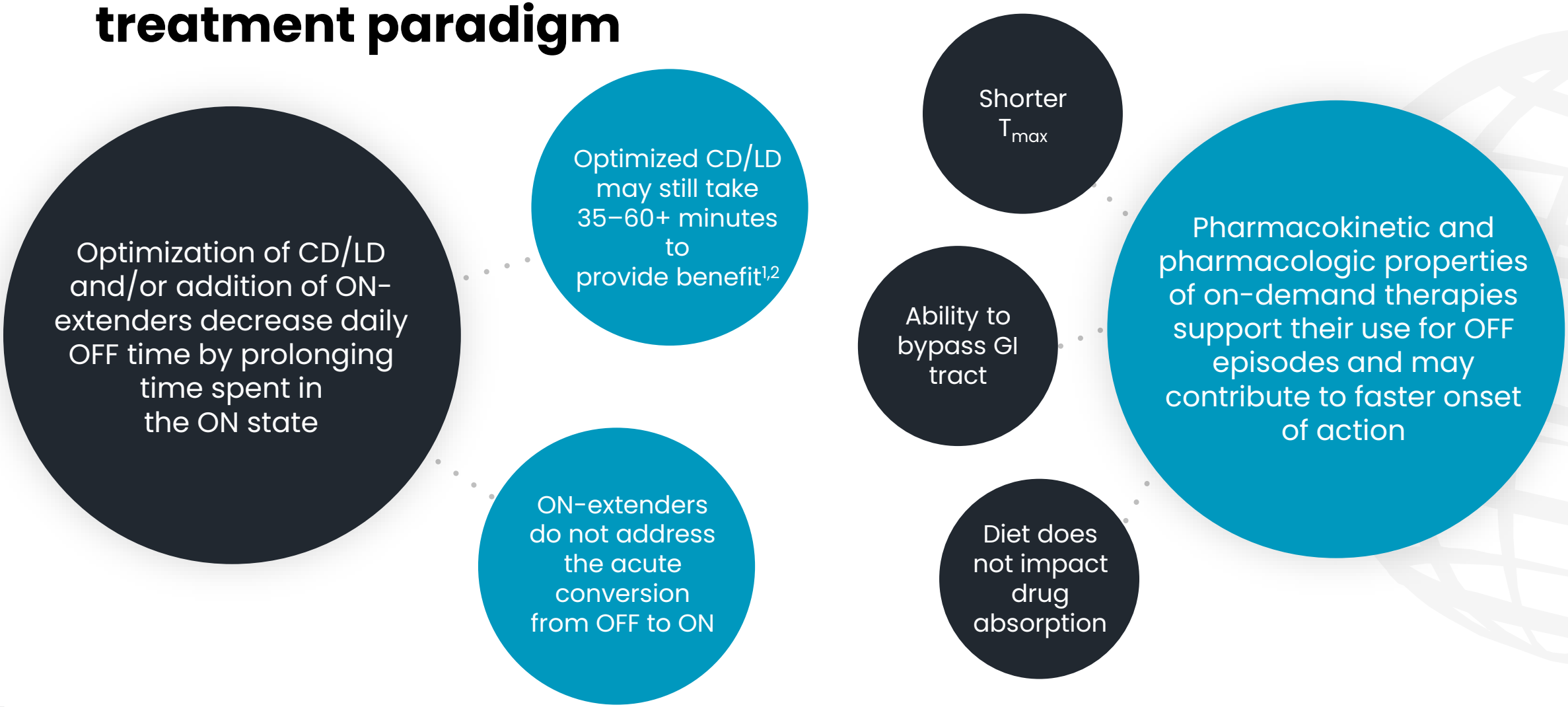


[a]Reduction in OFF time was assessed using patient diaries; [b]Data represent placebo-adjusted values.

1. Lieberman A, et al. *Neurology*. 1997;49:162-168; 2. Pahwa R, et al. *Neurology*. 2007;68:1108-1115; 3. Rascol O, et al. *Lancet*. 2005;365:947-954; 4. Rinne UK, et al. *Neurology*. 1998;51:1309-1314; 5. Rajput AH, et al. *Neurology*. 1997;49:1066-1071; 6. Ferreira JJ, et al. *Lancet Neurol*. 2016;15:154-165; 7. LeWitt PA, et al. *Ann Neurol*. 2008;63:295-302; 8. Elmer LW, et al. *CNS Drugs*. 2018;32:387-398.

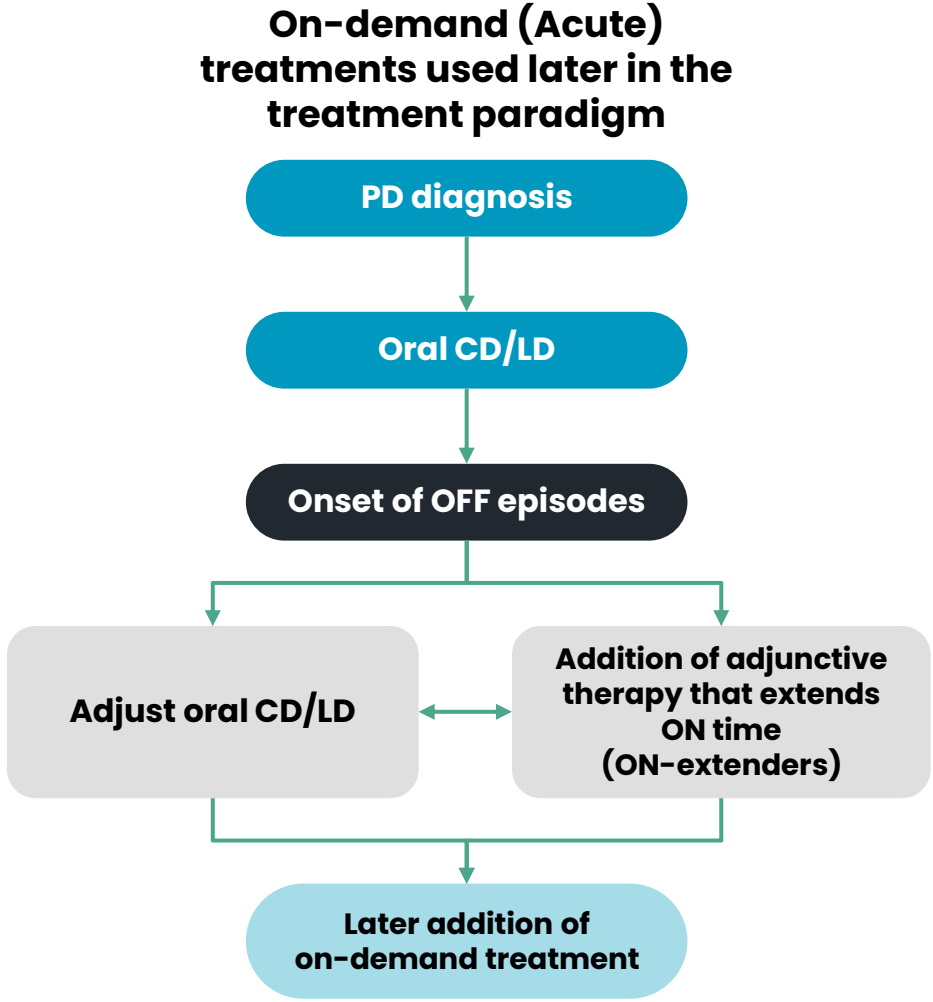
CD, carbidopa; CFB, change from baseline; ER, extended release; LD, levodopa.

How on-demand therapies fit in the current treatment paradigm



1. Stocchi F, et al. *Eur J Neurol*. 2019;26:821-826; 2. Isaacson S, et al. *Mov Disord Clin Pract*. 2017;4:78-83.
CD, carbidopa; GI, gastrointestinal; LD, levodopa; PD, Parkinson's disease; T_{max}, time to maximum concentration.

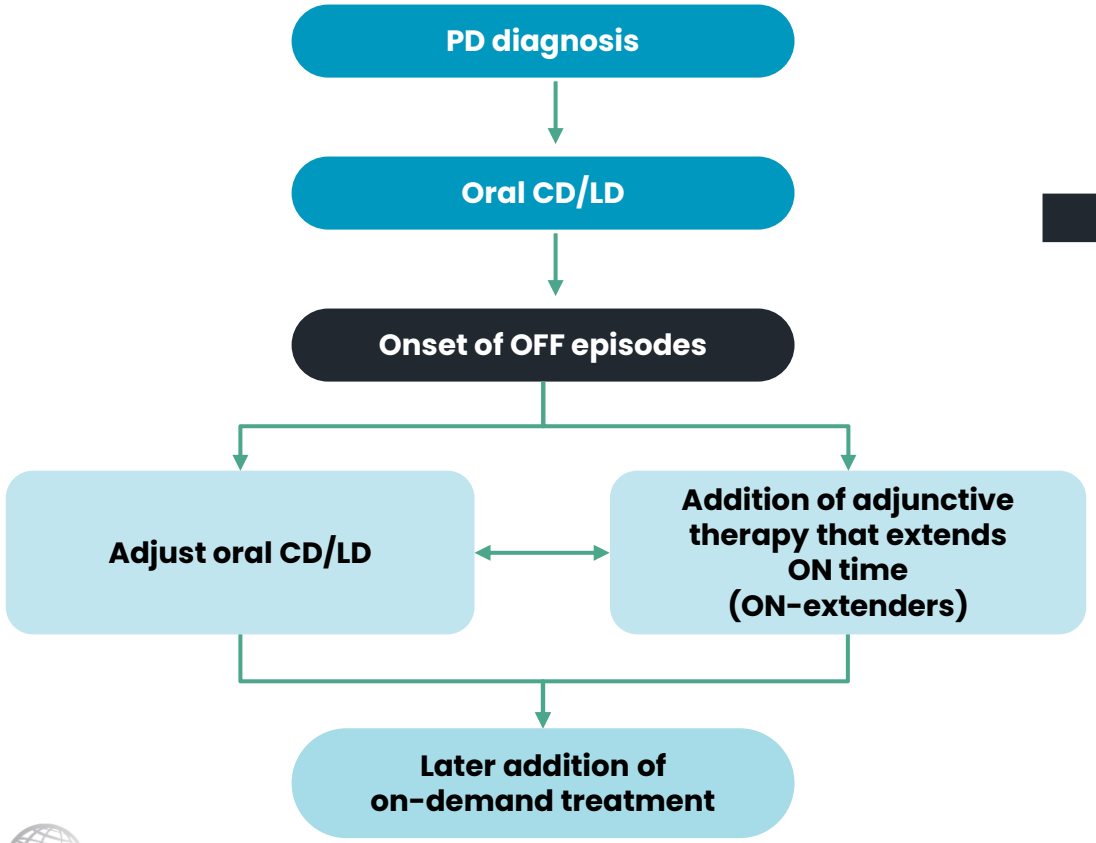
Current paradigm for the pharmacologic treatment of Parkinson's disease[1,2]



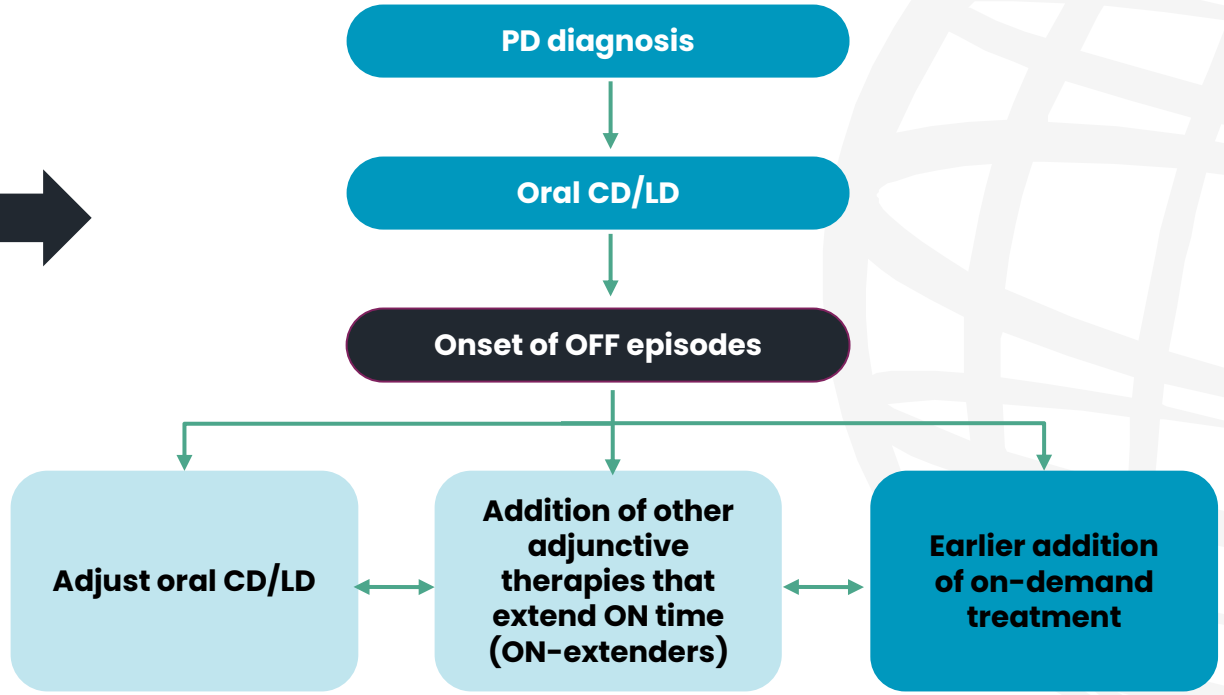
1. Armstrong MJ and Okun MS. *JAMA*. 2020;323:548-560; 2. Fox SH, et al. *Mov Disord*. 2018;33:1248-1266.
CD, carbidopa; LD, levodopa; PD, Parkinson's disease.

Shifting the treatment paradigm: complementary use of on-demand acute treatment for OFF episodes

On-demand treatments used later in the treatment paradigm[1,2]



On-demand treatment used at the onset of OFF episodes[3]



1. Armstrong MJ and Okun MS. JAMA. 2020;323:548-560; 2. Fox SH, et al. *Mov Disord*. 2018;33:1248-1266; 3. Isaacson S, et al. *Clin Park Relat Disord*. 2022;7:100161.
CD, carbidopa; LD, levodopa; PD, Parkinson's disease.

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Patient decision-making and empowerment

Desire for shared decision-making[a]

93% of patients preferred to be involved in decision-making for selecting a treatment for OFF

31% of patients want to decide themselves

62% want shared-decision making with their neurologist

Unmet needs

47% of patients had a mismatch between their preferred and experienced role in decision-making

Main barriers to shared-decision-making:
1. Patients perceiving there was no choice
2. Physician's own treatment preference

Patients require personalized information on all treatment options and improvement on how this information is communicated

[a]121 patients with PD were surveyed.
Nijhuis FAP, et al. *Front Neurol*. 2019;10:896.

Selecting patients: the Delphi panel on the pharmacological approach to OFF episodes in PD

Dr Stuart Isaacson

On-demand treatments in Parkinson's disease

Objective

Develop a clinical consensus on the use of on-demand therapies in PD, including when on-demand therapies should be initiated

This panel was conducted in a double-blinded manner, in which panelists were blinded to the identity of the Sponsor* and the Sponsor was blinded to the identity of the panelists until manuscript submission.

Rating form covered 6 major characteristics:

- **Patient's perspective on the functional impact of OFF episodes**
- **Levodopa dose**
- **Adjunctive therapy history**
- **Experiencing therapy-related side effects**
- **Type of OFF episodes**
- **Frequency of duration or OFF episodes**

* Funding for the panel was provided by Sunovion Pharmaceuticals Inc.

1. Isaacson SH, et al. Use of on-demand treatments for OFF episodes in Parkinson's disease: guidance from a RAND/UCLA modified Delphi consensus panel. Presented at: 4th Pan American Parkinson's Disease and Movement Disorder Congress (PAS); May 26-28, 2022; Miami, FL USA. Poster 123.

PD, Parkinson's disease.

Panelists

Panelists averaged of 25 years of clinical practice/advocacy experience

Physicians averaged 620 current patients with PD

All physicians had prescribed on demand therapy to an average of 13% patients (range 1-30%)

2 were members of P&T committees

Profession	10	Movement Disorder Specialists		1	Neurologist		1	Patient Advocate
Practice Setting	4	Academic		4	Community		4	Mixed
Country	8	US		1	Australia		1	Austria
	1	Spain		1	Thailand			

1. Isaacson SH, et al. Use of on-demand treatments for OFF episodes in Parkinson's disease: guidance from a RAND/UCLA modified Delphi consensus panel. Presented at: 4th Pan American Parkinson's Disease and Movement Disorder Congress (PAS); May 26-28, 2022; Miami, FL USA. Poster 123.

PD, Parkinson's disease; P&T, pharmacy-and-therapeutics.

Recommendations for management of OFF episodes with on-demand treatments

It is appropriate to prescribe on-demand treatments for patients whose OFF episodes:

1 Are disabling and interfere with **MOST** basic daily activities (e.g., hygiene, self-care, dressing, feeding, safety)

2 Are disabling and interfere with **SOME** instrumental daily activities (e.g., driving, shopping, remembering to take medication, managing finances) if they experience any of the following:

- Early morning OFF or >1 type of OFF (regardless of frequency)
- Frequent/long duration delayed ON episodes (>3 times/day), except if the patient is on low/medium dose LD (<600 mg/day) without any other adjunctive therapies
- Frequent/long duration wearing OFF episodes, except if the patient is on levodopa without other adjunctive therapies
- Less frequent/shorter wearing OFF episodes (≤2 times/day) and are on high dose LD (>600 mg/day) with an adjunctive therapy

3 **Do not interfere** with their daily activities but may impact their lives in other ways (e.g., fear/reluctance of leaving home, decreased job performance) if they experience all of the following:

Frequent early morning OFF, delayed ON, or >1 type of OFF **and** On high dose LD (>600 mg/day) and another adjunctive therapy (other than a dopamine agonist) **and** Experience therapy-related side effects

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1. Isaacson SH, et al. Use of on-demand treatments for OFF episodes in Parkinson's disease: guidance from a RAND/UCLA modified Delphi consensus panel. Presented at: 4th Pan American Parkinson's Disease and Movement Disorder Congress (PAS); May 26-28, 2022; Miami, FL USA. Poster 123.
LD, levodopa.

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Limitations

Despite diversity of panelist backgrounds and experiences, 12 panelists cannot represent full spectrum of clinicians in the Parkinson's field

- A different group of experts may have reached different conclusions from this exercise[1]
- The group included both US and ex-US panelists[1]
  - A secondary analysis showed overall agreement was higher when including only US panelists (86% vs 68%)[2]
  - Differences in ratings may reflect: the availability of only one on-demand therapy to ex-US panelists at the time of the panel, differences in approved adjunctive therapies, and differences in healthcare, training, exposure, etc.

The results of this exercise do not identify which individual on-demand treatment would be most appropriate

- On-demand therapies included levodopa inhalation powder, apomorphine sublingual film, and apomorphine subcutaneous injection[1]

1. Isaacson SH et al. Use of on-demand treatments for OFF episodes in Parkinson's disease: guidance from a RAND/UCLA modified Delphi consensus panel. Presented at: 4th Pan American Parkinson's Disease and Movement Disorder Congress (PAS); May 26-28, 2022; Miami, FL USA. Poster 123. 2. Sunovion data on file.