

The Place of On-Demand Therapy in the Treatment of OFF Episodes

Online Activity Details



This resource has been downloaded from a touchEXPERT BRIEFING, hosted on touchNEUROLOGY. The full activity, which includes video resources, can be accessed at:

<https://touchneurologytmc.com/parkinsons-disease/learning-zone/on-demand-therapy-for-off-episodes/>

This content is for healthcare professionals in the US only.

Learning Objectives



After watching the touchEXPERT BRIEFING activity, you should be able to articulate:

- ✓ The rationale for on-demand therapy to treat OFF episodes
- ✓ The clinical implications of on-demand therapy for OFF episodes
- ✓ The place of on-demand therapies in the treatment paradigm for treating OFF episodes

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Disclosures

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Dr Kremens serves as a consultant for Abbott, AbbVie, ACADIA, Acorda, Adamas, Allergan, Amneal, Avion, GE Healthcare, Kyowa Kirin, Lundbeck, Merz, Neurocrine, Sunovion, Supernus, Teva, and UCB. He has received research support from Acorda, Enterin, Revance and Voyager.

Dr Fernando Pagan

Dr Pagan has been a consultant/speaker for Acorda, Adamas, Amneal, Merz, Kyowa Kirin, Sunovion, Teva, US World Meds, Supernus. Scientific Advisory or Data Safety Monitoring board for Abbvie. Serving as an Editor, Associate Editor, or Editorial Advisory Board Member for Journal of Clinical Parkinsonism and related Disorders. Dr Pagan has stock in Keiferx. The institution of Dr Pagan has received research support from US World Meds. The institution of Dr Pagan has received research support from Novartis.

Dr Drew Falconer

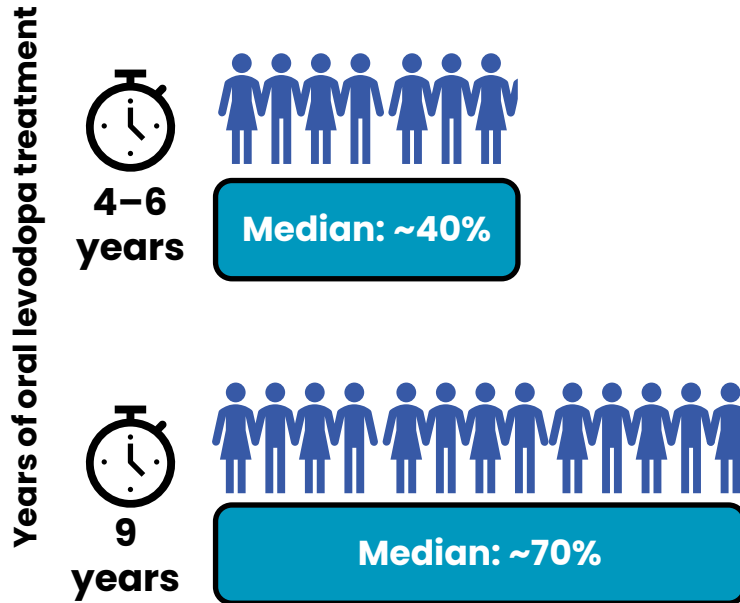
Dr Falconer has received consultancy or speaker fees from Abbott Laboratories, Abbvie, Amneal, Acorda, GE HealthCare, Kyowa Kirin, Neurocrine, Supernus and Sunovion. Dr Falconer also receives compensation as an FTC and Justice Department subject matter expert.

The Rationale for On-Demand Therapy Use in OFF Episodes



Onset and Progression of OFF Episodes

Prevalence of OFF episodes over time¹



Changing response to oral levodopa²

Early PD

A long duration of the desired clinical response resulting in good ON time

Moderate PD

Clinical response diminishes and OFF periods become more common

Advanced PD

Clinical response is short and OFF periods more frequent and harder to treat

Oral Levodopa Absorption Can Be Highly Variable

Factors affecting absorption



GI symptoms related to PD often are not clinically obvious

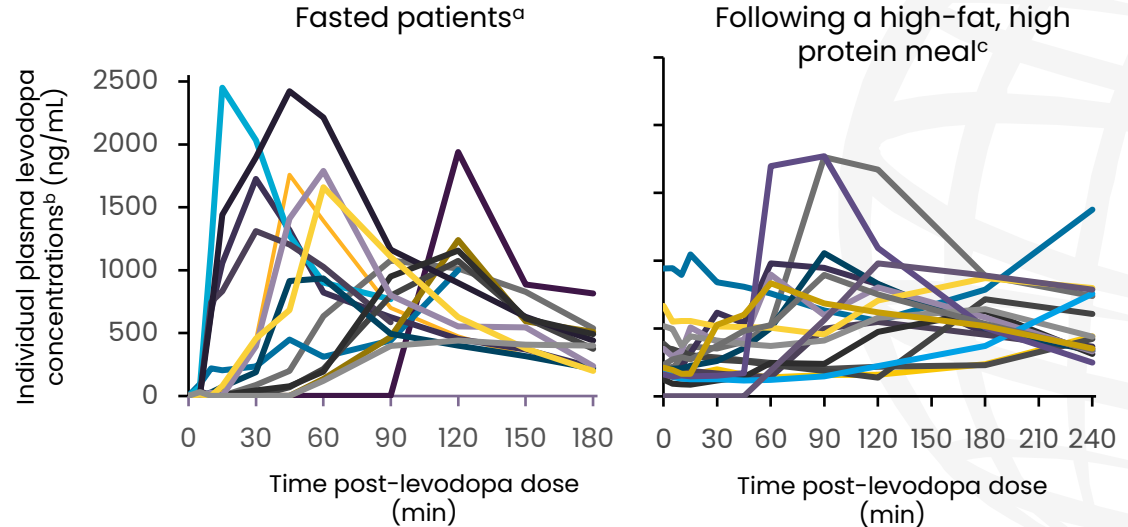


PD is associated with delayed gastric emptying and SIBO which can delay levodopa tablet absorption^{1,2}



Food can interfere with oral levodopa absorption^{1,2}

Oral levodopa plasma concentration³



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^aN=15, no food \geq 1 hour before and 1 hour after levodopa/carbidopa 25/100 mg dose; ^bVariable adjusted; ^cN=17; 4–5 hours after morning levodopa/carbidopa patients ate a meal.

1. Fasano A, et al. *Lancet Neurol.* 2015;14:625–639; 2. Tan AH et al, *Parkinsonism Relat Disord.* 2014;20(5):535–40; 3. Safirstein BE, et al. *Clin Ther.* 2020;42(6):1034–1046.

GI, gastrointestinal; PD, Parkinson's disease; SIBO, small intestine bacterial overgrowth.

Types of OFF Episodes

OFF episodes: periods when the medication does not provide benefit or symptoms return



Morning akinesia

Morning slowness or immobility before first oral levodopa dose



End-of-dose wearing OFF

When the benefits of oral levodopa do not last until the next dose



Failure to turn ON

When an oral levodopa dose fails to work



Delayed ON

Oral levodopa dose takes longer to work, particularly in the morning or following a meal



Unpredictable OFF

Unexpected swings between ON and OFF states

Variability in the Return of Motor and Non-motor Symptoms



Symptoms often return as a cascade, and subtle non-motor symptoms may precede the re-emergence of motor symptoms¹

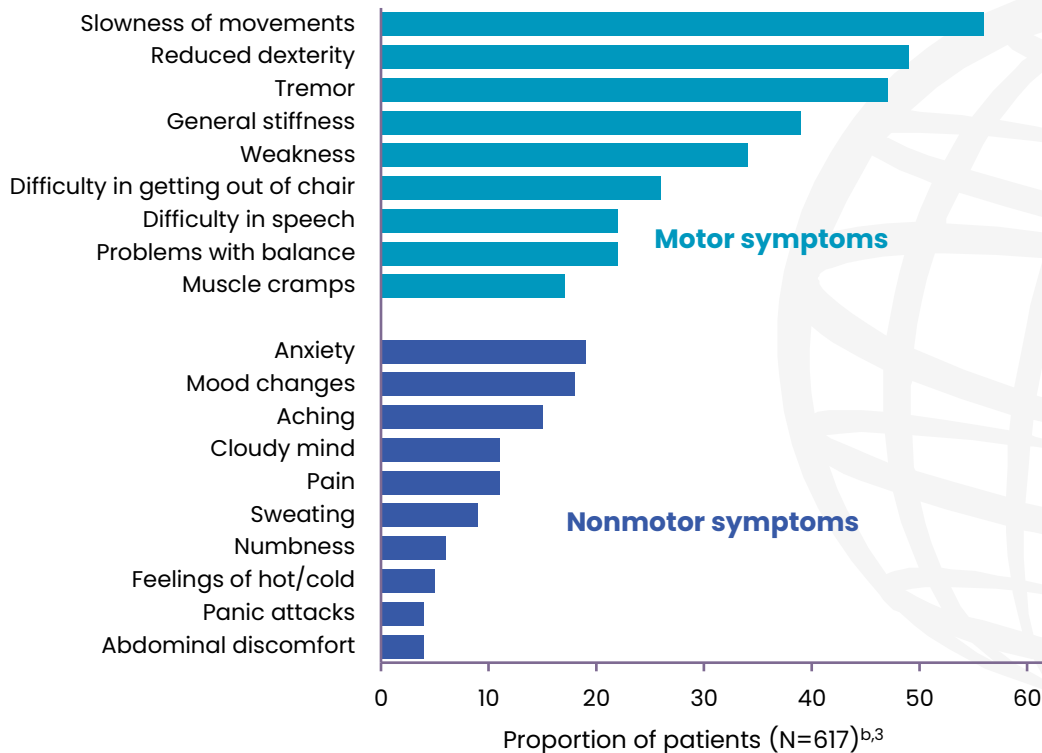


Difficult to predict or recognize:

- When return of symptoms will begin
- How severe symptoms will be
- How long symptoms will last



OFF periods have a significant negative impact on HRQoL^{a,2}



^aImpact on HRQoL of OFF episodes versus patients without OFF episodes, receiving levodopa or carbidopa measured via the 39-item Parkinson's Disease Questionnaire;

^b8 years mean duration of PD.

1. Stocchi F, et al. *Eur Neurol.* 2010;63(5):257-266; 2. Thach A, et al. *BMC Neurol.* 2021;21:46; 3. Stocchi F, et al. *Parkinsonism Relat Disord.* 2014;20(2):204-211.

HRQoL, health-related quality of life.

Impact of OFF Episodes on Patients and Caregivers



Increased patient and caregiver burden^{1,a}



Increased personal and role strain



Decreased emotional well-being



Progressive withdrawal from activities & social interactions



Increased relationship burden



Finances and control over one's life

^ameasured by the 22-item Zarit Burden Interview score.
1. Thach A, et al. Presented at: ISPOR 2020; May 18-20, 2020; Abstract PND86.



Conventional Treatment Options for OFF



Oral levodopa & ON-extenders^{1,2}

Additional levodopa doses

Extended-release levodopa

Dopamine agonists

MAO-B inhibitors

COMT inhibitors

Adenosine A2A receptor antagonist

Extended-release amantadine

1. Fox SH, et al. *Mov Disord.* 2018;33:1248-1266; 2. Supernus 2021. Available at: <https://www.supernus.com/sites/default/files/gocovri-prescribing-information.pdf> (accessed February 2023).

COMT, catechol-o-methyl-transferase; MAO-B, monoamine oxidase-B; SIBO, small intestine bacterial overgrowth

Limitations of Conventional Treatment Options



Continued daily OFF time

ON-extendors **reduce** OFF time by **~1–2 hours/day**, although patients **continue to experience ~4 hours/day** of OFF time¹



Lack of as-needed relief

Conventional options do not address OFF episodes as they occur; optimized oral levodopa may take up to 60 minutes to provide benefit^{2,3}



Dysfunctional GI system

Esophageal dysmotility and gastroparesis limits and alters absorption of oral therapies;^{4,5} 88% of patients had delayed gastric emptying of solids, yet only 36% exhibit GI symptoms e.g., nausea⁶



SIBO

25% of patients have SIBO, which both metabolises levodopa in the gut and limits absorption^{5,7}

1. Isaacson S, et al. *Clin Park Relat Disord.* 2022;7:100161; 2. Stocchi F, et al. *Eur J Neurol.* 2019;26:821–826; 3. Isaacson S, et al. *Mov Disord Clin Pract.* 2017;4:78–83; 4. Suttrup I, et al. *Neurogastroenterol Motil.* 2017;29(1); 5 Fasano A, et al. *Lancet Neurol.* 2015;14:625–639; 6. Goetz O, et al. *Neurogastroenterol Motil.* 2006;18(5):369–375; 7. Tan AH, *Parkinsonism Relat Disord.* 2014;20(5):535–40.

COMT, catechol-o-methyl-transferase; GI, gastrointestinal; MAO-B, monoamine oxidase-B; SIBO, small intestine bacterial overgrowth

On-Demand Therapies

Treatment for the return of PD symptoms,
administered by patient or caregiver during an episode

Characteristics



Time to treatment onset

Onset of action from 7–22 mins, with a duration of effect of 60–90 minutes.¹



Route of administration

Bypasses dysfunctional GI system^{1,2}



Impact of diet

Diet does not impact absorption

On-Demand therapies^{1–5}



Apomorphine
injection



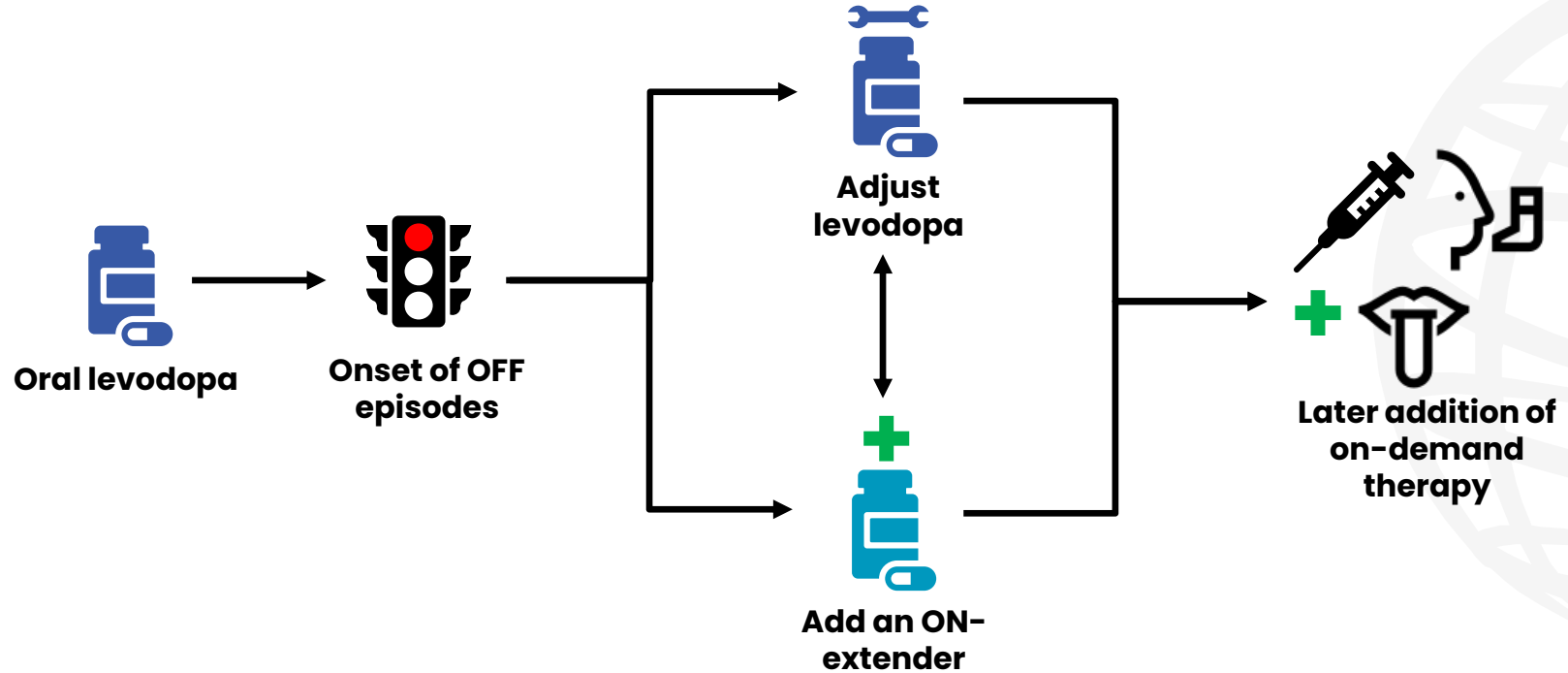
Levodopa
inhalation powder



Apomorphine
sublingual film

1. Hauser RA, et al. *Postgrad Med.* 2021;133:721–727; 2. Isaacson S, et al. *Clin Park Relat Disord.* 2022;7:100161; 3. FDA. APOKYN. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021264s0181b1.pdf (accessed March 2023); 4. FDA. INBRIJA. Available from: <https://www.inbrija.com/prescribing-information.pdf> (accessed March 2023); 5. Sunovion. KYNMOBI. Available from: <https://www.kynmobi.com/kynmobi-Prescribing-Information.pdf> (accessed March 2023).
GI, gastrointestinal; PD, Parkinson's disease.

Treatment of OFF: The Conventional Treatment Paradigm



Treatment of OFF: Proposed Paradigm Shift

Earlier, complementary use of on-demand therapies
ALONGSIDE levodopa adjustment and/or use of ON-extendors

Adjustment to regular medication



Adjust oral levodopa timing, dosing and/or formulation



Add supplemental medication such as on-extendors

On-demand therapy for the return of symptoms

Use **non-oral** medication as-needed:



Levodopa inhalation powder



Sublingual/subcutaneous apomorphine

The Clinical Implications of On-Demand Therapy for Treating OFF



When to Use On-Demand Therapy and Which Patients



When to use on-demand therapy?

Move from an approach of optimizing baseline PD therapies one change at a time



Migraine approach¹

Optimizing baseline therapies

+

Simultaneously supplementing with acute relief on-demand therapy



Patients for whom on-demand therapy may be appropriate?²

Off episodes occur despite optimized maintenance regimens

and/or

OFF episodes interfere with activities

and/or

OFF episodes cause anxiety about engaging in activities

Current Barriers to On-Demand Therapy Use



Limited time at office visits, with multiple issues for the patient to raise



Patients may be unaware they are having OFF episodes, or not be forthcoming on history (care partner history can help)



Insurance and out of pocket costs



Inadequate training on the proper use of the on-demand therapy¹



Not properly setting patient expectations for a given on-demand therapy

A Focused History is Key to Assessing Impact of OFF

A lack of OFF episode awareness can be mitigated by focused questioning of a patient's history



Do you ever find yourself thinking it's time for your next dose when it's not?



Are there times during the day when your symptoms return unexpectedly?



Are there times when you haven't done things you normally like, or need, to do? - tell me more about that?



Are there times throughout the day when you just don't feel well?



Do some doses take longer to work than others?

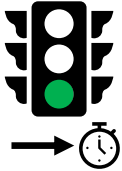


Do you experience symptoms at the same time of day?



Does your medicine not work as well after you eat?

Potential Impact of On-Demand Therapy



Reduce continued OFF episodes¹ despite optimized levodopa and on-extender treatment



Increased patient confidence in performing daily activities without unexpected disruptions¹



Provide patients with plan to return to ON rapidly and reliably¹



Empower patients to recognize and rapidly treat OFF episodes when they occur¹



Less frequent adjustment of baseline therapy and less frequent dosing intervals¹



Potential to reduce the negative impact of OFF on HRQoL²

Summary





Summary

1


Patients continue to experience OFF episodes, despite optimizing daily maintenance regimens

2

On-demand therapy can rapidly reverse OFF episodes, and should be utilized as a complementary treatment earlier in the disease

3

The earlier use of on-demand therapy may allow for a reduction in the burden of OFF episodes and empower patients to rapidly and reliably achieve relief from ongoing OFF episodes



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