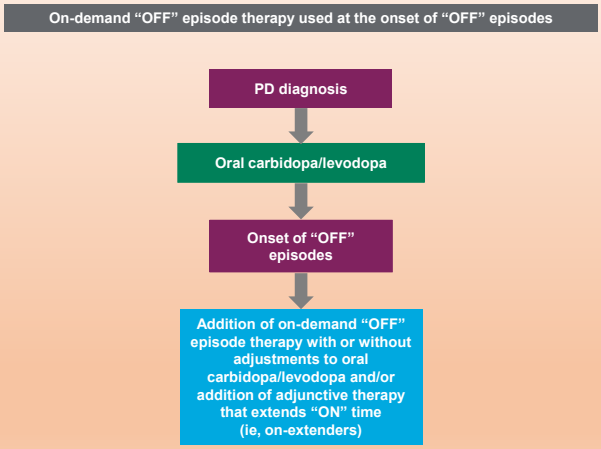
New “On-Demand” Therapies For PD: Racing A Thoroughbred Horse, Or Beating A Dead One?

Fernando L. Pagán, MD
Professor and Vice Chairman of Neurology
Director of Movement Disorders Program
Medical Director of Georgetown University Hospital
Washington, DC, USA

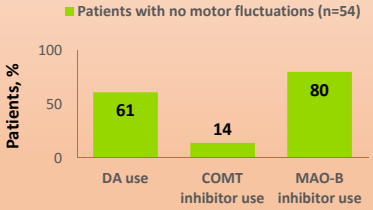
Changing The Treatment Paradigm



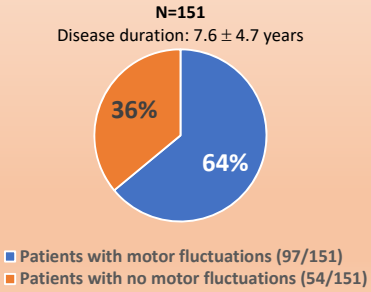
PD, Parkinson’s disease.

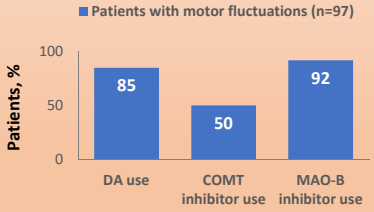
"OFF" Episodes Are Common With Traditional Antiparkinsonian Therapy Regimens

- "OFF" episodes are estimated to have a prevalence of ~25–50% within a period of 2–6 years of initiating carbidopa/levodopa treatment[1,2]
- In a single-visit pilot study of 151 patients with PD on stable doses of levodopa for ≥4 weeks, 64% reported experiencing motor fluctuations[3]



Disease duration: 6.6 ± 4.2 years



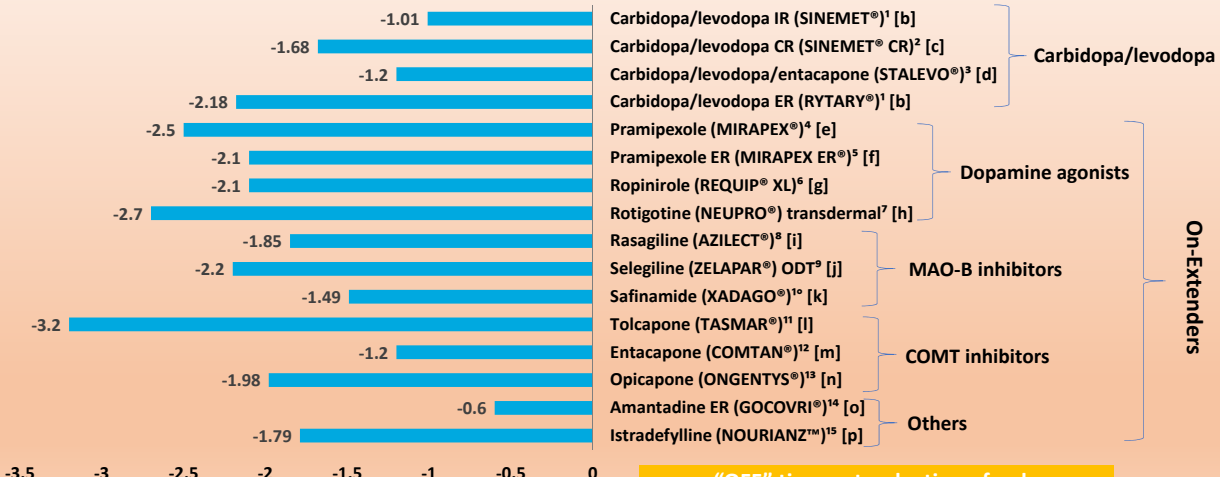


Disease duration: 8.1 ± 4.8 years

COMT, catechol-O-methyl transferase; DA, dopamine agonist; MAO-B, monoamine oxidase-B.

1. Chou KL, et al. *Parkinsonism Relat Disord*. 2018;51:9-16. **2.** Ahlskog JE, et al. *Mov Disord*. 2001;16:448-458. **3.** Stocchi F, et al. *Eur J Neurol*. 2019;26:821-826.

Carbidopa/Levodopa and On-Extenders Have a Limited Effect on Decreasing Daily "OFF" Time[a]



"OFF" time net reduction of only 0.6–3.2 hours/day against 3.2–7.0 hours/day of baseline daily "OFF" time

[a]Representative but not exhaustive list of currently available therapies (data from clinical trials).
CR, controlled release; ER, extended release; IR, immediate release.; ODT, orally disintegrating tablet.

On-Demand Therapies Are Available to Manage up to 5 "OFF" Episodes Per Day

Drug	FDA Approval/ Development Phase	Dosing and Frequency
Apomorphine hydrochloride injection (APOKYN®)[1]	Approved 2004	2–6 mg/"OFF" period (on-demand up to 5 times daily) Maximum of 20 mg total daily dose
Levodopa inhalation powder (INBRIJA®)[2]	Approved 2018	Maximum of 84 mg/"OFF" period (on-demand up to 5 times daily) Maximum of 420 mg total daily dose
Apomorphine sublingual film (KYNMOBI™)[3]	Approved 2020	10–30 mg/"OFF" period (on-demand up to 5 times daily)

FDA, Food & Drug Administration; POD, precision olfactory delivery.

1. APOKYN® (apomorphine hydrochloride injection), US WorldMeds, LLC. Louisville, KY, USA, 2020. **2.** INBRIJA®(levodopa inhalation powder), Acorda Therapeutics, Inc. Ardsley, NY, USA, 2019. **3.** KYNMOBI™ (apomorphine hydrochloride) sublingual film, Sunovion Pharmaceuticals Inc. Marlborough, MA, USA, 2020.

On-Demand Therapies Are Efficacious and Generally Well Tolerated for the Management of "OFF" Episodes

Drug	Mean Change in UPDRS Part III Scores (Active Drug vs Placebo) in Pivotal Study	Route of Administration-Specific Adverse Events
Apomorphine hydrochloride injection (APOKYN®)[1,2[a]]	• 20 minutes postdose[d]: –23.9 vs –0.1 (*P*<0.001) • Mean dose of active drug = 5.4 mg	Injection site reactions
Levodopa inhalation powder (INBRIJA®)[3,4[b]]	• 30 minutes postdose at week 12: –9.8 vs –5.9 (*P*=0.0088) • Randomized dose of active drug = 84 mg	Cough, upper respiratory tract infections, and sputum discoloration
Apomorphine sublingual film (KYNMOBI™)[5,6[c]]	• 30 minutes postdose at week 12: –11.1 vs –3.5 (*P*=0.0002)[e]	Oral adverse events

[a]A randomized, double-blind, placebo-controlled, 4-week, phase 3 study (20 patients in the APOKYN® arm with PD duration of 9.2 y, daily "OFF" time of 5.9 h, and 776 (± 98) mg daily levodopa; PD severity not reported).

[b]A randomized, double-blind, placebo-controlled, 12-week, phase 3 study (114 patients in the INBRIJA® 84 mg arm with PD duration of 7.9 y, daily "OFF" time of 5.4 h, and 819 (± 401) mg daily levodopa; PD severity not reported).

[c]A randomized, double-blind, placebo-controlled, 12-week, phase 3 study (54 patients n the KYNMOBI™ arm with PD duration of 8.7 y, 3.9 "OFF" episodes per day, Hoehn and Yahr stage 2 or 2.5 in 91%, and 1059 (± 563) mg daily levodopa)

[d]Endpoint was measured during inpatient phase of unspecified duration.

[e]Measurement was for MDS-UPDRS Part III.

D, day; h, hour; MDS, Movement Disorders Society; N/A, not available; POD, precision olfactory delivery; UPDRS, Unified Parkinson's Disease Rating Scale; y, years.

1. APOKYN® (apomorphine hydrochloride injection), US WorldMeds, LLC. Louisville, KY, USA, 2020. **2.** Dewey RB, et al. *Arch Neurol*. 2001;58:1385-92. **3.** INBRIJA®(levodopa inhalation powder), Acorda Therapeutics, Inc. Ardsley, NY, USA, 2019. **4.** LeWitt PA, et al. *Lancet Neurol*. 2019;18:145-154. **5.** KYNMOBI™ (apomorphine hydrochloride) sublingual film, Sunovion Pharmaceuticals Inc. Marlborough, MA, USA, 2020. **6.** Olanow CW, et al. *Lancet Neurol*. 2020;19:135-144.

Oral Carbidopa/Levodopa Can Be Associated With "OFF" Episodes Due to GI Tract Limitations

- Dysphagia is common in PD[1]
- Dietary protein can interfere with levodopa absorption[2]
- Gastroparesis can decrease postdose levodopa levels[1,3]
- Gastroparesis also delays levodopa peak[4]
- The potential role of the gut microbiome is also beginning to emerge[1]

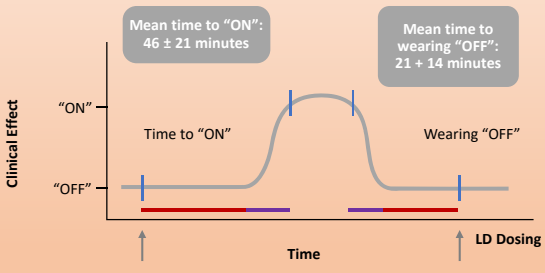
GI, gastrointestinal.

1. Pfeiffer RF. *Curr Treat Options Neurol*. 2018;20:54. **2.** Poewe W, et al. *Clin Interv Aging*. 2010;5:229-238. **3.** Muller T, et al. *Clin Neuropharmacol*. 2006;29:61-67. **4.** Doi H, et al. *J Neurol Sci*. 2012;319:86-88.

Delayed "ON" is a Therapeutic Problem Despite the Use of On-Extenders

Delayed "ON"

Patients spend a substantial amount of time waiting to turn "ON"[1,a]



Assessment of Delayed "ON" in Patients with PD and Motor Fluctuations (n=97)[2,b]

- Baseline carbidopa/levodopa and use of on-extenders:
  - **Mean daily dose of carbidopa/levodopa = 576 mg**
  - **50% used COMT inhibitors, 85% used dopamine agonists, and 92% used MAO-B inhibitors**
- Concerning their morning dose during the past week, 51% reported delayed "ON" at least once and 21% reported delayed "ON" every morning
- Mean time to "ON":
  - After morning dose: 35–40 min
  - After lunchtime dose: 34–37 min
- 56% reported >30 min duration to turn "ON" after the morning dose

[a]Based on a study of 20 patients with advanced PD receiving levodopa (mean total daily dose of 821 mg, in 5–9 divided daily doses).
[b]Single-visit pilot study in 97 consecutive patients with a disease duration of 8.1 y and Hoehn and Yahr stage of 2-3 when "ON."
COMT, cathchol-o-methyltransferase; MAO-B, monoamine oxidase-B.

1. Merims D, et al. *Clin Neuropharmacol*. 2003;26:196-198. **2.** Stocchi F, et al. *Eur J Neurol*. 2019;26:821-826.

Pharmacokinetic Properties Support Use of On-Demand Therapies

T_{max} of on-demand therapies is ~1/2 the T_{max} of oral carbidopa (or benserazide)/levodopa, and oral on-extenders[1-16]

On-demand therapies bypass the gastrointestinal tract, hence are not impacted by dietary considerations[17-19]

Class[a]	T_{max}	Food effect on T_{max}
On-demand[1-3]	10 minutes – 2 hours	None
Carbidopa (or benserazide)/ Levodopa[4-8]	30 minutes – 3 hours	Up to +2 hours with high-fat/high-protein/high-calorie meal
Dopamine agonists[9-11]	1–10 hours	Up to +1–3 hours with meal/high-fat meal
MAO-B inhibitors[12,13]	1–3 hours	None to slight delay with meal
COMT inhibitors[14-16]	1–4 hours	None to +4 hours with moderate fat/moderate calorie meal

[a]Representative but not exhaustive list of currently available therapies (data from prescribing information or from summary of product characteristics).
T_{max}, time to maximal concentration.

On-Extenders May Worsen Dyskinesia and Increase the Risk of Other Dopaminergic AEs

- Increasing daily doses of levodopa may cause dyskinesia[1]
- Increasing dosing frequency of levodopa may require the need to delay meals or manipulate the protein/fat content of meals, potentially leading to unintended weight loss[2-4]
- The addition of on-extenders to levodopa to manage "OFF" episodes may:[4-7]
  - Exacerbate existing dyskinesia
  - Increase the risk of other dopaminergic AEs (eg, somnolence, impulse control disorders, hallucinations/psychotic behavior, etc.)
  - Increases the overall complexity of the treatment regimen

1. Espay AJ, et al. *Neurol Clin Pract*. 2017;7:86-93. **2.** Chou KL, et al. *Parkinsonism Relat Disord*. 2018;51:9-16. **3.** Poewe W, et al. *Clin Interv Aging*. 2010;5:229-38. **4.** REQUIP® (ropinirole hyrochloride tablet, film coated) [Prescribing information]. Bridgewater, NJ, USA: Alembic Pharmaceuticals Inc.; 2019. **5.** AZILECT® (rasagiline mesylate) tablets, TEVA Neuroscience, Inc., Overland Park, KS, USA, 2014. **6.** ONGENTYS® (opicapone) capsules. Neurocrine Biosciences, Inc., San Diego, CA, 2020. **7.** Armstrong MJ and Okun MS. *JAMA*. 2020;323:548-560.

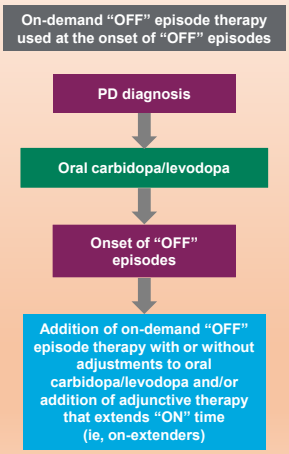
On-Extenders May Be Associated With Non-Adherence, Potentially Increasing Medical Costs in Non-Adherers

- Treatment changes that add new therapies or complexity to the regimen can be frustrating for patients with PD and may increase non-adherence[1]
- Over half of patients take at least 2 antiparkinsonian drugs in addition to multiple prescriptions for non-motor manifestations and other[2,a] comorbidities
- Compared with adherers, non-adherers have significantly higher rates of yearly hospitalizations, office visits, and ancillary care visits, with higher total medical costs despite lower prescription drug costs[3,b]
- Nonadherence was associated with a $3,451 (USD) yearly increase in medical costs[3,b]

[a]Cross-sectional survey of 130 ambulatory patients with mean PD duration of 6.9 y and Hoehn and Yahr stage of 2.6.
[b]Retrospective review of US managed care claims data in 3,119 patients with PD; PD duration and severity not reported.
USD, United States dollars.

1. Fleisher JE and Stern MB. *Curr Neurol Neurosci Rep*. 2013;13:382. **2.** Leoni O, et al. *Pharmacoepidemiol Drug Saf*. 2002;11:149-157. **3.** Davis KL, et al. *Mov Disord*. 2010;25:474-480.

Changing The Current Treatment Paradigm



- Carbidopa/levodopa and on-extenders have a limited effect on decreasing daily "OFF" time
- On-extenders may worsen dyskinesia increase the risk of other dopaminergic AEs, and be associated with non-adherence, potentially increasing medical costs in non-adherers
- On-demand therapies are efficacious and generally well tolerated for the management of "OFF" episodes
- Pharmacokinetic properties of on-demand therapies (ie, shorter T_{max}, bypassing the gastrointestinal tract, no impact of diet on absorption) further support the use of on-demand therapies

In Summary

- Clinical research data suggest that even adding more “extenders” or more L-dopa our patients will still experience “OFF Periods”
- We should learn from our Headache specialists:
  - Maintenance medications: L-dopa and extenders (Prophylactic HA meds)
  - On-Demand (Abortive HA meds)
- “Beating a dead horse” is probably what insurance companies have done to us to not Rx medications that can ultimately improve quality of lives of our PD patients. We should demand the best treatments for our PD patients.
- On Demand therapies should be offered sooner to our patients experiencing “OFF”