Movement Disorders
CLINICAL PRACTICE

BRIEF REPORT

Expert Consensus on the Use of *On*-Demand Treatments for OFF Episodes in Parkinson's Disease: A Modified Delphi Panel

Stuart H. Isaacson, MD,[1] Madhureeta Achari, MD,[2] Roongroj Bhidayasiri, MD,[3,4] Cynthia Comella, MD, FAAN,[5] Jill Giordano Farmer, DO, MPH,[6,7] Fiona Gupta, MD,[8] Sarah Jones, MPA, MS,[9] David Kreitzman, MD,[10] Daniel Kremens, MD, JD, FAAN,[11] Simon J.G. Lewis, MBBCh, BSc, FRCP, FRACP, MD,[12] Werner Poewe, MD,[13] Eduardo Tolosa, MD, PhD,[14] Cynthia Campos, MPH,[15] Sarah N. Gibbs, MPH,[15] and Michael S. Broder, MD, MSHS[15,]*

ABSTRACT: Background: On-demand treatments can treat OFF episodes in Parkinson's disease, however, there is limited information regarding when to prescribe them.
Objective: Develop expert consensus to determine appropriate clinical factors for considering on-demand treatments.
Methods: Using a RAND/UCLA modified Delphi panel method, a panel developed consensus on the use of on-demand treatments for OFF episodes.
Results: The panel agreed on-demand treatments were appropriate when OFF episodes were associated with greater functional impact and interfered with basic daily activities. The panel also agreed on-demand treatment may be appropriate for patients with morning akinesia and/or delayed ON of first levodopa dose and >1 type of OFF episode (eg, early morning OFF or wearing OFF regardless of frequency).
Conclusions: Experts agreed on-demand treatment is appropriate for many patients with OFF episodes. The greater the functional impact of OFF episodes, the more likely experts agreed that on-demand treatment is appropriate to prescribe.

Parkinson's disease (PD) is the most common neurodegenerative disorder affecting mobility with a global prevalence of 6.1 million people in 2016—a figure expected to double over the next generation.[1,2] As PD progresses, fluctuations in symptom control between benefit from levodopa (L-dopa) (ON) and when benefit is no longer present (OFF) are common and often persist despite attempts to optimize dose and timing, and the addition of adjunctive OFF therapies.[3,4] Effective, reliable, and rapid treatment of OFF episodes remain a major unmet need.[1]

Three pharmacological approaches are typically considered.[4–6] The first is adjusting the current oral L-dopa regimen by increasing the dose, altering dosing frequency, or trying extended

[1]*Parkinson's Disease and Movement Disorders Center of Boca Raton, Boca Raton, Florida, USA;* [2]*Integrated Neurology PA, Department of Physical Medicine and Rehabilitation, McGovern Medical School, University of Texas, Houston, Texas, USA;* [3]*Chulalongkorn Centre of Excellence for Parkinson's Disease and Related Disorders, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand;* [4]*The Academy of Science, The Royal Society of Thailand, Bangkok, Thailand;* [5]*Department of Neurosurgery and Neurological Sciences, Rush University Medical Center, Chicago, Illinois, USA;* [6]*Global Neuroscience Institute, Pennington, New Jersey, USA;* [7]*Department of Neurology, Drexel College of Medicine, Philadelphia, Pennsylvania, USA;* [8]*Department of Neurology, Mount Sinai Medical Center, Mount Sinai Beth Israel Morningside, Sinai West, The Mount Sinai Hospital, New York City, New York, USA;* [9]*Parkinson and Movement Disorder Alliance, Tucson, Arizona, USA;* [10]*Parkinson's Disease and Movement Disorders Center of Long Island, Commack, New York, USA;* [11]*Department of Neurology, Sidney Kimmel Medical College at Jefferson University, Philadelphia, Pennsylvania, USA;* [12]*Brain and Mind Center, School of Medical Sciences, University of Sydney, Sydney, New South Wales, Australia;* [13]*Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria;* [14]*Parkinson's Disease Research Program, University of Barcelona, Barcelona, Spain;* [15]*PHAR, Beverly Hills, California, USA*

***Correspondence to:** Michael S. Broder, PHAR, 280 S. Beverly Drive, Suite 404, Beverly Hills, CA 90212, USA; E-mail: mbroder@pharllc.com
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formulations (eg, extended release, sustained/controlled release) to prolong plasma L-dopa levels above threshold for clinical benefit. Another option is adding an adjunctive "on-extender." These include catechol-*O*-methyl transferase inhibitors to reduce peripheral L-dopa metabolism, selective monoamine oxidase B (MAO-B) inhibitors to reduce central dopamine metabolism, oral/transdermal dopamine-receptor agonists that directly bind to postsynaptic dopamine receptors and non-dopaminergic therapies that block glutamatergic or adrenergic receptors.

The third option is to add an *on*-demand medication as needed to treat OFF episodes. These were developed to address the significant variability of oral L-dopa benefit that reflects gastrointestinal (GI) dysmotility, competitive transport of dietary protein, short elimination plasma half-life, and the loss of buffering capacity resulting from progressive striatal denervation. These factors can delay L-dopa benefit, shorten ON, and lead to end-dose wearing off. Attempts to use orally dissolved, dispersible, or liquid L-dopa are also limited by the GI route of administration.

There are three available *on*-demand therapies that are not administered via the GI tract: inhaled L-dopa (Inbrija),[7] subcutaneous apomorphine injection (Apokyn, APO-go),[8] and sublingual apomorphine film (Kynmobi).[9] These medications bypass esophageal and gastric dysmotility and competitive intestinal absorption, and therefore have a more rapid and reliable onset of symptom benefit (time-to-ON) when taken during an OFF episode.

With the recent approval of these *on*-demand therapies, there is limited clinical guidance concerning when they should be initiated for OFF episodes. To address this need, we developed guidance using validated consensus methodology to identify circumstances when *on*-demand treatments can be introduced to treat OFF episodes. This consensus focused only on the use of these non-GI *on*-demand therapies; GI-absorbed (oral) L-dopa formulations that can be used as needed, but were not discussed.

Methods

We used the RAND/UCLA modified Delphi panel method, which systematically and quantitatively combines expert opinion and the latest clinical evidence.[10–13] We convened a panel of experts who reviewed a summary of clinical evidence on the use of *on*-demand treatments and rated the appropriateness of prescribing *on*-demand treatments across 432 patient scenarios before a meeting. Panelists discussed these ratings during an 8-hour professionally moderated discussion, and then rated the same scenarios a second time.

Scenarios were defined by clinical characteristics (Supplemental Table 1 in Data S1): patient's perspective on functional impact of OFF episodes, current L-dopa dose, current *on*-extender treatments used, whether the patient experienced treatment-related side effects, and type and frequency/duration of OFF episodes.

The study sponsor (Sunovion Pharmaceuticals) did not provide input on panelist selection, study design, methods, or interpretation of results. The panel was blinded to the identity of the sponsor and vice versa until a first draft manuscript was completed. Panelists received honoraria for their participation.

Additional details on methods are available in the Supplemental Data in Data S1.

Results

In the first-round ratings, there was agreement on 144 scenarios (33%). In the second-round ratings, agreement increased to 68% (n = 292). In total, 53% (n = 230) of scenarios were rated as appropriate (Table 1).

In general, the panel agreed that the greater the functional impact of OFF episodes on patients, the more appropriate it is to prescribe *on*-demand treatment (Table 2). If OFF episodes interfere with basic daily activities, such as performing self-care activities and maintaining personal safety, panelists agreed it is almost always appropriate to prescribe *on*-demand treatments. Experts also agreed there were certain circumstances when the frequency (ie, number/day) or duration of an OFF episode warranted on-demand treatment (Table 2). There was disagreement about the appropriateness of *on*-demand treatment for patients who are not on high dose L-dopa and/or adjunctive therapy and experience only wearing OFF episodes.

In patients who are less impaired—whose OFF episodes interfere with some instrumental daily activities, such as driving, cooking, and managing finances, but not their most basic activities—panelists agreed there are specific circumstances in

TABLE 1 *Distribution of first- and second-round ratings*

		Agreement		
n (%)	**Disagreement[a]**	**Appropriate[b]**	**Not sure/neither[c]**	**Inappropriate[d]**
First-round	288 (67)	109 (25)	11 (3)	24 (6)
Second-round	140 (32)	230 (53)	41 (9)	21 (5)

Note: Experts rated the appropriateness of prescribing on-demand treatments in 432 patient scenarios on a 1 to 9 scale, where 1 = highly inappropriate, risks outweigh the benefits; and 9 = highly appropriate, benefits outweigh the risks.
[a]Defined as ≥2 expert ratings of 1 to 3 and ≥2 expert ratings of 7 to 9.
[b]Defined as a group median of ≥7 to 9 without disagreement.
[c]Defined as a group median of ≥4 to <7 without disagreement.
[d]Defined as a group median of 1 to <4 without disagreement.

TABLE 2 *Expert recommendations on when it is appropriate to prescribe on-demand treatments for OFF episodes*

Functional impact of OFF episodes on daily activities	Expert recommendation on appropriateness of prescribing on-demand treatments for the patient to take as needed
OFF episodes interfere with most basic daily activities[a]	Appropriate in most circumstances
OFF episodes interfere with some instrumental daily activities[b]	Appropriate if the patient also experiences **any** of the following: • Early morning OFF episodes or >1 type of OFF episode (regardless of frequency) • Frequent/long duration[c] delayed ON episodes, except if the patient is on low/medium dose L-dopa[d] without any other *on*-extender treatments • Frequent/long duration[c] wearing OFF episodes, except if the patient is on L-dopa without any other *on*-extender treatments • Less frequent/shorter[e] wearing OFF episodes and are on high dose L-dopa[f] with an *on*-extender treatments
OFF episodes do not interfere with daily activities but can impact patient in other ways[g]	Appropriate if the patient also experiences **all** of the following: • Frequent/long duration[c] early morning OFF, delayed ON, or >1 type of OFF episode • Are on high dose L-dopa[f] and other *on*-extender treatment (other than a dopamine-receptor agonist) • Experience treatment-related side effects

Abbreviation: L-dopa, Levodopa.
[a]Examples: hygiene, self-care, dressing, feeding, safety.
[b]Examples: driving, shopping, remembering to take medication, managing finances.
[c]≥3 times/day or >25% of the waking day.
[d]≤600 mg/day or <4–5/day.
[e]≤2 times/day or ≤25% of waking day.
[f]>600mg/day or ≥6/day.
[g]E.g., fear/reluctance of leaving home, decreased job performance.

which prescribing *on*-demand treatment is appropriate (Table 2). The panel also agreed it may be appropriate to prescribe *on*-demand treatments in patients who experience less frequent delayed ON episodes and have dose-limiting side effects precluding further oral L-dopa and/or *on*-extender treatment adjustments, which would otherwise have preceded the use of *on*-demand strategies.

The panel also agreed it may be appropriate to prescribe *on*-demand treatments in patients whose OFF episodes do not interfere with their daily activities, but may impact their lives in other ways (eg, reluctance/fear of leaving home, impaired job performance) if they experience frequent early morning OFF (≥2 times/week), delayed ON, or >1 type of OFF episode; L-dopa has been optimized; and they experience L-dopa and/or *on*-extender treatment-related side effects. The panel continued to disagree on other circumstances when OFF episodes did not interfere with daily activities.

Details on the inappropriate use of *on*-demand treatment and sensitivity analysis of ratings by geography are available in the Supplemental Data in Data S1.

Discussion

Three non-GI administered medications are used for *on*-demand treatment of OFF episodes when oral L-dopa formulations fail to reliably and/or rapidly restore ON benefit of symptoms: subcutaneous apomorphine injection, sublingual apomorphine film, and inhaled L-dopa. Recent reviews of these *on*-demand treatments have discussed their development, use, advantages, and disadvantages.[14–16] In this study, we used a validated and reproducible method to develop guidance on when it may be appropriate to prescribe *on*-demand treatments for patients experiencing OFF episodes.

Using the modified Delphi method, 12 PD experts rated over 400 clinical scenarios of patients experiencing OFF episodes despite optimized L-dopa regimens and agreed *on*-demand treatment is appropriate to prescribe in many of them. Their use is generally appropriate for patients whose OFF episodes have a significant functional impact on their lives, follow a pattern of delayed ON, dose failure, or morning OFF, who use higher doses of L-dopa in addition to *on*-extender treatments, and who experience L-dopa and/or *on*-extender treatment-related side effects.

Clinical trials have established the efficacy of *on*-demand treatments[9,17,18] and are not designed to provide detailed guidance on when such treatments are most appropriate. Trials enroll selective groups of patients and may not necessarily include all those who could benefit from an *on*-demand treatment in a real-world setting; our scenarios included patients whose OFF episodes had a larger impact on their activities of daily living than would be typical in a clinical trial population. Consensus developed in this study aligns with and adds to prior clinical trials demonstrating the efficacy and safety of *on*-demand treatment to

rapidly reduce motor symptoms of OFF episodes, including in morning OFF.[19,20] In particular, experts highlighted that *on*-demand treatment could benefit patients whose OFF episodes have had a significant impact on quality of life.[9,17]

We used the RAND/UCLA modified Delphi panel method, which has been used extensively to develop quality measures and clinical guidance.[21] There is published evidence that guidelines developed using this method have content, construct, and predictive validity.[22] The method has been shown to produce guidance that improves health outcomes. Ratings of appropriateness have been found to be reliable with test–retest reliability >0.9 using the same panelists 6 to 8 months later[23] and κ statistics across several panels with different participants indicate reproducibility similar to those of some common diagnostic tests.[24]

Our study has limitations. First, for several of the scenarios we developed, there are no data from clinical trials on the overall efficacy of the *on*-demand approach and therefore, our study reflects only the consensus of 12 individual experts. In addition, we included panelists who practice outside of the United States (US) where these therapies are not available. Non-US panelists completed ratings based on their experience with subcutaneous apomorphine injection and non-experiential knowledge of other treatments, whereas US panelists had experience with all three on-demand treatments. Agreement was higher (86%) among US-only panelists (n = 8) than agreement among both US and non-US panelists combined (68%) (Supplemental Data in Data S1). Differences in ratings may reflect the availability of only one *on*-demand treatment to the non-US panelists, differences in approved adjunctive *on*-extender treatments, cultural and healthcare differences, and exposure to *on*-demand treatments, or other factors.

Further, panelists rated all three *on*-demand treatments as a class. These ratings cannot speak to differences between individual medications and are not inclusive of all options in clinical practice around the globe, which may include other medications that are absorbed in the GI system. Additionally, we did not address the use of continuous drug delivery approaches in the different scenarios. OFF-related motor and non-motor symptoms were also not individually discussed; the impact on non-motor symptoms alone should be considered in future clinical trials or expert panel discussions. Last, our guidance should not supersede patient-physician shared decision-making as factors beyond those addressed here can affect the decision to prescribe non-GI *on*-demand treatment, including current *on*-demand treatment use, ability to take the medications, restricted access because of formulary exclusion or cost, and other factors.

Existing guidelines do not clearly describe clinical use of *on*-demand treatments for OFF episodes. The Movement Disorder Society Evidence-Based Medicine Committee states that for advanced suitable PD patients, intermittent apomorphine injections are "'clinically' useful for motor fluctuations, particularly for OFF periods that require rapid reversal."[5] National Institute for Health and Care Excellence guidelines suggest *on*-demand treatments for advanced PD patients,[25] but clinical experience suggests that they could provide benefit earlier in the disease course. The American Academy of Neurology[26] does not have a guideline on the treatment of OFF episodes. Last, Olanow et al[14] recommend physicians work with patients to determine the best *on*-demand treatment "based on physician experience and patient preference, as well as ease of use, side effect profile, and tolerability."

We used a rigorous and comprehensive method to develop guidance on when *on*-demand treatments should be prescribed. Recommendations reflect areas of greatest agreement among a panel of experts based on current evidence. We hope these recommendations can guide clinicians in the appropriate use of on-demand treatments for patients with OFF episodes.

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

S.I.: 1B, 1C, 2B, 2C, 3B.
M.A.: 1B, 1C, 2B, 2C, 3B.
R.B.: 1B, 1C, 2B, 2C, 3B.
C. Comella: 1B, 1C, 2B, 2C, 3B.
J.G.F.: 1B, 1C, 2B, 2C, 3B.
F.G.: 1B, 1C, 2B, 2C, 3B.
S.J.: 1B, 1C, 2B, 2C, 3B.
D. Kreitzman: 1B, 1C, 2B, 2C, 3B.
D. Kremens: 1B, 1C, 2B, 2C, 3B.
S.L.: 1B, 1C, 2B, 2C, 3B.
W.P.: 1B, 1C, 2B, 2C, 3B.
E.T.: 1B, 1C, 2B, 2C, 3B.
C. Campos: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B.
S.N.G.: 1A, 1B, 1C, 2A, 2B, 2C, 3B.
M.S.B.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B. ■

Disclosures

Ethical Compliance Statement: Institutional Review Board approval was not required for the conduct of this study; no patient data was collected and therefore patient consent was not necessary for this work. We confirm that all authors have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Data S1. Supporting Information.