

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

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

Keywords: Parkinson's disease, OFF episode, on-demand treatment, movement disorder, neurology.

Relevant disclosures and conflict of interest are listed at the end of this article.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Received 18 May 2022; revised 20 December 2022; accepted 30 January 2023.

Published online 00 Month 2023 in Wiley Online Library ([wileyonlinelibrary.com](https://www.wileyonlinelibrary.com)). DOI: 10.1002/mdc3.13690

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

n (%)	Disagreement ^a	Agreement		
		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.

^aDefined as ≥ 2 expert ratings of 1 to 3 and ≥ 2 expert ratings of 7 to 9.

^bDefined as a group median of ≥ 7 to 9 without disagreement.

^cDefined as a group median of ≥ 4 to < 7 without disagreement.

^dDefined 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: <ul style="list-style-type: none"> • 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 <i>on</i>-extender treatments • Frequent/long duration^c wearing OFF episodes, except if the patient is on L-dopa without any other <i>on</i>-extender treatments • Less frequent/shorter^e wearing OFF episodes and are on high dose L-dopa^f with an <i>on</i>-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: <ul style="list-style-type: none"> • Frequent/long duration^c early morning OFF, delayed ON, or >1 type of OFF episode • Are on high dose L-dopa^f and other <i>on</i>-extender treatment (other than a dopamine-receptor agonist) • Experience treatment-related side effects

Abbreviation: L-dopa, Levodopa.

^aExamples: hygiene, self-care, dressing, feeding, safety.

^bExamples: 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.

^gE.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 later²³ 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.”²⁵ 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 Neurology²⁶ does not have a guideline on the treatment of OFF episodes. Last, Olanow

et al¹⁴ 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.

Acknowledgments

The authors thank Dr. David Beenhouwer, MD, for conducting the literature review for this project, Dr. Irina Yermilov, MD, MPH, MS, for her leadership and guidance throughout the project, and Hannah Dalglish, MPH for her project management, from PHAR.

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.

Funding Sources and Conflicts of Interest: SI: Received honoraria for research described in this article. Grants or research support from: AbbVie, Acadia, Acorda, Adamas, Addex, Amneal, Aptinyx, Axial, Benevolent, Biogen, Biovie, Cadent, Cala, Cerecor, Cerevel, Eli Lilly, Enterin, Global Kinetics, Impax, Intec

Pharma, Jazz, Kyowa Kirin, Lundbeck, Michael J. Fox Foundation, Neuralys, Neurocrine, Neuroderm, Novartis, Parkinson Study Group, Pharma2B, Praxis, Prilenia, Revance, Roche, Sage, Sanofi, Scion, Stoparkinson, Sunovion, Sun Pharma, Supernus, Teva, Theravance, Transposon, UCB. MA: Received honoraria for research described in this article. Leadership or fiduciary role in other society board, committee, or advocacy group paid or unpaid: VP, Texas Neurological Society, Harris County Medical Society Board of Ethics, Houston Area Parkinson's Society – MAB. RB: Received honoraria for research described in this article. Support for attending meetings and/or travel: Thailand Research Fund, Thailand Science Research and Innovation. Patents planned, issued, or pending: nocturnal monitoring device, Parkinson's gloves, laser-guided walking stick. Leadership or fiduciary role in other society board, committee, or advocacy group paid or unpaid: The Neurological Society of Thailand, International Parkinson's and Movement Disorder Society. CC1: Received honoraria for research described in this article. Leadership or fiduciary role in other society board, committee, or advocacy group paid or unpaid: International neurotoxins society, Movement Disorder Society, American Academy of Neurology. JGF: Received honoraria for research described in this article. FG: Received honoraria for research described in this article. SJ: Received honoraria for research described in this article. Grants or contracts from: Supernus, Merz, AbbVie. Leadership or fiduciary role in other society board, committee, or advocacy group paid or unpaid: CEO, Parkinson & Movement Disorder Alliance. DK1: Received honoraria for research described in this article. Grants or contracts from: Amneal, Acadia, Pharma2b, UCB, Biotie, Lundbeck, Pfizer, Addex, Neurocrine. DK2: Received honoraria for research described in this article. Research: Voyager Therapeutics, Revance, Enterin. SL: Received honoraria for research described in this article. Grants or contracts: NHMRC Leader Fellowship. WP: Received honoraria for research described in this article. Participation on a Data Safety Monitoring Board or Advisory Board: Britannia, Sunovion, Neuroderm. ET: Received honoraria for research described in this article. Grants or contracts from: Spanish Network for Research on Neurodegenerative Disorders (CIBER)- Instituto Carlos III (ISCIII), The Michael J. Fox Foundation for Parkinson's Research (MJFF). CC2, SNG, MSB: Employee of PHAR, LLC which was paid by Sunovion to conduct the research described in this manuscript.

Financial Disclosures for the Previous 12 Months: SI: Receipt of honoraria or consulting fees: AbbVie, Acadia, Acorda, Adamas, Addex, Affiris, Alexza, Allergan, Amneal, Britannia, Cala, Cerecor, Cerevel, Enterin, GE Healthcare, Global Kinetics, Impax, Impel, Kyowa Kirin, Lundbeck, Merz, Neurocrine, Neuroderm, Pharma2B, Revance, Roche, Sage, Scion Neurostim, Stoparkinson, Sunovion, Supernus, Teva, UCB. Participation in a company sponsored speaker's bureau: AbbVie, Acadia, Acorda, Adamas, Allergan, Amneal, Kyowa Kirin, Neurocrine, Sunovion, Supernus, Teva. MA: Payment for expert testimony: McKinney-Taylor LLC, Corley-Alle, LLC. RB: Royalties or licenses: Wiley Blackwell, Humana Press. Consulting fees: Lundbeck, Ipsen, Eisai. Payment or honoraria for lectures,

presentations, speaker bureaus, manuscript writing or educational events: Abbott, Lundbeck, BL Hua. CC1: Royalties or licenses: Cambridge, Wolters Kluwer. Consulting fees: Acorda Therapeutics, Allergan, Inc; Lundbeck Ltd.; Merz Pharmaceuticals; Acadia Pharmaceuticals; Ipsen Pharmaceuticals, Jazz Pharmaceuticals, Adamas Pharmaceutical, Neurocrine Biosciences Inc., Revance Therapeutic, Sunovion., AEON Biopharma. Payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing or educational events: Movement Disorder Society educational lecture, AAN educational lecture. JGF: The author declares no additional disclosures to report. FG: Consulting fees: Amneal, Neurocrine. SJ: The author declares no additional disclosures to report. DK1: Consulting fees: Amneal, Acorda, UCB, Teva, Acadia, USworld Med, Neurocrine. Payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing or educational events: Acadia, Amneal, Acorda, Adamas, Sunovion, Neurocrine, USworld Meds. DK2: Consultant/speaker bureau: Teva Pharmaceuticals, Sunovion, Amneal, Avion, Lundbeck, Acadia, USWorldMeds, Supernus, Adamas, Acorda, Kyowa Kirin, Neurocrine. Consultant: Abbvie, Merz, Allergan, Britannia. SL: Payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing or educational events: International Parkinson's and Movement Disorder Society. WP: Consulting fees: Britannia, Sunovion, Neuroderm. Payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing or educational events: Britannia, Sunovion. Support for attending meetings and/or travel: Sunovion. ET: Consulting fees: TEVA, Bial, Prevail Therapeutics, Boehringer Ingelheim, Roche and BIOGEN. CC2, SNG, MSB: Employee of PHAR, which was paid by each named entity to conduct research outside that described in this manuscript: AbbVie; Amgen; AstraZeneca; BMS; Boston Scientific Corporation; Celgene; Eisai; Genentech; Greenwich Biosciences; Ionis; Jazz; Novartis; Otsuka; Prothena; Recordati; Regeneron; Sage; Sanofi US Services; Sunovion; Takeda Pharmaceuticals USA. ■

References

1. Lebouvier T, Chaumette T, Paillusson S, Duyckaerts C, Bruley des Varannes S, Neunlist M, Derkinderen P. The second brain and Parkinson's disease. *Eur J Neurosci* 2009;30(5):735–741.
2. GBD 2016 Parkinson's Disease Collaborators. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the global burden of disease study 2016. *Lancet Neurol* 2018;17(11):939–953.
3. Chou KL, Stacy M, Simuni T, et al. The spectrum of “off” in Parkinson's disease: What have we learned over 40 years? *Parkinsonism Relat Disord* 2018;51:9–16.
4. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. *JAMA* 2020;323(6):548–560.
5. Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and movement disorder society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease: treatment of motor symptoms in PD. *Mov Disord* 2018;33(8):1248–1266.
6. Dietrichs E, Odin P. Algorithms for the treatment of motor problems in Parkinson's disease. *Acta Neurol Scand* 2017;136(5):378–385.
7. LeWitt PA, Hauser RA, Grosset DG, et al. A randomized trial of inhaled levodopa (CVT-301) for motor fluctuations in Parkinson's disease: inhaled levodopa (CVT-301) for fluctuating PD. *Mov Disord* 2016;31(9):1356–1365.

8. Dewey RB Jr, Hutton JT, LeWitt PA, Factor SA. A randomized, double-blind, placebo-controlled trial of subcutaneously injected apomorphine for parkinsonian off-state events. *Arch Neurol* 2001;58(9):1385.
9. Olanow CW, Factor SA, Espay AJ, et al. Apomorphine sublingual film for off episodes in Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Neurol* 2020;19(2):135–144.
10. Fink A, Kosecoff J, Chassin M, Brook RH. Consensus methods: characteristics and guidelines for use. *Am J Public Health* 1984;74(9):979–983.
11. Campbell SM. Research methods used in developing and applying quality indicators in primary care. *Qual Saf Health Care* 2002;11(4):358–364.
12. Fitch K, ed. *The Rand/UCLA Appropriateness Method User's Manual*. Rand: Santa Monica; 2001.
13. Broder MS, Gibbs SN, Yermilov I. An adaptation of the RAND/UCLA modified Delphi panel method in the time of COVID-19. *J Health Leadersh* 2022;14:63–70.
14. Olanow CW, Poewe W, Rascol O, Stocchi F. On-demand therapy for OFF episodes in Parkinson's disease. *Mov Disord* 2021;36(10):2244–2253.
15. Hauser RA, LeWitt PA, Comella CL. On demand therapy for Parkinson's disease patients: opportunities and choices. *Postgrad Med* 2021;133:721–727.
16. Castillo-Torres SA, Lees AJ, Merello M. Intermittent Apomorphine Use for off Period Rescue in Parkinson's Disease: A Pragmatic Review of over Three Decades of Clinical Experience. *Mov Disord Clin Pract* 2023; 10:190–208. <https://doi.org/10.1002/mdc3.13593>.
17. Farbman ES, Waters CH, LeWitt PA, et al. A 12-month, dose-level blinded safety and efficacy study of levodopa inhalation powder (CVT-301, Inbrija) in patients with Parkinson's disease. *Parkinsonism Relat Disord* 2020;81:144–150.
18. Carbone F, Djamshidian A, Seppi K, Poewe W. Apomorphine for Parkinson's disease: efficacy and safety of current and new formulations. *CNS Drugs* 2019;33(9):905–918.
19. Hauser RA, Isaacson SH, Ellenbogen A, et al. Orally inhaled levodopa (CVT-301) for early morning OFF periods in Parkinson's disease. *Parkinsonism Relat Disord* 2019;64:175–180.
20. Isaacson S, Lew M, Ondo W, Hubble J, Clinch T, Pagan F. Apomorphine subcutaneous injection for the management of morning akinesia in Parkinson's disease. *Mov Disord Clin Pract* 2017;4(1):78–83.
21. Boukledid R, Abdoul H, Loustau M, Sibony O, Alberti C. Using and reporting the Delphi method for selecting healthcare quality indicators: a systematic review. Wright JM, ed. *PLoS One* 2011;6(6):e20476.
22. Kravitz RL, Laouri M, Kahan JP, Sherman T, Hilborne L, Brook RH. Validity of criteria used for detecting underuse of coronary revascularization. *JAMA* 1995;274(8):632–638.
23. Merrick NJ, Fink A, Park RE, Brook RH, Kosecoff J, Chassin MR, Solomon DH. Derivation of clinical indications for carotid endarterectomy by an expert panel. *Am J Public Health* 1987;77(2):187–190.
24. Shekelle PG, Kahan JP, Bernstein SJ, Leape LL, Kamberg CJ, Park RE. The reproducibility of a method to identify the overuse and underuse of medical procedures. *N Engl J Med* 1998;338(26):1888–1895.
25. National Institute for Health and Care Excellence (Great Britain). Parkinson's disease in adults: diagnosis and management: full guideline [Internet]. 2017 [cited 2021 Mar 23]. <https://www.ncbi.nlm.nih.gov/books/NBK447153/>
26. Pringsheim T, Day GS, Smith DB, et al. Dopaminergic therapy for motor symptoms in early Parkinson disease practice guideline summary: a report of the AAN guideline subcommittee. *Neurology* 2021;97(20): 942–957.

Supporting Information

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

Data S1. Supporting Information.