6-30-2021

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Postgraduate Medicine

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ipgm20

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To cite this article: Robert A. Hauser, Peter A. LeWitt & Cynthia L. Comella (2021): On demand therapy for Parkinson's disease patients: Opportunities and choices, Postgraduate Medicine, DOI: 10.1080/00325481.2021.1936087

To link to this article: https://doi.org/10.1080/00325481.2021.1936087

Published online: 30 Jun 2021.

POSTGRADUATE MEDICINE
https://doi.org/10.1080/00325481.2021.1936087

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CLINICAL FOCUS: NEUROLOGICAL AND PSYCHIATRIC DISORDERS
REVIEW

On demand therapy for Parkinson's disease patients: Opportunities and choices

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ABSTRACT

Levodopa is the most effective symptomatic treatment for Parkinson's disease (PD), but a major treatment challenge is that over time, many patients experience periods of return of PD symptoms intermittently through the day, known as OFF periods. OFF periods typically manifest as a return of motor symptoms but can also involve non-motor symptoms and these periods can disrupt good control despite optimization of the oral levodopa regimen. OFF periods emerge in large measure due to a shortening of the duration of clinical benefit from oral levodopa, thought to be related to a progressive loss of dopamine neurons and their ability to store and release levodopa-derived dopamine over many hours. The problem is further compounded by impaired absorption of oral levodopa due to gastroparesis and other factors limiting its uptake in the small intestine, including competition for uptake by meals and their protein content. On-demand therapies are now available for the treatment of OFF episodes in PD and are administered intermittently, on an as-needed basis, on top of the patient's maintenance medication regimen. To be useful, an on-demand medication should take effect more rapidly and reliably than oral levodopa. Options for on-demand therapy for OFF periods have recently increased with the approval of levodopa inhalation powder and sublingual apomorphine as alternatives to the older option of subcutaneous apomorphine injection, each of which avoids the gastrointestinal tract and its potential for absorption delay. On-demand therapy is now available for patients experiencing episodic or intermittent need for rapid and reliable onset of benefit. On-demand therapy may also provide an alternative to more invasive treatment such as infusion of levodopa/carbidopa intestinal gel and for patients whose OFF episodes are not controlled despite deep brain stimulation.

ARTICLE HISTORY
Received 11 March 2021
Accepted 25 May 2021

KEYWORDS
Parkinson disease; levodopa; apomorphine; on-demand treatment; motor fluctuations; off periods

Introduction

The goal of treatment for Parkinson's disease (PD) varies with each patient's symptoms but, in general, treatment aims to reduce discomforts or disabilities in the quest of improving overall function and quality of life. Currently, there are no treatments that slow or stop disease progression [1,2]. Levodopa is the most effective symptomatic treatment for PD [1,3]. A major treatment challenge for this amino acid precursor of dopamine is that many patients eventually develop inconsistency in its effectiveness. Patients then experience a return of PD symptoms within relatively short periods of time despite their standard levodopa therapy, known as motor fluctuations or OFF periods [4]. OFF periods can also involve non-motor symptoms [5]. OFF periods may occur even with an oral regimen that has been adjusted to optimize its effect [4].

When PD patients are initially treated with oral levodopa preparations, they typically experience a good response that is maintained through the day when the medication is administered using a traditional TID regimen. However, over time, the duration of benefit from each levodopa dose shortens and the time to onset of benefit increases and becomes more variable. These two factors lead to response fluctuations through the day, consisting of times when there is good control of symptoms (called ON), and other times when benefit has worn off or not yet kicked in, with reemergence of parkinsonian signs and symptoms (called OFF). The exact reasons for the development of motor fluctuations are not fully elucidated, but it is thought that with the progressive loss of dopamine neurons over time, the ability of remaining neurons to store and release levodopa-derived dopamine over many hours is diminished and the duration of benefit from each levodopa dose shortens [5,6]. In addition, since levodopa is absorbed in the proximal small intestine, worsening gastroparesis may increase the time to absorption of oral levodopa, thereby delaying onset of benefit and increasing variability [7,8]. In addition, factors limiting levodopa's uptake in the small intestine, including competition for uptake by meals and their protein content, have a greater effect [9,10]. Infection with *Helicobacter pylori* may also be a factor as it has been shown to be associated with worse clinical motor outcomes in

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a number of studies when compared with antibiotic-treated or non-infected controls [11].

The incidence of OFF periods becomes increasingly prevalent with chronic levodopa therapy. The prevalence of motor fluctuations in prospective studies of levodopa-treated PD patients is almost 50% within 5 years of starting levodopa therapy and increases beyond two thirds after 9 years or more of treatment [1,12]. In the prospective, early detection of wearing off in Parkinson disease (DEEP) study of 617 patients with an average treatment duration of 6.6 years, wearing-OFF was observed in 56.9% of patients by neurologists and in 67.3% by the self-administered Wearing-Off Questionnaire (WOQ-19). Wearing-OFF was common even in patients with early PD as it was observed in 21.8% of patients with <2.5 years of disease duration by neurologists and 41.8% by the WOQ-19 [13]. Factors increasing risk for wearing OFF include younger age, female sex, and greater than average levodopa doses [13,14]. OFF periods are one factor that has a deleterious impact on activities of daily living and quality of life [14–17]. In the OFF PARK survey, the most troublesome symptoms associated with OFF periods were slowness, reduced dexterity, fatigue, and slowness in the morning (morning akinesia) [16]. Despite the challenge of improving control of PD to lessen OFF events, many patients and physicians do not recognize or even understand OFF symptoms and this problem is often insufficiently treated [18–20].

Various pharmacological treatments and medication adjustment strategies are used to manage OFF periods and motor fluctuations. These include shortening the interval between levodopa administrations and lowering individual doses (to reduce the likelihood of dyskinesias); using extended-release levodopa formulations; adding dopamine agonists (orally administered or transdermal patches), monoamine oxidase B inhibitors (MAO-B) inhibitors, catechol-O-methyltransferase (COMT) inhibitors, an adenosine A2A inhibitor (istradefylline), or amantadine; or switching to levodopa/carbidopa intestinal gel infusion [1]. Continuous subcutaneous apomorphine infusion is also available in many European countries [21].

Beyond baseline medication adjustments, OFF time can be reduced by deep brain stimulation (DBS) of the globus pallidus interna or subthalamic nucleus [22]. Aims for all of these treatments are to reduce the metabolic breakdown of levodopa (MAO-B and COMT inhibitors), provide additional and more sustained stimulation to dopamine receptors (dopaminergic agonists), provide more constant plasma levodopa concentrations (dose fractionation, extended-release formulations, and carbidopa/levodopa intestinal gel), or directly stimulate targets downstream from the nigrostriatal dopaminergic synapses (DBS, amantadine, or adenosine A2A receptor inhibition) [1,3,23,24]. All of these medications, additions or adjustments, and surgical interventions can become part of the patient's maintenance regimen and are typically not considered 'on-demand' or 'as needed' therapies. Despite the availability of these treatments, many patients still experience OFF episodes and additional treatments can be considered.

On-demand treatment in PD: general considerations

Another approach to helping patients manage OFF periods is to use an on-demand therapy. On-demand therapies are those that can be used as needed to bring about improvement quickly and reliably when an OFF episode occurs. To provide a relatively rapid response, those that are currently available bypass the GI tract and the difficulties of delayed absorption encountered by oral levodopa. These include subcutaneous apomorphine injection, sublingual apomorphine, and inhaled levodopa. These medications can be used on an as needed basis when the patient experiences an OFF episode. Such episodes may be expected or unexpected. For example, some patients may only use an on-demand therapy once a week, when an unexpected OFF episode occurs. For others, unpredictable OFF episodes may occur more frequently and on-demand treatment may be required several times a day. In other situations, the need for an on-demand therapy may not be so unexpected. For example, many patients find that their first morning oral levodopa dose takes a long time to kick in and would benefit from the addition of the regular use of an 'on-demand' therapy upon waking each morning. In a study of orally administered immediate-release and extended-release carbidopa/levodopa (Rytary®) in fasted PD patients with motor fluctuations, the mean onset of action was about 50 minutes (0.81/0.83 hours) [25]. In this situation, the use of an on-demand therapy every morning would become part of the patient's maintenance regimen. Another example might be the patient who experiences an OFF episode every day after eating lunch. There are also patients who use on-demand treatments to fill in gaps (i.e. OFF periods) between oral levodopa doses on a regular basis through the day if the duration of benefit is short and it takes a while for the next oral levodopa dose to kick in. In these cases, the 'on-demand therapy' is being scheduled on a regular basis and becomes part of the patient's maintenance regimen.

On-demand therapies for PD (Table 1)

Subcutaneous apomorphine

Apomorphine injection for subcutaneous use (Apokyn®, US WorldMeds, LLC, Louisville, KY) achieved US Food and Drug Administration (FDA) approval in 2004 as an acute, intermittent therapy for OFF episodes. It provides relief from OFF states for many patients at 10 minutes and its benefits may last for up to 2 hours [26,29]. It is administered via a multiple-dose pen injector. Due to possible AEs of nausea and vomiting, premedication with an antiemetic (trimethobenzamide) is recommended for initiation of treatment, and some patients continue to use it whenever they use apomorphine [38]. Since apomorphine was initially used for PD in the mid-1980s, there is a considerable number of open-label studies supporting its use for treating OFF periods [27]. In a randomized, double-blind, placebo-controlled study, 29 patients who experienced at least 2 hours of daily OFF time received subcutaneous apomorphine in both inpatient and outpatient settings. In the outpatient phase, injections reversed 95% of OFF

Table 1. Pharmacological on-demand treatments for Parkinson's disease OFF periods.

Drug	Indication (US)	Administration	Dose	Efficacy*	Common TEAEs*	Comment
Subcutaneous apomorphine (Apokyn®) [26-29	Indicated for the acute, intermittent treatment of hypomobility, 'off' episodes ('end-of-dose wearing off' and unpredictable 'on/off' episodes) in patients with advanced Parkinson's disease. Apokyn has been studied as an adjunct to other medications	• Subcutaneous injection using Apokyn pen injector and glass cartridge • Cartridge contains 3 mL/30 mg apomorphine HCl (10 mg/mL) • Single cartridge, pen and needle can deliver doses up to 1 mL (10 mg) in 0.02 mL (0.2 mg) increments • Max 5 doses/day	• Starting dose 0.2 mL starting dose • Titrate up to 0.6 mL depending on effectiveness and tolerance	• Time to onset of action: 7.3–22 min • Duration of effect: 62.6–96 min • Reduction in OFF time: 1) 58% vs placebo 2) 2 hours vs placebo • Significant improvement in UPDRS-III scores vs placebo • Significant efficacy as recorded by Columbia Parkinson's disease score	• Nausea and/or vomiting • Dyskinesia • Dizziness/postural hypotension • Rhinorrhea • Somnolence/drowsiness • Yawning • Hallucination/confusion • Edema/swelling of extremities	• Premedicate with antiemetic (e.g. trimethobenzamide) to minimize nausea and vomiting at start of treatment • Contraindicated with 5HT3 antagonists, including antiemetics ondansetron, granisetron, dolasetron, palonosetron, alosetron
Sublingual apomorphine (Kynmobi™) [30,31]	Indicated for the acute, intermittent treatment of OFF episodes in patients with Parkinson's disease	• Sublingual film, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg dose strengths • Max 5 doses/day	• Initial dose 10 mg • Titrate up to 30 mg depending on effectiveness and tolerance	• Improvement in UPDRS-III score noted at 15 min post dose (1st measurement timepoint)† • Duration of effect: up to 90 min (last timepoint) • Significant improvement in UPDRS-III scores vs placebo (LS mean treatment difference vs placebo −7.6 30 min after dosing at week 12) • 35% of apomorphine patients turned ON 30 min post dose vs 16% on placebo	• Nausea • Oral/pharyngeal soft tissue swelling • Oral/pharyngeal soft tissue pain and paresthesia • Dizziness • Somnolence • Most common AEs leading to discontinuation were oropharyngeal disorders (17%)	• Premedicate with antiemetic (e.g. trimethobenzamide) to minimize nausea and vomiting at start of treatment • Contraindicated with 5HT3 antagonists
Inhaled levodopa (Inbrija®) [32-37]	Indicated for the intermittent treatment of OFF episodes in patients with Parkinson's disease treated with carbidopa/levodopa	• Orally inhaled using a provided inhaler and capsules • One dose per OFF period • Max 5 doses/day	• One dose consists of 2 × 42 mg capsules (84 mg)	• Improvement in UPDRS-III score noted at 10 min post dose (first measurement timepoint)† • Duration of effect: up to 60 min (last timepoint) • Significant improvement in UPDRS-III scores vs placebo (LS mean treatment difference vs placebo −3.07 30 min after dosing at week 12 (84 mg)) • 58% of Inbrija 84 mg patients turned ON by 60 min post dose vs 36% on placebo	• Cough • Upper respiratory tract infection • Sputum discolored • Most common AE leading to discontinuation was cough (2%)	• Contraindicated with nonselective MAO inhibitors or in those who have taken a nonselective MAO inhibitor within 2 weeks • Not recommended in those with asthma, COPD, or another chronic underlying lung disease

Note: 'improvements' are from a predose, OFF state. Negative UPDRS scores represent improvement.
*Summary of double-blind studies. †Subjects were on standard anti-Parkinsonian regimens including levodopa.
AE, adverse event; LS, least squares; TEAE, treatment-emergent adverse event; UPDRS-III, Unified Parkinson Disease Rating Scale Part III (motor).

episodes, as compared with 23% for placebo ($P < 0.001$). Similar results were observed with inpatient testing [39]. In a study of 56 patients with advanced PD, a significant response was seen at the prespecified end point of 20 minutes, an effect that lasted at least 90 minutes after administration. Maximum improvement was detected at 40 minutes, though anti-parkinsonian effect can begin as early as 4 minutes after injection. Continued efficacy with repeated use over 3 months was demonstrated in 62 patients with advanced PD who showed significant improvement in the Unified Parkinson's Disease Rating Part III (motor) scale (UPDRS-III) compared with placebo when tested at 10 minutes post administration [40]. Subcutaneous apomorphine was also demonstrated to be effective for managing morning akinesia. In a study of patients (n = 127) on levodopa therapy with morning akinesia, the mean time to ON was reduced from 60.9 ± 18.1 minutes with levodopa alone to 23.7 ± 14.6 minutes with levodopa plus subcutaneous apomorphine. Nausea and dizziness were the most common AEs [41]. In

a long-term open-label safety study (n = 546) of patients using subcutaneous apomorphine daily, the most common AEs were nausea and vomiting, dyskinesia, dizziness, somnolence, hallucination, yawning, and injection site bruising [42]. An expert consensus guideline that recommended subcutaneous apomorphine emphasized that management of AEs was the key to successful therapy [43]. Patient acceptance has been limited due to aversion to or discomfort with self-administered injections, and the development of skin nodules or ulcers at injection sites. Prescribers should be aware that subcutaneous apomorphine contains sodium metabisulfite. Patients with a sulfite sensitivity may experience allergic-type reactions, including urticaria, rash, pruritus, angioedema, anaphylactic symptoms, and life-threatening or less severe asthmatic attacks. Patients who experience any hypersensitivity/allergic reaction to subcutaneous apomorphine should avoid taking it again [28].

Sublingual apomorphine

Sublingual apomorphine (Kynmobi™, Sunovion Pharmaceuticals, Inc., Marlborough, MA) is a buffered form of apomorphine that is administered via a layered thin film. When placed under the tongue for 3 minutes, the film dissolves and releases the drug. It was approved by the FDA in 2020 for a similar indication to subcutaneously injected apomorphine [31]. Prior efforts at development of an oral apomorphine were unsuccessful because after gastrointestinal absorption, the drug undergoes extensive hepatic first-pass metabolism [44]. Sublingual apomorphine overcomes this limitation through direct delivery of the drug into the circulation across the buccal surface [45]. Sublingual apomorphine may be perceived as a more practical treatment than subcutaneous apomorphine due to its convenience. Like subcutaneous injection of the drug, premedication with trimethobenzamide in an effort to reduce possible nausea and vomiting is recommended [46]. Concomitant use of 5HT3 antagonist anti-emetics such as ondansetron are contraindicated in light of the possibility for causing profound hypotension. In a randomized, controlled phase 3 study in 109 patients, sublingual apomorphine was more effective than placebo in improving motor function 30 minutes after administration, as measured by the Movement Disorder Society UPDRS Part 3 (MDS-UPDRS-III). The least squares mean treatment difference for dosing with up to 35 mg apomorphine vs placebo was −7.6 rating points (P = 0.0002). A self-rated 'full on' within 30 minutes was reported in 35% of apomorphine patients compared with 16% of placebo patients (P = 0.050). The most common adverse events were oropharyngeal events such as mouth and pharyngeal irritation in 31% of patients; this led to trial discontinuation in 17%. Nausea occurred in 28% of the apomorphine patients during the double-blind phase of the study, and somnolence and dizziness were reported in 13% and 9%, respectively [30]. Similar to subcutaneous apomorphine, sublingual apomorphine contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes.

Inhaled levodopa

Another on-demand treatment is levodopa inhalation powder (Inbrija®, Acorda Therapeutics, Inc. Ardsley, NY). This product received FDA approval in 2018 for the intermittent treatment of OFF episodes in PD patients also being treated with carbidopa/levodopa [47]. Levodopa inhalation powder uses a dry powder inhaler system (Arcus® technology) for delivery of a levodopa therapeutic dose from two capsules by oral inhalation into the lungs for direct and rapid absorption into the circulation, thereby avoiding the delays that the gastrointestinal tract can impose for levodopa uptake [48]. Patients inhale the powdered drug from the passive delivery system by slowly inhaling [49]. The use of levodopa inhalation powder is not recommended for individuals with asthma, chronic obstructive pulmonary disease, or other chronic lung disease [47]. In its phase 3 study, two doses of levodopa inhalation powder (60 and 84 mg) were evaluated in a randomized placebo-controlled trial (n = 351) lasting 12 weeks. The improvement in UPDRS-III score from pre-dose to the primary study end point assessment at 30 minutes post-dose at week 12 was significantly greater with inhaled levodopa 84 mg than with placebo. The most common AE in the inhaled levodopa 84 mg group was cough (15%). Most cough was mild in intensity and represented an irritant effect from inhaling dry powder. Three patients discontinued the study due to cough [34]. Levodopa inhalation powder was also shown to be safe for use as an early morning OFF treatment in a separate, double-blind crossover safety study in 36 patients [33]. A pharmacokinetic study in 23 fed patients demonstrated that an 84 mg dose of inhaled levodopa increased plasma levodopa concentrations much more rapidly and with less variation in concentration than an oral dose of carbidopa/levodopa 25/100 mg. Plasma concentrations of inhaled levodopa showed a mean increase of ~140 ng/mL by 5 minutes and ~240 ng/mL by 15 minutes after inhalation, whereas for oral carbidopa/levodopa, a substantial increase in plasma levodopa concentration was not seen until 60 minutes post-dose. Between-subject levodopa plasma concentration variability for inhaled levodopa 84 mg was generally less than for oral carbidopa/levodopa 25 mg/100 mg [37].

Potential candidates for on-demand therapy

One of the biggest challenges to the implementation of on-demand therapies is a recognition of their impact on quality-of-life measures as reported by patients. Many patients are unaware of how to recognize OFF periods and what treatment options are available. Patient-physician communication about OFF period experiences can be submerged in a typical outpatient visit if not specifically questioned.

As summarized above, there are three on-demand medication options for patients who are experiencing OFF periods. How these medications fit into PD treatment guidelines has not yet been clarified. Levodopa inhalation powder and

sublingual apomorphine may be preferred over apomorphine subcutaneous injections by some patients as they have non-invasive delivery, are easy to administer, and are intended for safe combination with existing treatment regimens [46,49]. The mean duration of action of subcutaneous and sublingual [50] apomorphine is less than one hour, and both modalities have treatment-limiting side effects. Hypotensive responses, nausea, and vomiting can occur even with low doses of the drug. In contrast, lowered blood pressure is not a limiting adverse event with inhaled levodopa powder. Its duration of effect has not yet been characterized in controlled clinical trials as evaluation of efficacy has only been measured out to 60 minutes post-dose [51]. A 60-minute duration of action is also typical of subcutaneous apomorphine administration.

At present, the main value of on-demand medications is to equip patients with the means for rapid and reliable relief of OFF symptoms. It is worth stating, however, that the treatment of non-motor symptoms, many of which fluctuate in concert with OFF periods, remains a largely unmet need in Parkinson's disease and non-motor symptoms constitute an important part of a patient's quality of life. None of the on-demand medications discussed above have been systematically evaluated for these symptoms, but this remains an active area of research [5,52].

In future development of consensus treatment guidelines for PD, inclusion of on-demand therapies may eliminate this current gap in treatment recommendations and suggest how on-demand therapies might best be used in clinical practice. Further trials directly comparing the efficacy and tolerability of these treatments would also be beneficial. Some patients may want or need a rapid-acting medication for regular or situational use (for example, for the first dose of the day after awakening or when socializing at dinnertime), while others may control OFF episodes solely by adjustments to their existing regimen of oral medications. In general, patients who are receiving oral immediate-release carbidopa/levodopa 3-times per day and are experiencing wearing OFF motor fluctuations on a regular basis throughout the day need to decrease the time between levodopa intake by using 4–5 doses per day (based on a 3-4-hour duration of effect). If a patient has made such an adjustment and is, nonetheless, still experiencing wearing OFF fluctuations regularly, a maintenance adjunct medication (such as an inhibitor of COMT or MAO-B, or an adenosine A2a antagonist) may be considered. However, on-demand therapies may be an important part of a therapeutic regimen when changes in maintenance regimens do not reliably eliminate OFF episodes.

An obvious, attractive target for on-demand therapies is morning OFF. Morning OFFs are experienced by many patients with motor fluctuations while awaiting onset of effect for their first dose of levodopa. Some patients may not be troubled or inconvenienced by the delay. Others may have to prepare for work or have household or other responsibilities requiring their attention; some may become frustrated or upset by this motor dysfunction; some simply may not like the inconvenience of waiting. In these cases, on-demand therapies may provide motor benefit more quickly than oral levodopa alone.

Another scenario where on-demand therapies may fill an unmet need is for those patients who would benefit from 'spot' therapy on occasion or who experience troublesome OFF episodes at unexpected times. The patient who reports unwanted OFF episodes even just a few times per week and without a predictable pattern might also be a good candidate for on-demand therapy. In addition, some patients anticipating an OFF episode might feel more comfortable carrying this treatment option every day. For some people, the need for an on-demand dose may be as infrequent as once per month, though the availability of such treatment may enhance their motivation and perception of safety, encouraging them to continue with more activities outside the home. Even the patient on immediate-release carbidopa/levodopa who leads an active lifestyle may want to stick with the convenience of that regimen as long as possible and supplement with an on-demand therapy only at times when OFF episodes interfere with activities.

On-demand therapies may also be useful for patients who experience OFF episodes in relation to meals. Although the timing of medication intakes can be adjusted to mealtimes, there can still be a disruption of regular levodopa effects for several hours after meals. Each of the on-demand treatments bypass the GI tract and can address the problem of meal-related OFF periods.

Many patients with advanced PD experience OFF periods that are highly unpredictable despite multiple maintenance medications and cannot be managed with dosage adjustment or fractionation. For some of these patients, on-demand therapies may be preferred as an alternative to intestinal infusion with levodopa/carbidopa gel or DBS.

Finally, on-demand therapies may be considered for treating overnight OFF episodes when relatively rapid relief is sought in order to regain mobility or relieve Parkinsonian symptoms to get back to sleep.

Conclusion

The options for on-demand therapy for OFF periods have increased with the approval of levodopa inhalation powder and sublingual apomorphine as alternatives to the initial option of subcutaneous apomorphine injection. On-demand medications may be added to oral medication regimens when OFF periods are inadequately controlled. As motor fluctuations become more frequent and capricious, the use of on-demand therapy should be considered in patients who have episodic needs for rapid and reliable onset of action. On-demand therapy may also provide an alternative to more invasive treatment such as levodopa/carbidopa intestinal gel and for patients whose OFF episodes are not controlled despite DBS.

Acknowledgments

Editorial support for the development of this paper was provided by Robin Smith, PhD, of The Curry Rockefeller Group, and this support was funded by Acorda Therapeutics, Inc.

Funding

This paper was funded by Acorda Therapeutics, Inc.

Declaration of financial/other relationships

Robert A. Hauser received consulting fees from AbbVie, Acadia Pharmaceuticals, Acorda Therapeutics, Adamas Pharmaceuticals, Affiris, Alliance for Ageing Research, AlphaSights, Amneal Pharmaceuticals, Apopharma, Aptis partners LLC, Aranca, Axovant, Britannia, Cadent, CAVR, Cerespir, ClearView, Clinical SCORE LLC, CNS Ratings LLC, Compass Group, Decision Resource Group (DRG), Dedham Group, Defined Health, Denali, Enterin, Ernest and Young S.L., Extera, Gerson Lehman Group Inc., Global Kinetic Consulting (GKC), Guidepoint Global (GLG), Health Advances, Huron, Impax Laboratories, Impel Neuropharma, Inhibikase, InSearch Consulting, Insignia Strategies, International Stem Cell Corporation, Intrace, IQVIA, Jazz Pharmaceuticals, Kaiser, Kashiv Pharma, KeiferRX LLC, KeyQuest, KX Advisors, Kyowa Kirin Pharmaceuticals, L.E.K consulting, Lundbeck A/S, Medscape, MediTech, Michael J Fox Foundation, Movement Disorder Society, MPTA, NeuroChallenge Foundation for PD, Neurocrine Biosciences Inc., Neuroderm, NOVUS, Orion, Parkinson's Foundation, Parkinson's Study group, Penn Technology Partnership, Pennside partners, Perception OpCo (CEREVEL Therapeutics LLC), Prescott Medical Group, Regenera Pharma, ROCHE (F. Hoffmann Ltd.), Schlesinger Associates, Scion Neurostim LLC, Seelos Therapeutics, Slingshot Insights, Sunovion Pharmaceuticals Inc, TEVA Pharmaceuticals, The Lockwood Group, Tolmar Inc, US World Meds. Dr. Hauser participated in company sponsored speaker bureaus for Acorda Therapeutics, Adamas Pharmaceuticals, Amneal Pharmaceuticals Inc., Kyowa Kirin Pharmaceutical Development, Neurocrine Biosciences, and US WorldMeds. Dr Hauser has received research support from AbbVie Inc, Acorda Therapeutics, AstraZeneca, Axovant Sciences, Biogen Inc, Cavion, Centogene, Cerevance, Cerevel, Covance, Enterin Inc, Global Kinetics Corp., Impax Laboratories LLC, Intec Pharma Ltd, Jazz Pharmaceuticals, NeuroDerm Ltd., Lundbeck, Michael J Fox Foundation for Parkinson's Research, Neuraly, Pharma2B, F. Hoffman-La Roche, Revance Therapeutics Inc, Sanofi-Genzyme, and Sunovion Pharmaceuticals

Dr Hauser received grant support from the Parkinson's Foundation. Dr Hauser has stock option ownership in Axial Biotherapeutics and Inhibikase Therapeutics Inc.

Peter A. LeWitt has served as a consultant and has been an investigator in clinical trials sponsored by Impax Laboratories Inc. He has also served as a consultant or advisor for Acorda Therapeutics, Amneal, Appello, Axovant Biosciences, Biogen, Cavion, Denali Therapeutics, F. Hoffmann-La Roche, Impel Neuropharma, Intec, Ipsen, Kyowa Kirin Hakko, Lundbeck A/S, Merck, Merz, Mitsubishi Tanabe Neuropharma, Neurocrine Biosciences, NeuroDerm Ltd, Noven, Parkinson Study Group, Prexton Therapeutics, Revance Therapeutics, Saccadous, Supernus, and US WorldMeds and has received speaker honoraria from Acorda Therapeutics, Britannia, the American Academy of Neurology, The International Parkinson's Disease and Movement Disorders Society, Kyowa Kirin Hakko, Neurocrine Biosciences, Pallidan Labs, US WorldMeds, and the World Parkinson Congress. He is compensated for services as editor in chief of *Clinical Neuropharmacology* and serves without compensation on the editorial boards of *Journal of Neural Transmission, Translational Neurodegeneration*, and *Journal of Parkinson's Disease*. His employers have received clinical research grant support from Acorda Therapeutics, Amneal, Aptinyx, Biotie, Bukwang, Cereval, Denali Therapeutics, Impax Labs, The Michael J. Fox Foundation for Parkinson's Research, Pharma 2B, F. Hoffmann-La Roche, Revance, Sunovion, Sun Pharma, and Supernus.

Cynthia L. Comella serves on the editorial board of *Clinical Neuropharmacology* and *Sleep Medicine*. She receives compensation/honoraria for services as a consultant or an advisory committee member: Acorda Therapeutics, Allergan, Inc; Lundbeck Ltd.; Merz Pharmaceuticals; Acadia Pharmaceuticals; Ipsen Pharmaceuticals, Jazz Pharmaceuticals, Neurocrine Biosciences Inc., Revance Therapeutic, Sunovion, and AEON Biopharma. She receives royalties from Cambridge University Press and Wolters Kluwer. She receives research support from the Parkinson's Disease Foundation.

Peer reviewers in this manuscript have no relevant financial or other relationships to disclose.

Declaration of interest

No potential conflict of interest was reported by the author(s).

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