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REVIEW

Clinical Use of On-Demand Therapies for Patients with Parkinson's Disease and OFF Periods

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ABSTRACT

On-demand therapies for Parkinson's disease (PD) provide rapid, reliable relief for patients experiencing OFF periods; however, practical guidelines on the use of these therapies are not generally available. This paper reviews the use of on-demand treatments. Motor fluctuations occur in nearly all patients with PD after long-term use of levodopa. As the goal of PD treatment is to provide good ON time, on-demand treatments that have a more rapid reliable onset than the slower-acting oral medications provide rapid relief for OFF periods. All current on-demand treatments bypass the gastrointestinal tract, providing dopaminergic therapy directly into the blood stream by subcutaneous injection, through the buccal mucosa, or by inhalation into the pulmonary circulation. On-demand treatments are fast acting (10- to 20-min onset), with maximum, reliable, and significant responses reached within 30 min after administration. Oral medications pass through the gastrointestinal tract and thus have slower absorption owing to gastroparesis and competition with food. On-demand therapies, by providing fast-acting relief, can have a positive impact on a patient's quality of life when patients are experiencing OFF periods.

Keywords: Apomorphine; Levodopa; On-demand therapy; Parkinson's disease; Rescue therapy

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Key Summary Points

On-demand therapies for Parkinson's disease provide rapid, reliable relief for patients who are experiencing OFF periods

To many healthcare providers, it may be unclear how these on-demand therapies fit into the existing treatment paradigm

OFF periods occur in nearly all patients with PD with long-term use of levodopa

On-demand treatments that have a more rapid onset than oral medications are useful additions for OFF periods, and can have a positive impact on a patient's quality of life at any stage of the disease

Healthcare providers should consider offering on-demand therapies to patients with OFF periods

INTRODUCTION

On-demand therapies for Parkinson's disease (PD) are available to provide rapid, reliable relief for patients who are experiencing OFF periods [1, 2]. Oral levodopa (LD), administered with an L-dopa decarboxylase inhibitor such as carbidopa (CD), remains the gold-standard treatment for PD. Other medications, such as dopamine agonists, catechol-*O*-methyltransferase (COMT) and monoamine oxidase-B (MAO-B) inhibitors, adenosine A_{2A} antagonists, and *N*-methyl-D-aspartate (NMDA) antagonists, provide adjunctive treatment. In patients with medication-resistant motor fluctuations and dyskinesia, other treatment options include CD/LD enteral suspension (CLES) and deep brain stimulation (DBS) [3].

To many healthcare providers (HCPs), it may be unclear how on-demand therapies fit into the existing treatment paradigm, and how to initiate these therapies. The purpose of this review is to provide practical recommendations on the use of on-demand treatments for OFF periods in patients with PD.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Role of On-demand Therapies for Parkinson's Disease

The first rescue treatment for PD OFF periods, apomorphine for subcutaneous injection, was approved in the USA approximately 20 years ago [4].

In the authors' opinion, on-demand treatments are underutilized as there are no guidelines on the use of these therapies, and experts often differ on when to use them. The International Parkinson and Movement Disorder Society Evidence-Based Medical Review for motor symptoms in Parkinson's disease and the American Academy of Neurology guidelines only mention the use of subcutaneous apomorphine as on-demand therapy, but do not discuss when or how it should be used in clinical practice [5, 6]. Even most treatment guidelines have not clearly defined when to use them [7–12].

In migraine headaches, rescue therapy is a widely used and understood term [13], but there is no standard or consensus term for these therapies in PD. HCPs use terms such as on-demand, rescue, as needed, or acute treatments of OFF periods to describe them. For this review, we will use the term on-demand therapy.

Defining OFF Periods

In general, oral CD/LD provides an approximately 25% improvement in PD motor symptoms [14] and, in initial stages of the disease, this improvement is consistently present throughout the day (sometimes referred to as the honeymoon period). An OFF period is when an individual dose of oral carbidopa/levodopa (CD/LD) is not providing the usual symptomatic benefit in PD symptoms. OFF time refers to the cumulative duration of all the OFF periods during a day. Eventually, nearly all patients develop motor fluctuations and OFF

periods. The type, duration, and severity of OFF-period symptoms may vary during the day [2, 15–17]. In addition to motor symptoms like tremor, bradykinesia, gait, and balance difficulties, nonmotor symptoms, such as fatigue, anxiety, cognitive difficulties (brain fog), attention problems, panic attacks, depression, and apathy, may occur as part of OFF periods [18–20]. In some patients, nonmotor OFF symptoms can have a greater impact on a patient's quality of life than motor symptoms [21]. OFF periods can have a significant impact on the patient and caregiver [22, 23], and can affect the patient's quality of life and increase caregiver burden.

Development of OFF Periods

Long-term use of LD results in motor fluctuations (OFF periods) and dyskinesia [24, 25]. Patients with PD who take LD are believed to have long-duration and short-duration responses [26, 27]. In early disease, the long-duration response, resulting from the buffering capacity of dopaminergic neurons, masks the effects of plasma LD fluctuations due to individual dosing. OFF periods are often predictable at first, but, with disease progression, they become unpredictable. As the disease progresses and striatal dopaminergic neurons are lost, the ability of these neurons to buffer the fluctuating LD levels from oral administration becomes impaired, and the fluctuating plasma LD levels, along with the short half-life of LD, are associated with the occurrence of OFF periods. It is believed that fluctuating plasma LD levels may correlate with neuronal dopamine levels, and, when the level of LD declines below a certain point, PD symptoms reoccur. Eventually, the symptom response becomes parallel to the level obtained from each dose of LD, and mimics the LD half-life of 90 min [15, 26, 28].

In addition to the loss of the buffering capacity of dopaminergic neurons and the short half-life of LD, gastrointestinal (GI) issues play an important role in OFF periods. GI tract dysfunction is common in patients with PD, with GI symptoms experienced in approximately 60–80% of patients [29–31]. GI dysfunction and delayed gastric emptying impair the absorption of LD, which occurs in the proximal small intestine [32, 33]. *Helicobacter pylori* infection is also more frequent in patients with PD, and may additionally impair absorption of oral LD in the GI tract [31, 34]. Furthermore, a protein-rich meal is likely to impair LD absorption, as large neutral amino acids compete with LD for the active-transport system that allows them to cross the small intestine and blood–brain barrier [35, 36]. Finally, small intestinal bacterial overgrowth can also impair LD absorption in the gut [37]. These GI issues affect the rise in plasma LD levels, and therefore play a role in motor fluctuations and the occurrence of OFF periods.

In the authors' experience, patients often use oral CD/LD from their own baseline medication regimen as on-demand therapy, with or without HCP guidance, to manage their OFF periods. Although it may be helpful for some patients, the GI issues make the use of oral CD/LD an unreliable on-demand therapy. In addition, oral CD/LD does not provide a consistent or rapid rise in plasma LD levels. Table 1 shows that alternative oral LD formulations and adjunct medications have only a limited effect on reducing daily OFF time.

Identifying PD Patients with OFF Periods

The principal types of OFF periods are shown in Fig. 1. The American Academy of Neurology recommends that physicians should ask patients with PD about the presence of OFF periods at every clinic visit [38]. The best way to evaluate if a patient is having OFF time is by obtaining a thorough history, specifically inquiring about OFF periods. This is critical, because often patients may not realize that they are experiencing them. This can be done by, for example, asking the patient to describe their symptoms throughout the day. Is the patient having an OFF period when they wake up? Early morning OFF is often under-recognized. In one study using a monitoring wrist device, it was reported that 85% of the PD patients with motor fluctuations had early morning OFF periods [39]. Some of the questions that may help HCPs recognize if their patients are experiencing OFF periods are shown in Fig. 2. A good question to ask the patient is: how long does it take for your first day's dose of oral CD/LD to start working? A standard dose of CD/LD

Table 1 Alternative levodopa formulations and adjunct medications have a limited effect on daily OFF time

Class	Drug	Trial comparator[a]	Duration	Change in daily OFF time vs. standard therapy, h	References
LD (ER) capsules	CD/LD ER	CD/LD ER vs. CD/LD IR	13 weeks	− 1.17	Hauser et al. 2013 [69]
LD (CLES)	CLES	CLES vs. PBO[b]	12 weeks	− 1.91	Olanow et al. 2014 [70]
COMT inhibitor	Entacapone	Entacapone vs. PBO	6 months	− 1.1	Rinne et al. 1998 [71]
	Opicapone	Opicapone vs. PBO (+ 1 year open label)	14–15 weeks	− 0.9 (50 mg/day)	Lees et al. 2017 [72]
	Tolcapone	Tolcapone vs. PBO	6 weeks	− 2.0 (100 mg 3 × daily) − 2.5 (200 mg 3 × daily)	Adler et al. 1998 [73]
MOA-B inhibitor	Rasagiline	Rasagiline vs. PBO	26 weeks	− 0.94 (1.0 mg/day) − 0.49 (0.5 mg/day)	PSG 2005 [74]
	Zydis selegiline	Zydis selegiline vs. PBO	12 weeks	− 1.6	Waters et al. 2004 [75]
	Safinamide	Safinamide vs. PBO	24 weeks	− 1.3	Schapira et al. 2017 [76]
Dopamine agonist	Apomorphine (SC injection)	Apomorphine (SC) vs. PBO	4 weeks	− 2.0	Dewey et al. 2001 [56]
	Pramipexole ER	Pramipexole ER vs. PBO[c]	18 weeks	− 0.7	Schapira et al. 2011 [77]
	Pramipexole IR	Pramipexole IR vs. PBO[c]	18 weeks	− 1.1	Schapira et al. 2011 [77]
	Ropinirole-PR	Ropinirole vs. PBO	24 weeks	− 1.8	Pahwa et al. 2007 [78]
	Rotigotine transdermal patch	Rotigotine patch vs. PBO	24 weeks	− 1.8 (8 mg/day) − 1.2 (12 mg/day)	LeWitt et al. 2007 [79]
NMDA receptor antagonist	Amantadine ER	Amantadine ER vs. PBO	13 weeks	− 1.1	Oertel et al. 2017 [80]
			24 weeks	− 0.8	Pahwa et al. 2017 [78]

Table 1 continued

Class	Drug	Trial comparator[a]	Duration	Change in daily OFF time vs. standard therapy, h	References
Adenosine A_{2A} receptor antagonist	Istradefylline	Istradefylline vs. PBO	12 weeks	− 1.2	LeWitt et al. 2008 [81]

CD carbidopa, *CLES* CD/LD enteral suspension, *COMT* catechol-*O*-methyltransferase, *ER* extended release, *IR* immediate release, *LD* levodopa, *MAO-B* monoamine oxidase-B, *NMDA N*-methyl-D-aspartate, *PBO* placebo, *PR* prolonged release, *SC* subcutaneous

[a]Patients on maintenance L-dopa decarboxylase inhibitor/LD + other antiparkinsonian medication

[b]Randomized to oral CD/LD plus PBO intestinal gel infusion, or CLES plus oral PBO

[c]Parallel trial of pramipexole ER and pramipexole IR vs. PBO

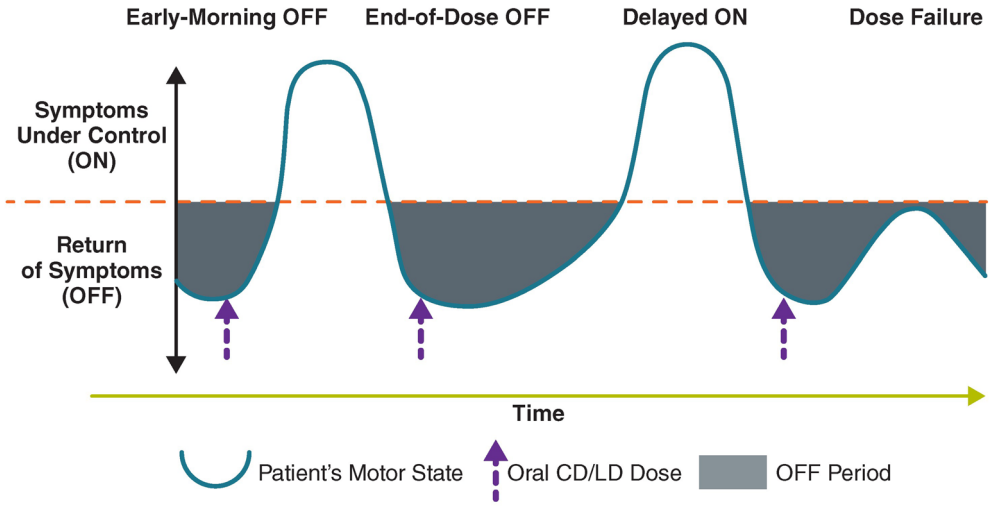

Fig. 1 Different types of OFF: *Early-morning OFF,* or morning akinesia, is when the first oral dose of the day takes a long time to work. *End-of-dose wearing OFF* is the process when the oral dose no longer relives symptoms leading to the patients being OFF. *Delayed ON* (similar to morning akinesia) is when the oral dose takes very much longer to relieve symptoms than usual (often because of GI dysfunction). *Dose failure* or *no ON* is when oral CD/LD does not produce an ON state [15, 16, 82, 83]. *CD/LD* carbidopa/levodopa, *GI* gastrointestinal

usually becomes effective about 20 min after ingestion. If a patient continues to be in the OFF state after 40 min, they should be considered to be having a delayed ON [40]. The duration of benefit of a single oral CD/LD dose determines the presence of end-of-dose wearing OFF. Some patients report having OFF periods when they miss a CD/LD dose, or if they delay taking a dose. For these patients, the time to ON becomes an important consideration for on-demand therapy use. If the patient does not show any improvement in their symptoms after taking an oral dose of LD, the patient has dose failure or "no ON." Often, a free-flowing line of questioning is more helpful than asking patients directly if they have OFF periods,

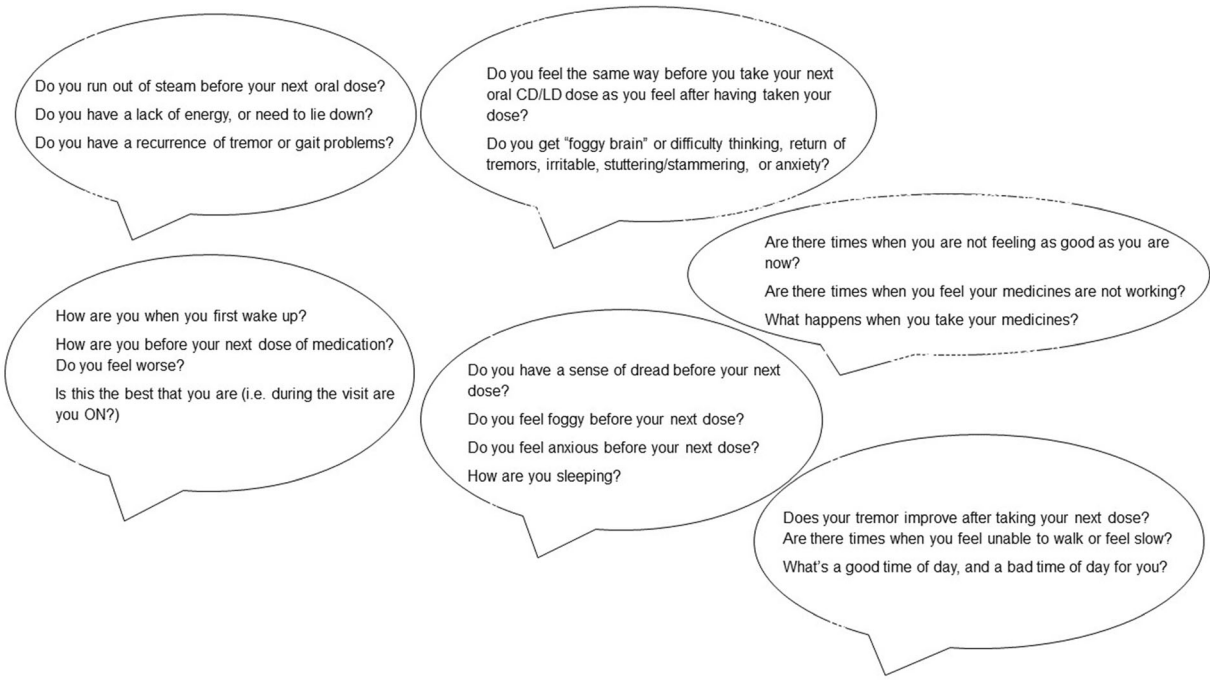

Fig. 2 Examples of questions that can be used to ask patients about their OFF periods

because their understanding of OFF may be limited. The use of this kind of dialogue is supported by the results of a survey of physicians, patients, and care partners [41]. An issue that may arise when talking with patients about OFF periods is that there can be lexicological and other miscommunications between physicians and patients. For example, in one study, many patients misunderstood why their physician was asking them how often and when they had PD symptoms and thought they were asking about their medication adherence [42]. The same study also reported that patients tended to talk in terms of anecdotal, personal life narratives, and, in this case, only 3 out of 29 patients and no care partners used the term "wearing OFF". In the OFF-PARK survey, Matthews et al. showed that 30% of patients and 17% of care partners, who previously had said they understood wearing OFF, in reality gave the wrong answer to a question about the relationship between OFF-period symptoms and medication timing, and 53% of these patients and 36% of care partners did not answer when they were asked what wearing OFF meant [43].

There are a number of questionnaires that assess patient status, for example, the Wearing OFF Questionnaires (WOQ), WOQ-32, WOQ-19, and WOQ-9 [44]. The WOQ-9, in particular, was designed to be completed easily in a clinic. There are also patient home diaries, in which patients record their ON or OFF states during a set period of time at regular intervals during the day [45].

Wearable sensors provide an opportunity to obtain more consistent data, in the form of wrist-worn activity sensors, or other sensors attached to different areas of the body that can detect tremor, bradykinesia, and dyskinesia [46, 47]. The advantage of wearable sensors is that they can provide continuous measurement over long periods and do not rely on the patient completing diaries or questionnaires. Therefore, the accuracy of defining OFF periods could increase. Sensors are currently not widely used, and their utility in clinical settings needs to be further studied. However, as algorithms that analyze the data from wearable sensors further improve, it seems very likely that their use will increase in the future.

Selecting Patients for On-Demand Therapy

On-demand therapy can be used for PD patients experiencing OFF periods including early morning OFF; delayed ON; (end of dose) wearing OFF; dose failure, or no ON; or OFF periods after food intake (Fig. 1) [1, 2, 15, 48]. The majority of PD patients with motor fluctuations experience early morning OFF periods which can significantly impact their quality of life [49, 50]. Early morning OFF periods are reported even in patients on multiple adjunctive therapies including CD/LD infusion therapies [51]. Delayed ON is another major contributor to the total OFF time during the day. One study reported that delayed ON comprised nearly 70% of the total daily OFF time for the day [52]. Although wearing OFF is frequently predicted by the patients, dose failures are often unpredictable. OFF periods due to food intake might limit protein intake by patients and lead to weight loss, especially muscle volume loss [31].

Current On-Demand Treatments

On-demand treatments bypass the GI tract and provide dopaminergic therapy directly to the blood stream, by subcutaneous injection, through the buccal mucosa, or by inhalation into the pulmonary circulation (Table 2). There are currently three approved on-demand therapies to treat OFF periods: subcutaneously injected apomorphine [4], sublingual apomorphine, and inhaled LD. They produce a rapid, reliable benefit because they are absorbed directly into the circulation and do not have to pass through the GI tract [1, 2]. It has been shown with pharmacokinetic studies that using oral LD produces a slower and more inconsistent increase in plasma LD compared with inhaled LD (Fig. 3). As a result of on-demand therapies' rapid and consistent absorption, onset of relief of motor symptoms is fast (within about 10–20 min), with a duration of effect of 60–90 min [53–55].

In clinical trials with on-demand therapies, the primary outcome measure was improvement in the Unified Parkinson's Disease Rating Motor (UPDRS III) scores [1, 2, 48], where improvements of 4–20 points were observed over placebo depending on the study, drug, and sample population [54–57]. Significant improvements in motor function after administration have also been observed after 30–60 min [54, 55]. Onset of action (as seen by better UPDRS III scores) start at about 10–15 min post-dose [53–55]. Duration of effect is about 60–90 min [53–55]. OFF time reductions have also been observed (e.g., an improvement of 2 h for subcutaneous apomorphine over placebo) [56]. Nonmotor symptoms have not been investigated in randomized controlled trials of on-demand therapies, but many nonmotor symptoms during OFF periods could improve with dopaminergic treatment [15, 18, 58]. On-demand medication can be administered up to five times daily. Only one dose should be used for an individual OFF period [4, 59, 60].

Subcutaneous Apomorphine

Apomorphine is a non-ergot dopamine agonist with D1 and D2 receptor affinity and with potent antiparkinsonian benefits [53], which were recognized in the 1950s [61]. Apomorphine is extensively and rapidly sulfonated in the GI tract, and hence cannot be administered orally. Subcutaneous apomorphine is administered through a pen injector [4]. The usual dose to obtain an ON state is between 2 and 6 mg (0.2–0.6 mL). Subcutaneous apomorphine improved UPDRS III scores by 23.9 points compared to 0.1 for placebo and resolved OFF periods in 95% of the patients [56]. The beneficial effect usually begins in 10–15 min and lasts for up to 90 min [2, 57, 62]. In an open label study to assess the effect of apomorphine on time to ON in PD patients with morning akinesia, patients receiving subcutaneous apomorphine achieved ON in approximately 24 min compared to 61 min with oral CD/LD. In addition, fewer patients had dose failures with apomorphine (7%) compared to oral CD/LD (46%) [63].

Common adverse events for subcutaneous apomorphine include nausea, vomiting, somnolence, dizziness or light-headedness, and yawning. Many patients also experience

Table 2 On-demand treatments available in the United States

Drug/year of FDA approval	Administration	Dose	Efficacy outcomes[a]	Comments	Contraindications/ precautions
Subcutaneous apomorphine (Apokyn®)	Subcutaneous injection using multiple-dose Apokyn pen injector and glass cartridge containing 3 mL/ 30 mg apomorphine HCl (10 mg/mL)	Starting dose 0.2 mL	*Primary endpoint* Mean change vs. placebo in UPDRS III at 20 min post-dose − 23.9 vs. − 0.1 (difference − 23.8) $P < 0.001$. Mean dose 5.4 mg	First dose requires medical supervision/ titration for optimum doses	Contraindicated with 5-HT3 antagonists, including the anti-emetics ondansetron, granisetron, dolasetron, palonosetron, alosetron
Approved: 2004 [56, 57, 63]	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 per day	Titrate up to 0.6 mL depending on effectiveness and tolerance	*Secondary outcomes* Hand tapping score improvement vs. placebo: 88% vs. − 4%; $P < 0.001$ Webster Step Seconds improvement: − 65 vs. 0; $P < 0.001$	Injection required; limits patient acceptance Skin reactions such as soreness and itching may occur Requires device assembly to use	

Table 2 continued

Drug/year of FDA approval	Administration	Dose	Efficacy outcomes[a]	Comments	Contraindications/ precautions
Sublingual apomorphine (Kynmobi™)	Sublingual film, 10-, 15-, 20-, 25-, 30-mg dose strengths	Initial dose 10 mg	*Primary endpoint* Mean change vs. placebo in MDS-UPDRS III at 30 min post-dose: − 11.1 vs. − 3.5 (difference − 7.6) $P = 0.0002$). Mean dose 19.6 mg	Film held under tongue for 3 min without swallowing	Contraindicated with 5-HT3 antagonists, including the anti-emetics ondansetron, granisetron, dolasetron, palonosetron, alosetron
Approved: 2020 [55, 60]	Max 5 doses per day	Titrate up to 30 mg depending on effectiveness and tolerance	*Secondary outcomes* Response rate of self-rated full ON response within 30 min post-dose vs. placebo at week 12: 35% vs. 16% (OR 2.81) $P = 0.043$	Oropharyngeal AEs are common Premedication with anti-emetic not required for many patients	
			Response rate of self-rated full ON response within 30 min post-dose lasting at least 30 min vs. placebo at week 12: 31% vs. 14% (OR 2.80) $P = 0.05$	Can titrate at home	

Table 2 continued

Drug/year of FDA approval	Administration	Dose	Efficacy outcomes[a]	Comments	Contraindications/ precautions
Inhaled levodopa (Inbrija®)	Orally inhaled using a provided inhaler and capsules	Single dose of 84 mg (two 42-mg capsules)	*Primary endpoint* Mean change vs. placebo in UPDRS III at 30 min post-dose − 9.83 vs. − 5.91 placebo (LS difference − 3.92) $P = 0.0088$	Requires device assembly to use	Not recommended in people with asthma, COPD, or another chronic underlying lung disease
Approved: 2018 [54, 59]	One dose per OFF period Max 5 doses per day		*Secondary outcome* Achieve and maintain ON state at 60 min post-dose: 58% vs. 36% on placebo (OR 2.65) $P = 0.0027$	Cough and discolored sputum most common AEs Relatively low dose of LD	

5-HT3 serotonin, *AE* adverse event, *COPD* chronic obstructive pulmonary disease, *FDA* United States Food and Drug Administration, *HCl* hydrochloride, *LD* levodopa, *LS* least squares, *OR* odds ratio
[a]From double-blind studies; significant ($P \leq 0.05$) outcomes shown
Modified from Hauser et al. 2021 [1] and Olanow et al. 2021 [2]

injection site skin reactions [26%], including bruising [16%], granuloma [4%], and pruritus [2%]) [4]. Skin reactions can be minimized by rotating the site of injection, local massage, ultrasound, or injecting steroids in the nodules. In clinical practice, the first dose of subcutaneous apomorphine must be given under medical supervision. The authors recommend initiating the first dose with 0.1 mL subcutaneously and observing the patient for any acute side effects including nausea, vomiting, or orthostatic hypotension. Blood pressure should be monitored for approximately 60 min, or longer if the patient continues to have an orthostatic drop in blood pressure. We recommend continuing the 0.1-mL dose for 2–4 days and then increasing the dose to 0.2 mL for 2–-4 days and keep increasing the dose to efficacy. If the patient has nausea, 5HT3 antagonists (including anti-emetics, like ondansetron, granisetron, dolasetron, etc.) are contraindicated [4].

Sublingual Apomorphine

Due to the limitations and lack of widespread acceptance of subcutaneous apomorphine, a sublingual formulation was approved by the FDA. The apomorphine strip consists of a bilayer film with apomorphine in one layer and a buffer designed to minimize mucosal irritation in the other layer. Sublingual apomorphine is absorbed from the oral cavity and bypasses the first-pass metabolism in the GI tract. The approved dose of sublingual apomorphine is 10–30 mg [55, 64]. In a phase III study [55], sublingual apomorphine improved MDS-UPDRS III scores by 7.6 points compared to placebo at week 12. In the home environment sublingual apomorphine provided a full ON response within 30 min in approximately 79% of subjects

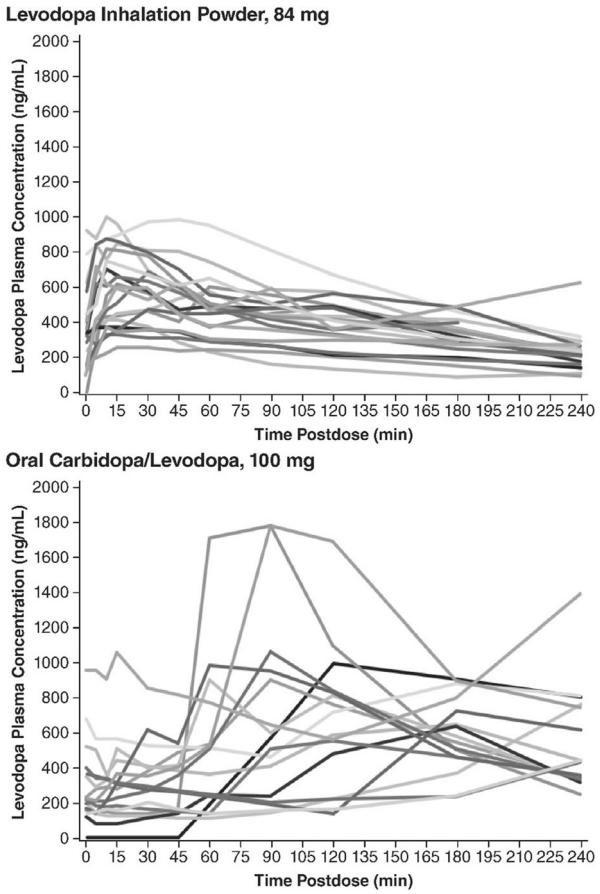

Fig. 3 Individual plasma LD profiles after a single inhaled dose of LD inhalation powder and after a single ingested dose of CD/LD in patients with PD and in a fed state. In this study, levodopa was more rapidly absorbed when inhaled as LD inhalation powder (84 mg) than when ingested via an oral CD/LD tablet (100 mg), with C_{10min} and C_{30min} values of 522.9 and 531.5 ng/mL for LD inhalation powder, respectively, and 247.3 and 300.9 ng/mL for oral LD/CD. The patients' plasma LD profiles also had much less variability after LD inhalation powder than after oral CD/LD ingestion (range of t_{max} values was 5–90 min for LD inhalation powder vs. 57–240 min for oral CD/LD. LD inhalation powder $n = 20$, CD/LD $n = 17$. C_{10min}, C_{30min}, observed concentrations at 10 and 30 min; *CD* carbidopa, *LD* levodopa, t_{max} time to maximum plasma concentration. Adapted from Safirstein et al. [87]

compared to 31% with placebo. Improvements began as soon as 15 min after administration. Oropharyngeal adverse effects are the most common side effects, occurring in approximately 31% of the patients and leading to 17% of patients discontinuing therapy. They included oral mucosal erythema, dry mouth, lip swelling, lip edema, throat irritation, and glossodynia. Other adverse effects were similar to subcutaneous apomorphine [55].

In clinical practice, similar to subcutaneous apomorphine, the first dose of sublingual apomorphine must be given under medical supervision [60]. The authors recommend initiating the first dose with 10 mg placed under the tongue, and the patient should be instructed to not chew or swallow for approximately 3 min, the time it takes for the film to disintegrate. Orthostatic blood pressure should be monitored for approximately 60 min unless the patient continues to have an orthostatic drop in blood pressure. We recommend continuing the 10-mg dose for 2–4 days and then increasing the dose to 15 mg for 2–4 days and then keep increasing the dose to efficacy. If the patient has nausea, 5HT3 antagonists including anti-emetics such as ondansetron, granisetron, and dolasetron are contraindicated.

Levodopa Inhalation Powder

The challenges with oral CD/LD include the variability in absorption and bioavailability that would produce reliable and consistent plasma levodopa levels and hence brain dopamine levels. Bypassing the GI tract, inhaled levodopa was developed to provide a rapid and consistent rise in plasma LD levels and in brain dopamine levels. LD inhalation powder is formulated as dry powder particles (diameter < 5.6 μm), highly porous for lung deposition. A single dose requires the inhalation of the contents of two capsules (each containing 42 mg LD) using the supplied inhaler. Each dose supplies 84 mg LD (equivalent to approximately 50 mg of oral LD), and it rapidly enters the blood stream via the pulmonary circulation [65, 66].

In a phase III study, inhaled LD provided a mean improvement of 3.9 points compared to placebo in the UPDRS III score 30 min after administration [54]. A small safety study ($n = 36$) was also conducted using inhaled levodopa for early morning akinesia. LD inhalation powder (even without additional carbidopa) taken immediately after the first

morning oral CD/LD dose was well tolerated, and the median time to ON was 25 min compared to 35.5 min with placebo [67]. The most significant adverse event occurring in about 15% of patients was cough, due to the irritant effect of dry powder entering the lungs [54]. Other adverse effects included upper respiratory tract infection, sputum discoloration, and nausea. The use of LD inhalation powder is not recommended in patients with concomitant lung disease, especially asthma or chronic obstructive pulmonary disease [59]. In clinical practice, the first dose of inhaled LD does not need to be given under medical supervision. Due to throat irritation with the dry powder, we recommend patients take some water before the inhalation to moisten the throat and reduce the likelihood of cough. There is no dose titration required.

Selecting On-Demand Therapy

On-demand therapies are most useful for patients who can identify when they are having, or are beginning to experience, OFF. For those patients whose symptoms are highly variable or who have difficulties identifying their OFF periods, it may be difficult for the patient to know when best to take the treatment. We recommend patients use on-demand therapy at the beginning of the OFF period and upon awakening for early morning akinesia. Rarely, patients with severe motor OFFs or tremor may find it difficult to use these on-demand therapies. A caregiver may be required to help in these cases. The need for medical supervision of the initial titration of the apomorphine may be a barrier for some patients [48]. Although on-demand treatments are approved for use up to five times a day, in the pivotal clinical trials they were used only on average 2–2.5 times per day [54, 56]. In a recent survey of theoretical on-demand treatment options, people with PD (98% had OFF periods) preferred on-demand treatments that were non-invasive, that produced a rapid ON in 15 min, that controlled symptoms for longer ($\geq$ 2 h), and that had no out-of-pocket costs associated with their use [68]. In real-world settings, and considering patient preferences and potential adverse events, the choice of on-demand treatments has to be individualized after consideration and discussion with the patient.

Although there are advantages of using on-demand therapies, there can be some drawbacks to their use. The cost of the drug could be a major disincentive. In addition, not every patient can tolerate on-demand therapy. Some patients may prefer having OFF symptoms rather than experience the adverse effects of the therapy, and some may not be able to recognize the OFF periods, or might find the OFF periods not bothersome enough to take additional medications.

CONCLUSION

Long-term LD use is associated with OFF periods which, as PD progresses, become more frequent and intractable. Patients may have difficulty describing their OFF periods, and HCPs often do not query about them specifically. Given the availability of new on-demand treatments (injectable apomorphine, sublingual apomorphine, and inhaled LD), fast-acting therapies that bypass the GI tract, it is time to reevaluate when these therapies should be used. As they are safe and effective for OFF periods, and due to the marked negative impact of the OFF periods, we need to consider using them earlier when patients have motor fluctuations. Figure 4 shows a summary of treatments for PD that include on-demand therapies which should especially be considered for early-morning OFF, delayed ON, dose failures, and for OFF periods due to food interactions, since oral adjunctive therapies are often not helpful in such cases.

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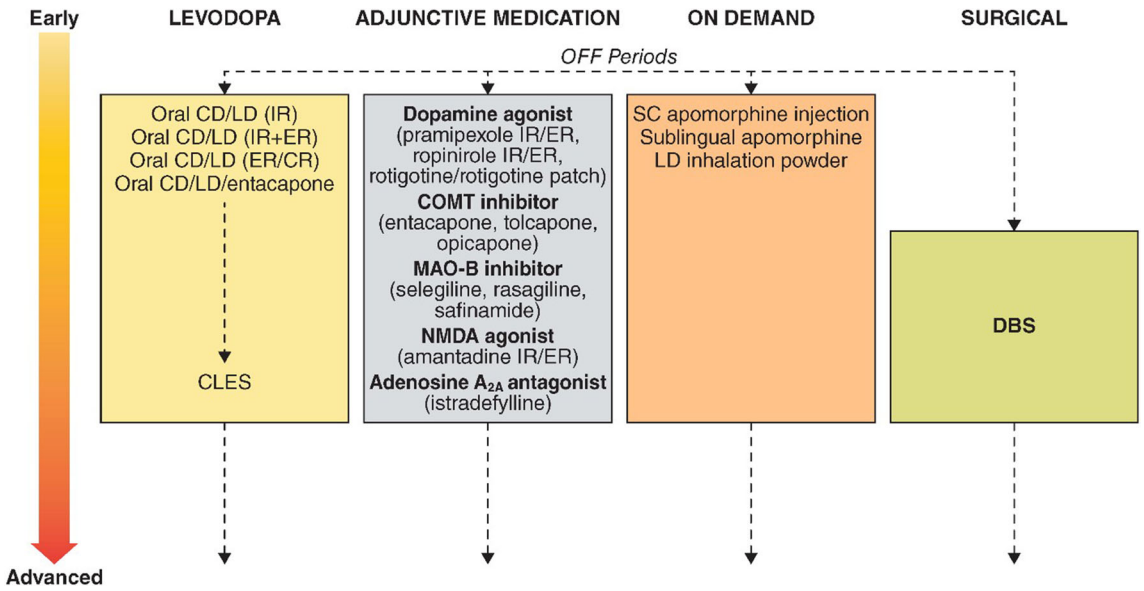

Fig. 4 Treatment options for motor fluctuations from early to advanced PD incorporating on-demand treatment [84–86]. *CD* carbidopa, *CLES* CD/LD enteral suspension, *COMT* catechol-*O*-methyltransferase, *CR* controlled release, *DBS* deep brain stimulation, *ER* extended release, *IR* immediate release, *LD* levodopa, *MAO-B* monoamine oxidase-B, *NMDA N*-methyl-D-aspartate, *SC* subcutaneous

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REFERENCES

1. Hauser RA, LeWitt PA, Comella CL. On demand therapy for Parkinson's disease patients: opportunities and choices. Postgrad Med. 2021;133(7):721–7.

2. Olanow CW, Poewe W, Rascol O, Stocchi F. On-demand therapy for OFF episodes in Parkinson's disease. Mov Disord. 2021;36(10):2244–53.

3. Connolly BS, Lang AE. Pharmacological treatment of Parkinson disease: a review. JAMA. 2014;311(16):1670–83.

4. Supernus Pharmaceuticals. Apokyn® (apomorphine hydrochloride injection). Full Prescribing Information. Supernus Pharmaceuticals; 2020.

5. Pahwa R, Factor SA, Lyons KE, et al. Practice parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006;66(7):983–95.

6. 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. Mov Disord. 2018;33(8):1248–66.

7. Deuschl G, Antonini A, Costa J, et al. European Academy of Neurology/Movement Disorder Society—European Section guideline on the treatment of Parkinson's disease: I. Invasive therapies. Eur J Neurol. 2022;29(9):2580–95.

8. Ferreira JJ, Katzenschlager R, Bloem BR, et al. Summary of the recommendations of the EFNS/MDS-ES review on therapeutic management of Parkinson's disease. Eur J Neurol. 2013;20(1):5–15.

9. Grimes D, Fitzpatrick M, Gordon J, et al. Canadian guideline for Parkinson disease. CMAJ. 2019;191(36):E989–1004.

10. Miyasaki JM, Martin W, Suchowersky O, Weiner WJ, Lang AE. Practice parameter: initiation of treatment for Parkinson's disease: an evidence-based review: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2002;58(1):11–7.

11. 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):942–57.

12. Zesiewicz TA, Sullivan KL, Arnulf I, et al. Practice Parameter: treatment of nonmotor symptoms of Parkinson disease: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2010;74(11):924–31.

13. Gilmore B, Michael M. Treatment of acute migraine headache. Am Fam Physician. 2011;83(3):271–80.

14. Hauser RA, Auinger P, Oakes D, Parkinson Study Group. Levodopa response in early Parkinson's disease. Mov Disord. 2009;24(16):2328–36.

15. 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.

16. Olanow CW, Stern MB, Sethi K. The scientific and clinical basis for the treatment of Parkinson disease (2009). Neurology. 2009;72(21 Suppl 4):S1-136.

17. Melamed E, Bitton V, Zelig O. Delayed onset of responses to single doses of L-dopa in parkinsonian fluctuators on long-term L-dopa therapy. Clin Neuropharmacol. 1986;9(2):182–8.

18. Storch A, Schneider CB, Klingelhofer L, et al. Quantitative assessment of non-motor fluctuations in Parkinson's disease using the Non-Motor

Symptoms Scale (NMSS). J Neural Transm (Vienna). 2015;122(12):1673–84.

19. Santos-Garcia D, de Deus Fonticoba T, Suarez Castro E, et al. Non-motor symptom burden is strongly correlated to motor complications in patients with Parkinson's disease. Eur J Neurol. 2020;27(7): 1210–23.

20. Storch A, Schneider CB, Wolz M, et al. Nonmotor fluctuations in Parkinson disease: severity and correlation with motor complications. Neurology. 2013;80(9):800–9.

21. Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KR. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. Mov Disord. 2011;26(3):399–406.

22. Kremens DE. Shifting the paradigm: earlier use of on-demand therapy for treating OFF time in Parkinson disease. NeurologyLive. 2022;5(4):4.

23. Rastgardani T, Armstrong MJ, Gagliardi AR, Marras C. Understanding, impact, and communication of "Off" periods in Parkinson's disease: a scoping review. Mov Disord Clin Pract. 2018;5(5):461–70.

24. Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord. 2001;16(3):448–58.

25. Jankovic J. Motor fluctuations and dyskinesias in Parkinson's disease: clinical manifestations. Mov Disord. 2005;20(S11):S11–6.

26. Nutt JG, Woodward WR, Carter JH, Gancher ST. Effect of long-term therapy on the pharmacodynamics of levodopa. Relation to on-off phenomenon. Arch Neurol. 1992;49(11):1123–30.

27. LeWitt PA. Levodopa therapy for Parkinson's disease: pharmacokinetics and pharmacodynamics. Mov Disord. 2015;30(1):64–72.

28. Nutt JG, Holford NH. The response to levodopa in Parkinson's disease: imposing pharmacological law and order. Ann Neurol. 1996;39(5):561–73.

29. Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. Curr Treat Options Neurol. 2018;20(12):54.

30. Fasano A, Visanji NP, Liu LW, Lang AE, Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. Lancet Neurol. 2015;14(6):625–39.

31. Pfeiffer RF, Isaacson SH, Pahwa R. Clinical implications of gastric complications on levodopa treatment in Parkinson's disease. Parkinsonism Relat Disord. 2020;76:63–71.

32. Muller T, Erdmann C, Bremen D, et al. Impact of gastric emptying on levodopa pharmacokinetics in Parkinson disease patients. Clin Neuropharmacol. 2006;29(2):61–7.

33. Nyholm D, Lennernas H. Irregular gastrointestinal drug absorption in Parkinson's disease. Expert Opin Drug Metab Toxicol. 2008;4(2):193–203.

34. Narozanska E, Bialecka M, Adamiak-Giera U, et al. Pharmacokinetics of levodopa in patients with Parkinson disease and motor fluctuations depending on the presence of *Helicobacter pylori* infection. Clin Neuropharmacol. 2014;37(4):96–9.

35. Nutt JG, Woodward WR, Hammerstad JP, Carter JH, Anderson JL. The "on-off" phenomenon in Parkinson's disease. Relation to levodopa absorption and transport. N Engl J Med. 1984;310(8):483–8.

36. Wang L, Xiong N, Huang J, et al. Protein-restricted diets for ameliorating motor fluctuations in Parkinson's disease. Front Aging Neurosci. 2017;9: 206.

37. Fasano A, Bove F, Gabrielli M, et al. The role of small intestinal bacterial overgrowth in Parkinson's disease. Mov Disord. 2013;28(9):1241–9.

38. American Academy of Neurology. Parkinson's Disease Quality Measurement Set Update. Minneapolis: American Academy of Neurology. https://www.aan.com/siteassets/home-page/policy-and-guidelines/quality/quality-measures/16pdmeasureset_pg.pdf. Accessed 10 May 2022.

39. Isaacson SH, Pahwa R, Pappert EJ, Torres-Russotto D. Evaluation of morning bradykinesia in Parkinson's disease in a United States cohort using continuous objective monitoring. Clin Park Relat Disord. 2022;6: 100145.

40. Chana P, Kuntsmann C, Reyes-Parada M, Saez-Briones P. Delayed early morning turn "ON" in response to a single dose of levodopa in advanced Parkinson's disease: pharmacokinetics should be considered. J Neurol Neurosurg Psychiatry. 2004;75(12):1782–3.

41. Rastgardani T, Armstrong MJ, Gagliardi AR, Grabovsky A, Marras C. Communication about OFF periods in Parkinson's disease: a survey of physicians, patients, and carepartners. Front Neurol. 2019;10:892.

42. Levit A, Zebendon C, Walter L, O'Donnell P, Marras C. Communication gaps about OFF periods between physicians and patients with Parkinson's

disease: a patient-physician dialogue analysis. Res Rev Parkinsonism. 2019;9:3–8.

43. Matthews H, Stamford J, Saha R, Martin A, Off-Park Survey Steering Group. Exploring issues around wearing-off and quality of life: the OFF-PARK survey of people with Parkinson's disease and their care partners. J Parkinsons Dis. 2015;5(3):533–9.

44. Stacy M. The wearing-off phenomenon and the use of questionnaires to facilitate its recognition in Parkinson's disease. J Neural Transm (Vienna). 2010;117(7):837–46.

45. Hauser RA, Friedlander J, Zesiewicz TA, et al. A home diary to assess functional status in patients with Parkinson's disease with motor fluctuations and dyskinesia. Clin Neuropharmacol. 2000;23(2):75–81.

46. Adams JL, Dinesh K, Snyder CW, et al. A real-world study of wearable sensors in Parkinson's disease. NPJ Parkinsons Dis. 2021;7(1):106.

47. Channa A, Popescu N, Ciobanu V. Wearable solutions for patients with Parkinson's disease and neurocognitive disorder: a systematic review. Sensors (Basel). 2020;20(9):2713.

48. Isaacson SH, Pagan FL, Lew MF, Pahwa R. Should "on-demand" treatments for Parkinson's disease OFF episodes be used earlier? Clin Parkinsonism Relat Disord. 2022;7: 100161.

49. Onozawa R, Tsugawa J, Tsuboi Y, Fukae J, Mishima T, Fujioka S. The impact of early morning off in Parkinson's disease on patient quality of life and caregiver burden. J Neurol Sci. 2016;364:1–5.

50. Rizos A, Martinez-Martin P, Odin P, et al. Characterizing motor and non-motor aspects of early-morning off periods in Parkinson's disease: an international multicenter study. Parkinsonism Relat Disord. 2014;20(11):1231–5.

51. Pahwa R, Aldred J, Gupta N, et al. Patterns of daily motor-symptom control with carbidopa/levodopa enteral suspension versus oral carbidopa/levodopa therapy in advanced Parkinson's disease: clinical trial post hoc analyses. Neurol Ther. 2022;11(2):711–23.

52. Merims D, Djaldetti R, Melamed E. Waiting for ON: a major problem in patients with Parkinson disease and ON/OFF motor fluctuations. Clin Neuropharmacol. 2003;26(4):196–8.

53. 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):905–18.

54. LeWitt PA, Hauser RA, Pahwa R, et al. Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Neurol. 2019;18(2):145–54.

55. 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):135–44.

56. 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):1385–92.

57. Pahwa R, Koller WC, Trosch RM, Sherry JH, A. P. O. Study Investigators. Subcutaneous apomorphine in patients with advanced Parkinson's disease: a dose-escalation study with randomized, double-blind, placebo-controlled crossover evaluation of a single dose. J Neurol Sci. 2007;258(1–2):137–43.

58. Martinez-Fernandez R, Schmitt E, Martinez-Martin P, Krack P. The hidden sister of motor fluctuations in Parkinson's disease: a review on nonmotor fluctuations. Mov Disord. 2016;31(8):1080–94.

59. Acorda Therapeutics, Inc. Inbrija® (levodopa inhalation powder, for oral inhalation use). Full prescribing information. Pearl River: Acorda Therapeutics, Inc.; 2022.

60. Sunovion Pharmaceuticals. Kynmobi™ (apomorphine hydrochloride sublingual film) Full prescribing information. Marlborough: Sunovion Pharmaceuticals, Inc.; 2022.

61. Schwab RS, Amador LV, Lettvin JY. Apomorphine in Parkinson's disease. Trans Am Neurol Assoc. 1951;56:251–3.

62. Pfeiffer RF, Gutmann L, Hull KL Jr, Bottini PB, Sherry JH, APO302 Investigators. Continued efficacy and safety of subcutaneous apomorphine in patients with advanced Parkinson's disease. Parkinsonism Relat Disord. 2007;13(2):93–100.

63. 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.

64. Sublingual apomorphine (Kynmobi) for Parkinson's disease. Med Lett Drugs Ther. 2020;62(1609):165–6.

65. Hauser RA, LeWitt PA, Waters CH, Grosset DG, Blank B. The clinical development of levodopa inhalation powder. Clin Neuropharmacol. 2023;46(2):66–78.

66. Lipp MM, Hickey AJ, Langer R, LeWitt PA. A technology evaluation of CVT-301 (Inbrija): an inhalable therapy for treatment of Parkinson's disease. Expert Opin Drug Deliv. 2021;18(11):1559–69.

67. 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;64:175–80.

68. Thach A, Sutphin J, Coulter J, Leach C, Pappert E, Mansfield C. Patient preferences for treating "OFF" episodes in Parkinson's disease: a discrete choice experiment. Patient Prefer Adherence. 2021;15: 1187–96.

69. Hauser RA, Hsu A, Kell S, et al. Extended-release carbidopa-levodopa (IPX066) compared with immediate-release carbidopa-levodopa in patients with Parkinson's disease and motor fluctuations: a phase 3 randomised, double-blind trial. Lancet Neurol. 2013;12(4):346–56.

70. Olanow CW, Kieburtz K, Odin P, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. Lancet Neurol. 2014;13(2):141–9.

71. Rinne UK, Larsen JP, Siden A, Worm-Petersen J. Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. Nomecomt Study Group. Neurology. 1998;51(5): 1309–14.

72. Lees AJ, Ferreira J, Rascol O, et al. Opicapone as adjunct to levodopa therapy in patients with Parkinson disease and motor fluctuations: a randomized clinical trial. JAMA Neurol. 2017;74(2): 197–206.

73. Adler CH, Singer C, O'Brien C, et al. Randomized, placebo-controlled study of tolcapone in patients with fluctuating Parkinson disease treated with levodopa-carbidopa. Tolcapone Fluctuator Study Group III. Arch Neurol. 1998;55(8):1089–95.

74. Parkinson Study Group. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. Arch Neurol. 2005;62(2): 241–8.

75. Waters CH, Sethi KD, Hauser RA, Molho E, Bertoni JM, Zydis Selegiline Study Group. Zydis selegiline reduces off time in Parkinson's disease patients with motor fluctuations: a 3-month, randomized, placebo-controlled study. Mov Disord. 2004;19(4): 426–32.

76. Schapira AH, Fox SH, Hauser RA, et al. Assessment of safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson disease and motor fluctuations: a randomized clinical trial. JAMA Neurol. 2017;74(2):216–24.

77. Schapira AH, Barone P, Hauser RA, et al. Extended-release pramipexole in advanced Parkinson disease: a randomized controlled trial. Neurology. 2011;77(8):767–74.

78. Pahwa R, Stacy MA, Factor SA, et al. Ropinirole 24-hour prolonged release: randomized, controlled study in advanced Parkinson disease. Neurology. 2007;68(14):1108–15.

79. LeWitt PA, Lyons KE, Pahwa R, SP 650 Study Group. Advanced Parkinson disease treated with rotigotine transdermal system: PREFER Study. Neurology. 2007;68(16):1262–7.

80. Oertel W, Eggert K, Pahwa R, et al. Randomized, placebo-controlled trial of ADS-5102 (amantadine) extended-release capsules for levodopa-induced dyskinesia in Parkinson's disease (EASE LID 3). Mov Disord. 2017;32(12):1701–9.

81. LeWitt PA, Guttman M, Tetrud JW, et al. Adenosine A_{2A} receptor antagonist istradefylline (KW-6002) reduces "off" time in Parkinson's disease: a double-blind, randomized, multicenter clinical trial (6002-US-005). Ann Neurol. 2008;63(3):295–302.

82. Stacy M, Bowron A, Guttman M, et al. Identification of motor and nonmotor wearing-off in Parkinson's disease: comparison of a patient questionnaire versus a clinician assessment. Mov Disord. 2005;20(6):726–33.

83. Stocchi F. The levodopa wearing-off phenomenon in Parkinson's disease: pharmacokinetic considerations. Expert Opin Pharmacother. 2006;7(10):1399–407.

84. Antonini A, Moro E, Godeiro C, Reichmann H. Medical and surgical management of advanced Parkinson's disease. Mov Disord. 2018;33(6):900–8.

85. Connolly B, Fox SH. Treatment of cognitive, psychiatric, and affective disorders associated with Parkinson's disease. Neurotherapeutics. 2014;11(1):78–91.

86. Dietrichs E, Odin P. Algorithms for the treatment of motor problems in Parkinson's disease. Acta Neurol Scand. 2017;136(5):378–85.

87. Safirstein BE, Ellenbogen A, Zhao P, Henney 3rd HR, Kegler-Ebo DM, Oh C. Pharmacokinetics of inhaled levodopa administered with oral carbidopa in the fed state in patients with Parkinson's disease. Clin Ther. 2020;42(6):1034–46.