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Review

Drugs to the Rescue: Comparison of On-Demand Therapies for OFF Symptoms in Parkinson's Disease

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Abstract. Patients with Parkinson's disease often suffer from OFF symptoms disrupting their daily routines and adding to disabilities. Despite polypharmacy and adjustments to medication schedules, they often do not experience consistent relief from their motor symptoms. As the disease progresses, impaired gastric emptying may evolve, making it even more challenging for dopaminergic drugs to provide consistent results. This review focuses on a group of drugs that have the pharmacokinetic advantage of a much earlier onset of action by virtue of their non-oral routes of absorption. We compare the current marketed options: subcutaneous apomorphine, sublingual apomorphine, and inhaled levodopa. Subcutaneous apomorphine is the speediest to take effect, whereas sublingual apomorphine offers the longest clinical effect. Inhaled levodopa has the most favorable side effect profile among the three options. An inhaled form of apomorphine is currently under development, having passed safety and efficacy studies. Each of these drugs has unique characteristics for the user, including different side effect profiles and onset of action. The best choice for a patient will depend on individual needs and circumstances. In this review, we explore those nuances to allow clinicians to select the best option for their patients.

Keywords: Parkinson's disease, dopaminergic drugs, apomorphine, levodopa

INTRODUCTION

For more than a half century, carbidopa-levodopa (CD-LD) has been the most effective symptomatic treatment option for Parkinson's disease (PD) [1]. Despite its effectiveness at its peak action, many patients evolve a clinical response to this drug that is irregular and typically has shorter dose-by-dose responses than what is experienced when the drug is first administered. This clinical phenomenology has been described as the transition from the "long-duration" to the "short-duration" response pattern [2]. Eventually, the majority of LD-treated patients experience dose-by-dose fluctuations roughly linked to the peripheral pharmacokinetics of LD [3–5]. Both regular and irregular occurrence of wearing off between LD doses is often perceived by patients as frustrating, disabling, and burdensome alteration in quality of life even though, at its best, levodopa continues to be effective [3–5]. "Off" states in the LD–responsive patient are often perceived as more disabling than the same patient's experience of dyskinesias [6].

Motor fluctuations are often envisioned as a phenomenon developing only in later stages of PD. However, there is considerable evidence that motor fluctuations occur in earlier years. For example, the

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Early DEtection of wEaring off in Parkinson disease (DEEP) study found that, while 80.4% of PD patients become fluctuators after 10 years, 41.8% experience some degree of motor fluctuations within 2.5 years after the start of LD [7].

There are several factors contributing to variability in LD pharmacokinetics for the PD patient. After a patient ingests a dose of CD-LD, there are multiple barriers to LD before arriving at its brain target in the striatum. Unlike most orally administered drugs, the efficient uptake of LD can be hampered by factors such as delayed gastric emptying (a feature of the systemic autonomic dysfunction that develops eventually for 70–100% of patients with PD [8]). Other factors that can interfere with efficient drug uptake include small intestine bacterial overgrowth [9], competition for LD absorption by dietary L-neutral amino acids (from digested protein) and fatty acids in the small intestine [10], and first-pass hepatic metabolism of LD and distribution elsewhere [11]. Additionally, there is a poorly understood phenomenon of "no-on" in which patients fail to achieve clinical benefit despite timely intake of their usual CD-LD dose [12]. Studies with continuous intrajejunal infusion of levodopa also demonstrate that a patient achieving constant plasma concentrations of the drug can still experience "off" time [13].

Given the capricious response pattern that LD often provides, there have been multiple approaches envisioned to increase the regularity of adequate LD arriving at the striatum. The peripheral conversion of LD into dopamine is mostly inhibited by CD and benserazide (which are roughly equipotent L-aromatic amino acid decarboxylase (L-AAAD) inhibitors that are unable to cross the blood-brain barrier). L-AAAD inhibitors achieve this goal with conventional dosing of, typically, 25 mg combined with each LD dose. However, neither of the L-AAADs accomplishes full inhibition of the enzyme at intake of 25 mg t.i.d. [14]. Two additional classes of drugs are used to prolong the clinical effects of LD dosing through enzyme inhibition. These are the monoamine oxidase B (MAO-B) inhibitors (selegiline, rasagiline, and safinamide) and the catechol-O-methyltransferase (COMT) inhibitors entacapone, tolcapone, and opicapone [15]. Avoiding metabolic diversion of LD to 3-O-methyldopa increases the net bioavailability of an administered LD dose. Attempts to circumvent the gastrointestinal (GI) dysfunction in PD have been made with the transdermal dopaminergic agonist rotigotine [16], though the orally administered dopaminergic agonists are long acting and, unlike LD, are not subject to delayed or irregular uptake. Another route of non-enteral drug administration for PD is the use of subcutaneous apomorphine infusion [17]. Improving enteral uptake of CD and LD has been achieved with these drugs placed in a micro-suspension and delivered continuously through a per-gastric jejunal tube connected to an external pump that [18]. Patients often try various measures to improve LD uptake, such as drinking a warmed or carbonated beverage with the pills, sometimes pulverized. There is no evidence for effectiveness, as is the case for the use of an orally disintegrating LD tablet.

Another challenge for the treatment of motor fluctuations is the need for a patient and caregiver to properly recognize them. For example, a multicenter survey showed that, while 80% of PD patients confirmed that they understood the term "wearing-off", only 30% gave an accurate explanation of what actually happens. In the same study, their caregivers did not fare any better; 74% of them claimed they knew the meaning of this term but only 17% correctly described the "wearing off" phenomenon [19]. Furthermore, neurologists evaluating a group of patients detected wearing-off in 56.9% of instances while patients completing a wearing-off questionnaire identified it 67.3% of the time. This disparity highlights the shortcomings of recognition of "off" time and wearing-off, particularly in patients experiencing PD for only a few years [7].

An important insight into the problem of motor fluctuations was a report that highlighted delayed onset of medication effect [20]. In a careful analysis of medication effect in PD patients studied for the timing of motor fluctuation experiences, the authors found that total daily time waiting for the orally administered LD to initiate its clinical effect amounted to twice as much as the time in the post-dose wearing off phase. In other words, for patients chronically receiving LD and experiencing motor fluctuations, the delayed onset of medication effect contributed substantially more to the total experience of undermedicated states (and even with an optimized oral dosing schedule). This observation is important in considerations of contemporary therapeutics for motor fluctuations since drugs commonly used for motor fluctuations slow LD absorption or delay its metabolism but do not speed up medication onset. As a result, there have been considerable impetus for options to solve the need for rapid and reliable symptom-relieving therapy that could be used by the patient on demand. Because of GI changes

mentioned above, the ideal pharmaceutical strategy should employ an absorption route different from the enteral one. The ideal on demand therapy would involve achieving peak medication plasma concentration more quickly and more reliably than typically achieved with oral LD, and with sufficient duration to carry over into the period when the scheduled oral medication intake of LD has reached an effective plasma concentration.

For on demand treatment, three drug formulations have been developed. Development of each culminated in randomized, placebo-controlled clinical trials for PD patients experiencing motor fluctuations. Two of the products involve a dopaminergic agonist, apomorphine; the third is a LD micropowder created for pulmonary inhalation. The latter product is marketed in the U.S. as Inbrija™ and recently approved for marketing in Germany. For several decades, apomorphine for intermittent subcutaneous injections has been available worldwide. In the U.S. this product received regulatory approval in 2004 as Apokyn™ (although apomorphine was previously listed on the US Pharmacopeia formulary for subcutaneous administration). Recently, a generic formulation of another apomorphine solution for injection was approved for the US market. The third FDA approval for an on-demand PD treatment is for sublingual (transbuccal) apomorphine, Kynmobi™, administered from drug-impregnated dissolvable strips. In this report, we review pharmacological and clinical properties for each of these on-demand treatment options to highlight similarities and differences. Our goal is to contrast what is known about the three therapies so that clinicians can undertake an evidence-based choice of the most appropriate drug for patients.

SUBCUTANEOUS APOMORPHINE

Apomorphine was the first drug to be used for rapid control of wearing off in PD. Although developed in the mid-19th century, its first use in PD was 7 decades ago [21]. The latter study was conducted in an era preceding knowledge about dopamine deficiency in PD and the pharmacological actions of apomorphine mimicking those of dopamine [22]. For achieving anti-Parkinsonian effect, apomorphine needs to be injected into subcutaneous tissue, which leads to a speedy absorption. Its absorption kinetics are partly dependent on the site chosen for injection. For example, subcutaneous placement within the abdominal wall leads to a better absorption as compared to injections into the thigh [23, 24].

Apomorphine exerts most of its anti-Parkinsonian effect by potent activation of postsynaptic dopamine D2-type receptors. *In vitro* it exhibits high binding affinity for the dopamine D4 receptor and moderate affinity for dopamine D1, D3 and D5 receptors. Its anti-Parkinsonian properties are derived primarily from acting on the D1-family of receptors (D1 and D5 along with the D2 (D2 and D3) family of receptors. Apomorphine differentiates itself from other dopaminergic agonists by moderate affinity for several non-dopaminergic receptors, including adrenergic 1_D, 2_B, and 2_C receptors, and serotonergic 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors [25, 26]. Approximately 3% of the drug penetrates from the plasma compartment into the cerebrospinal fluid (CSF) [27]. Comparing drug concentrations in plasma and CSF, there is an approximately 10-minute delay in the peak CSF concentration as compared to plasma [26]. A crossover-design study of apomorphine treatment on 10 patients with PD demonstrated that subcutaneous apomorphine's clinical effect lasts around one hour [28] (see Table 1).

Subcutaneous apomorphine has a shorter onset of action when compared to the clinical actions of orally administered immediate-release levodopa, beginning as early as 8 to 15 minutes [17, 29]. A 3-month trial of subcutaneous administration found its clinical actions to remain uniform in enacting its improvement of "off" states. Measurements made using the motor portion of the Unified Parkinson Disease Rating Scale (UPDRS) part III found improvements from Baseline of 59% at 20 minutes after subcutaneous injection. Patient-reported improvement in mobility was recognized as early as 7.5 minutes after subcutaneous injections [30].

A long-term use study by Pfeiffer and colleagues [30] investigated the effects of extra doses of subcutaneous apomorphine added to a previously determined optimal dose. This study showed that the incremental effect of an additional 2 mg beyond a previously-determined optimal dose did not lead to any further improvement in anti-Parkinsonian effect, suggesting an all-or-none threshold for apomorphine's actions (much as has been demonstrated for LD [31]). These results also argue against the concern that tachyphylaxis might occur with repeated long-term use of apomorphine. Up to 7% of subcutaneous doses previously determined to be optimal eventually fail to promote an "on" state by one hour after injection (dose failure) [32].

Table 1
Comparison of on-demand therapies for motor symptoms

	Time to "on" state	Time to peak plasma concentration	Duration of effect	Adverse effects	Other comments	Stage of development
FDA approved drugs						
Subcutaneous apomorphine injection	8–15 min	10–20 min	62 ± 13 min	Nausea (26.8%), dizziness (16.5%), yawning (10.2%), somnolence (7.9%), hypotension (7.9%), and syncope (< 1%)	Dose failure rate of 7%. An antiemetic has often used concomitantly. Contraindicated in coronary artery disease or cerebrovascular disease due to concern for vasospasm	Approved by the FDA in 2004
Sublingual apomorphine (APL 130277)	10–20 min	30 min	> 90 min	Nausea (28%), somnolence (13%), dizziness (9%), fatigue (7%), oral mucosal erythema (7%), rhinorrhea (7%), dry mouth (6%), fall (6%), headache (6%), hyperhidrosis (6%)	An antiemetic (trimethobenzamide) was initially recommended for concomitant use, though no longer available	Approved by the FDA in 2020
Inhaled levodopa (CVT-301)	30 min*	10 min	> 60 min in 58% of patients	Cough (15%), nausea (5%), dyskinesia (4%), upper abdominal pain (4.3%), hypotension (< 1%), atrial fibrillation (< 1%)	Not used in patients with pulmonary disease	Approved by the FDA in 2018
Investigational products						
AZ-009	10 min	2 min	Between 20–50 min	Cough (71%), throat irritation (71%), fatigue (57%), headache (28%), yawning (28), dizziness (14%)	Novel inhaler device	Phase 1 clinical trial completed in November 2020

*When given as a morning dose while patients have been off oral CD-LD.

Clinical practice regarding use of apomorphine hydrochloride as an on-demand treatment has been extensively reviewed in the international medical literature since its first reported experience more than 25 years ago [33]. Most of the reports dealing with on-demand treatment have found a dose range between 2–5 mg to provide well-tolerated "on" effects in a reliable manner [34–36]. Determining an optimal dose generally needs a gradual titration process for determining a clinically useful result without adverse effects. A titration process is generally utilized in starting apomorphine, beginning with 2 mg. In the U.S., the titration regimen involved increasing dose up to 6 mg, sequentially in 1 mg test increments [37]. The adverse effect of nausea is a common dose-related experience with apomorphine (and it can occur even with the lowest dose tested). In countries having access to the peripherally active dopamine receptor blocker domperidone, this drug is generally co-administered at the start of apomorphine therapy. Domperidone is not recommended for chronic use, however. In the U.S., where domperidone is not available, there is no effective substitute of drugs with dopamine receptor blocking only in the periphery and at the area postrema of the brain. Until recently, trimethobenzamide was recommended as an antiemetic for use during the titration process [29, 38]. However, subsequent analysis of trimethobenzamide effectiveness against nausea and its need for use in apomorphine titration was thrown into contention with the publication of a randomized clinical trial that established its lack of efficacy and ease of starting apomorphine therapy without an antiemetic [39]. Many patients have started on-demand apomorphine injections without experiencing any of its potential side-effects (nausea, vomiting, or hypotension). Clinical experience suggests that concomitant chronic use of an oral dopaminergic agonist provides cross tolerance against nausea and vomiting (PAL, personal observation). Table 1 lists the adverse effect profile of intermittent apomorphine treatment.

SUBLINGUAL APOMORPHINE

The marked clinical efficacy of on-demand subcutaneous apomorphine injection was the inspiration for the other approaches reviewed above for reversal of "off" states. The reliable and rapid onset of drug effect is also the goal of several pharmaceutical firms that are working to develop apomorphine formulations that can be administered by the upper nasal passages, either with using the drug in powder form or as a liquid spray. Another formulation has progressed to marketing in the U.S. and Canada and consists of rapidly dissolving film strips containing various amounts of apomorphine hydrochloride (10, 15, 20, 25, or 30 mg). This product was developed with buffering to minimize localized mucosal irritation that apomorphine can cause. Sublingual apomorphine is applied under the tongue for transmucosal absorption. This route of administration requires that patients should not swallow for 2-3 minutes to maximize absorption. Apomorphine is not effectively absorbed in the GI tract and would undergo rapid first-pass metabolism through sulfonation [40]. With sublingual apomorphine, a process of dose titration is recommended. In the marketed product patients begin with a 10 mg sublingual dose strip and, over several hours, then sequentially ramp up dose in 5 mg increments (to a maximum of 30 mg) until a full "on" response is achieved. In the clinical trials of this product, a maximum dose of 35 mg was used. In this study, which used a product designated as CTH-300, the reference for a full "on" state was compared to optimal effects of LD [40, 41]. Clinical trial experience with sublingual apomorphine showed it often causes nausea as a side effect, and the current unavailability of trimethobenzamide in the U.S. (plus its relative inefficacy against nausea and vomiting induced by dopaminergic drugs) has been a limiting factor in the use of this product. In Canada, domperidone is available for use with sublingual apomorphine.

The clinical efficacy of sublingual apomorphine was demonstrated in clinical trials with CTH-300 [40, 41]. The pivotal study was a randomized, double-blind, placebo-controlled, Phase III trial. Its titration period and maintenance phase lasted 12 weeks [41]. For this study, the primary endpoint was a change from pre-dose to 30 minutes post-dose in the revised version of the UPDRS (MDS-UPDRS) part 3 score at week 12. The results indicated that the motor response at 30 minutes post-dose was superior to the placebo; this held true at the 12-week mark. A clinical response could be seen as early as 15 minutes post-dose and was sustained at 90 minutes post-dose. Of note, only about one-third of patients treated with sublingual apomorphine had, at 30 minutes post-dose, a full "on" response when tested at the 12-week study visit. This observation is at odds with earlier response findings in the study at the time of randomization. Only patients who achieved a full "on" response from sublingual apomorphine during the initial study titration phase went on to randomization for continuation in the maintenance phase. The study had dropouts due to side effects both in the titration phase (9%) and during the maintenance phase (28%). The most common cause for patients choosing to leave the study were oropharyngeal irritation (see Table 1 for a listing of reported adverse reactions) [41].

In a comparison of the pivotal trials for inhaled LD and sublingual apomorphine Thach et al. [42] compared placebo-adjusted treatments at week 12 from the SPAN-PD trial [43] and the CTH-300 trials [41]. There was no significant difference in the UPDRS part III score at the 15–20 minutes or the 30 minutes time points. There was a significant difference at the 60 minutes mark with sublingual apomorphine having a lower UPDRS part III score by a mean of 8.8 points. This is a moderate clinically significant difference based on the estimates by Shulman et al. [44]. Since the CTH-300 trial used the MDS-UPDRS scale the authors did a previously validated adjustment in the scores by subtracting 7 points from the scores. This method has been previously validated [45] and the adjusted value is expected to be within 3 points of the UPDRS part III score 50% of the time and within 9 points 95% of the time. In this comparison, the daily reduction in "off" time was greater in the sublingual apomorphine group by 1.3 hours in comparison to inhaled LD. It is difficult to compare these results since this was calculated from patient diaries in the SPAN-PD trial but was not reported in the CTH-300 trial, and the total daily "off" time was estimated from in-clinic data and outpatient diaries [42].

INHALED LEVODOPA POWDER

This formulation is a micropowder developed specifically for pulmonary absorption of LD, with pharmaceutical characteristics similar to other inhaler-delivered drugs [46, 47]. Inhaled LD powder was designed to reach the bloodstream rapidly and in concentrations capable of providing a clinically sig-

nificant effect for PD patients [48, 49]. The inhaler system consists of peel-to-open pouches containing capsules; for the intended dose of 84 mg of LD, patients insert 2 capsules sequentially into the self-actuated inhaler device. Human factors testing found that > 90% of PD patients in the "off" state was able to prepare the device for effective self-administration of the drug [50]. Preclinical studies investigating pulmonary uptake of LD revealed dose-related rise in plasma concentrations rapidly after inhalation [50, 51]. This occurred in the absence of administered CD, although the therapeutic goal of this product is for administration after a patient has already ingested the first daily dose of oral CD-LD.

As mentioned earlier, the challenge for improving LD efficacy can be characterized by both delay in the onset of oral LD effect and the re-emergence of Parkinsonian symptoms within 2-3 hours even with efforts to extend the drugs effect with adjunctive medications. Most studies of plasma LD pharmacokinetics and correlations to pharmacodynamics reveal a delay of at least 15–20 minutes before oral intake translates into anti-Parkinsonian effect [1]. Given these circumstances, patients depending on oral medication to rescue themselves from an "off" state or the anticipated occurrence of "off" in the near future may wish to elevate their circulating LD concentration to maintain an "on" state. The pulmonary route of administration offers the potential for raising plasma LD to therapeutic concentrations by bypassing the impediments intrinsic to the GI route of administration.

In the pharmacokinetic studies of the commercial product of inhaled LD powder (used in the completely "off" state), the peak plasma concentration after an 84 mg dose of inhaled LD rose, on average, to about 0.6 μg/ml [52]. This plasma concentration needs to be contrasted with the threshold serum concentration that usually achieves the "on" state, which has been reported to be about 1.0 μg/ml [31]. The gap between the inhaled LD concentration peak from inhaled LD powder and the drug's typical "on" threshold points is a practical "pearl" for how this form of on-demand therapy should be used. Patients should realize that inhaled LD needs to be self-administered as soon as possible after recognition that wearing off is starting to occur. At that point, the plasma LD concentration from the prior oral LD dose has typically dropped to a level for which the adjunctive inhaled LD dose will add enough of a rise to enhance the total concentration to a supra-threshold concentration exerting clinical benefit. Another practical implication of inhaled LD is the situation of on-demand treatment for a patient upon awakening from sleep and before the first oral doses of LD are ingested. An approximately 0.6 μg/ml plasma concentration of levodopa is unlikely to achieve an "on" state. This is borne out in a clinical investigation reporting marked delay or failed "on" state when inhaled LD was tested as the first levodopa intake of the day [32]. In a pharmacokinetics study [53], the inhalation route was compared to oral administration, with tablets taken with a high-fat and protein containing meal. The investigators found that the inhaled route of LD administration led to increased serum concentration as soon as 5 minutes post-dose and peak concentration was at 10 minutes after intake.

The pivotal study for inhaled LD powder (the SPAN-PD trial) was a randomized, double blind, placebo-controlled, multicenter, phase III trial. Enrolled in this study were PD patients who experienced motor fluctuations and at least 2 hours of daily "off" time. The first part of the study was the double-blind period that randomized patients into one of three treatment groups of inhaled placebo or LD powder at two doses: 60 mg and 84 mg. At the 12-week assessment, 58% of the patients randomized to the inhaled LD groups had a sustained "on" response lasting at least 60 minutes (the last assessment). In this study, cardiovascular adverse effects included one case of hypotension and one case of atrial fibrillation attributed to the drug [53]. The safety of pulmonary administration of LD powder was monitored from baseline to 12 weeks with spirometry and carbon monoxide diffusing capacity assessments [43]. Neither of these pulmonary assessments indicated any change from the use of the inhaled LD formulation.

INVESTIGATIONAL INHALED FORMULATION OF APOMORPHINE

An inhalational form of apomorphine is an experimental product currently under development (AZ-009; Alexza Pharmaceuticals, Inc.). A published report [54] described a randomized clinical trial comparing inhaled AZ-009 to subcutaneously injected apomorphine in healthy volunteers. The drug is delivered through the Staccato inhalation system (also developed by Alexza Pharmaceuticals) and subjects were instructed to inhale through the mouthpiece with a steady deep breath and hold their breath for as long as possible up to 10 seconds. The drug was given in

1 mg and 2 mg presentations and was administered in doses of 3 mg administered as three oral inhalations of 1 mg, or a dose of 4 mg as two oral inhalations of 2 mg.

Another phase of the same study explored its efficacy in PD patients. Peak plasma concentration of AZ-009 was achieved at 2 minutes in comparison to subcutaneous apomorphine, which was delayed to 30 minutes, although previously published studies have shown a much more rapid peak level concentration for the subcutaneous route [55] (see Table 1) and an earlier clinical onset of action. The efficacy arm of the study tested three doses of the drug (2 mg, 3 mg, and 4 mg). At each of these doses, there was similar reduction in the MDS-UPDRS part 3 with an observed decline in the effect at the 30-minute post-dose time point [54]. A randomized controlled double-blind clinical trial has established the safety of administering apomorphine via the nasal inhalation route. The most common side effect was dose-dependent cough and throat irritation (see Table 1). The component of the study that addressed this drug's use as an on-demand therapy for "off" symptoms included 8 patients, participating in a crossover design. The results of this trial found that the "on" state was achieved at 10 minutes post-dose in half of the patients tested [54].

DISCUSSION

When the pattern of clinical response for oral LD dosing has entered into its "short duration" (dose-by-dose) phase, PD patients who have lost the regularity and reliability of medication control are often inconvenienced by the capricious effects of their usual therapeutic regimen. To overcome this continuing problem, the three treatment options we reviewed offer a means for relatively rapid recovery from "off" states. This previously unmet need for improved therapeutics adds to the other pharmacological strategies available for extending LD effect or adding to longer-acting dopaminergic stimulation (such as dopaminergic agonists or use of the adenosine A2a receptor antagonist istradefylline). The 3 marketed products and the intranasal apomorphine treatment under development differ in their efficacy and adverse effect profiles, and accordingly, the prescription choice may rest on several decision factors. In the following section, we review and compare the salient information of these products based on published data from their development pathways. There has been only limited post-marketing surveillance to report in this review for inhaled LD or sublingual apomorphine, and those interested in other pertinent information that might be of interest to patients (such as their cost per dose or coverage by U.S.-based health insurance) will need to search elsewhere. One factor that might influence the choice of treatment for some patients is the requirement of subcutaneous apomorphine to be self-injected by needle. "Needlephobia" is probably a major factor in decisions by patients to seek out other options. Apomorphine also might prompt concern (based solely on its name and not its pharmacological properties) that this medication is a narcotic or might be habit-forming. Ultimately, the decision to adopt the use of an on-demand therapy might have to do with a patient's personalized view of the experience in living with motor fluctuations. Some patients or physicians may think that these drugs are more appropriate for more advanced PD, when in fact patients could benefit from their use earlier [56]. Physicians can also benefit from knowing key differences among the products so their advocacy can be evidence-based.

Table 1 compares the pertinent properties of these drugs as studied in clinical trials and pharmacokinetic investigations. In particular, the timing of medication effects is highlighted. It is pertinent to consider that a typical oral LD dose, if not delayed by food in the stomach, reaches its therapeutic plasma concentration threshold (approximately 1 μg/ml) within 30 minutes. As pointed out in Fig. 1, comparisons between the three products need to consider the different study designs and methodologies used for assessment and reporting of study data. For example, the SPAN-PD study of inhaled LD powder assessed patients for its primary outcome using the UPDRS Motor Examination (Part 3) [43] whereas the CTH-300 study of apomorphine sublingual strips used the Motor Examination (Part 3) portion of the MDS-UPDRS for its determination of primary endpoint [41]. Another important distinction between these studies is that the first evaluation of motor symptoms after the on-demand drug administration was at 10 minutes in the inhaled LD powder study and at 15 minutes post-dosing for the sublingual apomorphine strips study. For subcutaneously injected apomorphine, the first time point was at 10 minutes [30]. These features of study methodology influence comparisons between the three products as to how quickly they act on Parkinsonism. The different initial post-treatment timepoints in the studies reviewed indicate the challenge in understanding which of the

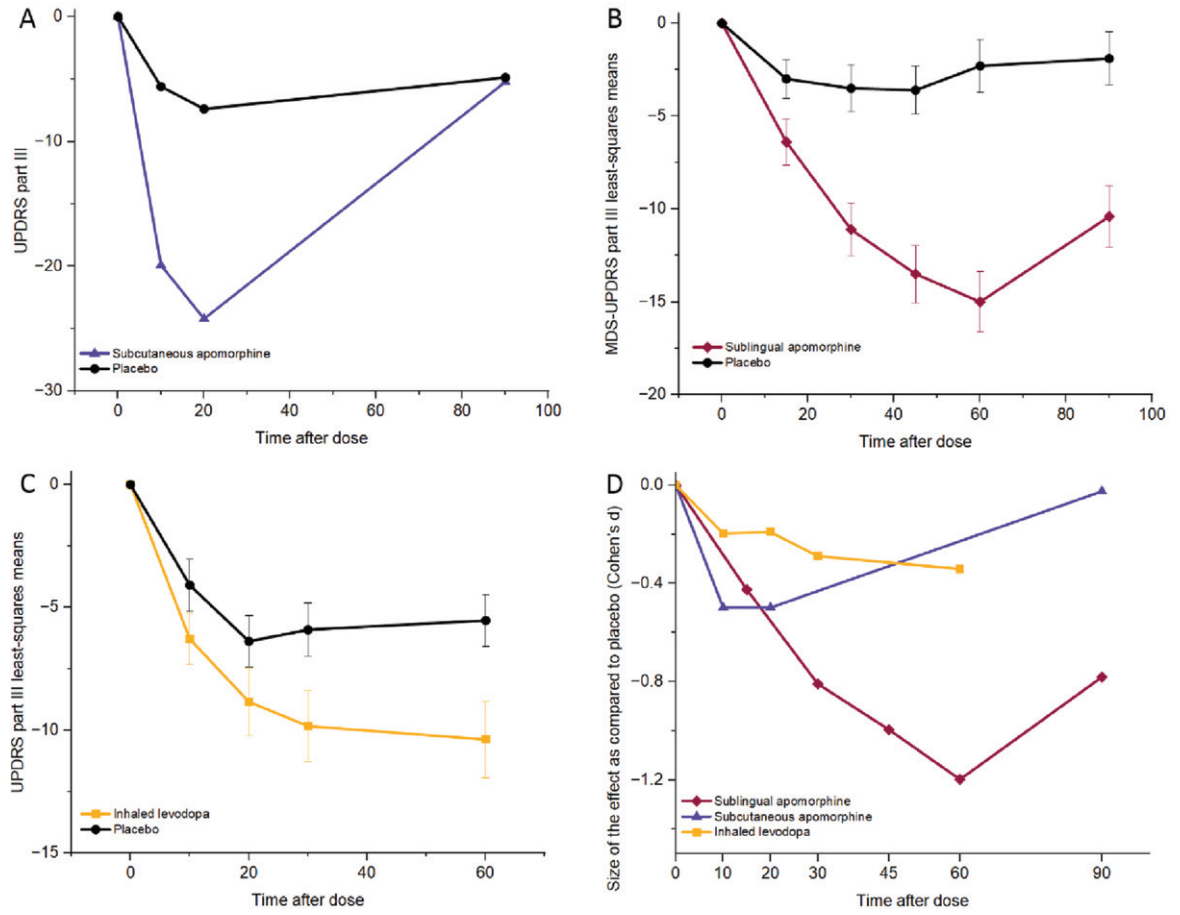

Fig. 1. Effect of on-demand therapies in motor symptoms. A) subcutaneous apomorphine, B) sublingual apomorphine strips, C) inhaled LD powder. D) A comparison of the effect size (Cohen's d) as compared to the placebo group in each of the studies. Note that there are differences in the design of each of these clinical trials that should be taken into account while comparing them (see Table 2). Data adapted from [30, 41, 43].

Table 2
Comparison of major clinical trials for on-demand therapies

Subcutaneous apomorphine [30]	Sublingual apomorphine [41]	Inhaled levodopa [43]
• $n = 62$ (35 in the treatment arm, 27 in the placebo arm)	• $n = 109$ (54 in the treatment arm and 55 in the placebo arm)	• $n = 351$ (235 in the treatment arm, 116 in the placebo arm)
• The drug was administered after the onset of the first daily OFF episode after intake of their usual anti-Parkinsonian medication in the morning.	• The drug was administered in the morning after withholding at least 12 h of all anti-Parkinsonian medications.	• The drug was self-administered after intake of their usual antiparkinsonian medication, at the onset of an OFF episode up to five times per day.
• Patients reported onset of effect as early as 7.5 min and lasted for at least 40 min.	• One-third of the treatment arm discontinued the drug mostly due to oral irritation.	• Eight patients in the treatment group dropped out due to side effects
• Two patients dropped out of the placebo group for lack of benefit.	• Excluded patients treated with DBS and patients with oral pathology	
• Preceded by a 12-week study that proved tolerability of at least two doses daily.		
• Excluded patients with dementia		

Table 3
Clinical comparison of the currently FDA-approved on-demand drugs for motor symptoms in PD

	Pros	Cons	Ideal for . . .
Subcutaneous apomorphine	• The one with the longest clinical experience • Shortest time to clinical improvement	• Needles are involved • Patients may need to self-inject, which requires some degree of motor dexterity • Can cause hypotension and syncope • Not recommended for patients with significant vascular disease	• Patients who need a quick time-to-on • Use as the first dose of the day in patients that have a long time-to-on with the oral medication
Sublingual apomorphine	• Easiest to use • Largest magnitude of motor improvement in clinical trials	• Oral irritation can occur • Not recommended for patients with significant vascular disease • Less consistent and slower than the subcutaneous administration route	• Patients who need the simplest administration route
Inhaled levodopa	• Builds on the levodopa already administered orally	• Not recommended for patients with pulmonary disease	• Uses when patients who take oral levodopa and just begin to wear off

three products has the fastest onset. Similarly, the lack of study data collection after 60 minutes for inhaled LD trial means that its duration of action cannot be compared to the two apomorphine studies, whose data was collected out to 90 minutes post-dosing.

Another difference in comparisons of the on-demand therapies pertains to the study methodologies for their primary endpoints. Both apomorphine studies investigated patients when they were determined to be in a fully "off" state. In contrast, the SPAN-PD study with inhaled LD took another approach. Patients were instructed to administer the drug as soon as they recognized the first inklings of transition from "on" to "off" states. Hence, the magnitude of motor improvement would be expected to be less than if they had been allowed to decline to a more severe "off" state, as was the plan for the studies of the apomorphine formulations. Comparing the two delivery methods for apomorphine, Fig. 1 indicates that the subcutaneous route was much faster than sublingual administration, although the sublingual route has a more reliable clinical response in terms of achieving the on state [57]. The three on-demand formulations can also be compared as to tolerability. Despite its propensity to cause coughing (leading to a few study dropouts on this basis), inhaled LD had fewer dopaminergic side effects than the apomorphine-based treatments. Site injection of apomorphine can produce skin nodules and bruising as a drawback to chronic use. Mouth irritation with sublingual apomorphine was a common side-effect and may have been a major factor for the relatively higher dropout rate for the clinical trial than the other on-demand therapies.

The three on-demand therapies are each expensive treatment options. In the U.S., the price of these branded products greatly exceeds the cost of LD and the other marketed PD drugs. Since U.S. patients sometimes have to contribute to purchases of prescription medications, the cost-effectiveness and perceived value of on-demand therapies can be an important consideration as to a trial or continued use. This matter has been investigated in one study that was carried out to compare the three on-demand treatments [58]. It should be noted that this study was conducted by the sponsor of Kynmobi™ (Sunovion Pharmaceuticals) and several authors were Sunovion employees. The latter study used calculations of accumulated price of on-demand therapy for each of on-demand therapies over a 10-year period and in different clinical scenarios. Its conclusions were that the least expensive of the on-demand drugs was sublingual apomorphine. This report also found that this product had the highest utility with a small increase in quality-adjusted life-years (QALYs) by 0.019 compared with subcutaneous apomorphine, and 0.235 compared to inhaled LD [58]. These conclusions require further validation. At present, the best treatment option for every patient remains to be determined based not only on cost but also factors of efficacy and tolerability. The information provided in Tables 1 and 3, and Fig. 1 summarize information that may help in making prescription choices.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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