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Management of OFF condition in Parkinson disease

Jessa Koch, PharmD, BCPP, APh[1]

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Abstract

Parkinson disease (PD) impacts nearly 1 million individuals in the United States. Nearly every patient with PD will require therapy with dopamine in the form of levodopa as the disease progresses. In more advanced stages of the disease, patients will experience motor fluctuations and require adjustment to their medication regimens to maintain good control of their symptoms. During the last 10 years, several new therapeutic treatment options have come to the market to treat motor fluctuations and improve patient quality of life. Some of these agents represent additional options to previously available drug classes, such as the catechol-*O*-methyl transferase (COMT) inhibitor, opicapone, and monoamine-oxidase B-inhibitor (MAO-B inhibitor), safinamide, as well as new dosage forms for available therapeutics. One new agent, istradefylline, has a novel mechanism in the treatment of PD. The place in therapy for these newer therapeutic options will be explored through a series of patient cases. This article focuses on evidence-based recommendations for the use of these newer options in the management of patients experiencing OFF episodes.

Keywords: motor fluctuation, Parkinson disease, end-of-dose wearing OFF, levodopa, on-demand therapy

[1](Corresponding author) Associate Professor, Loma Linda University School of Pharmacy, Loma Linda, California, jkoch@llu.edu, ORCID: https://orcid.org/0000-0003-0376-4228

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Introduction

Parkinson disease (PD) is one of the most prevalent movement disorders and is the second most common neurodegenerative disease in the world, impacting more than 8 million individuals worldwide.[1] Although a resting tremor tends to be one of the most common presenting symptoms of individuals with PD, tremor is not required for diagnosis and is only present in two-thirds of patients.[2] A clinical diagnosis of PD is based on expert examination, and a patient must exhibit signs of bradykinesia and at least 1 of 2 other features: resting tremor and/or rigidity. Supportive criteria for a diagnosis of PD include a clear and dramatic benefit to dopaminergic therapy.[3] Once diagnosed, the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is often used to evaluate the severity and progression of PD.[4] Health care professionals may undergo training on this assessment tool for a nominal fee.

Although classified as a movement disorder, specifically a disorder of the extrapyramidal system, PD includes both motor and nonmotor symptoms. Examples of motor symptoms include hypokinetic (small) movements, shuffling gait, rigidity, bradykinesia, hypophonia, micrographia, and dysarthria (difficulty speaking). Some common nonmotor features of PD include anxiety, apathy, depression, insomnia, fatigue, bladder dysfunction, orthostatic hypotension, and pain. To date, there is no cure for PD, and it is considered to be a progressive disease, with treatment being symptomatic.[5] Pharmacologic treatments for the motor

Take-Home Points:

1. Nearly every patient with a diagnosis of Parkinson disease will require therapy with levodopa and will eventually develop motor fluctuations as part of the progression of the disease. The most common motor fluctuations include end-of-dose wearing OFF, dyskinesias, delayed ON condition, and unpredictable wearing OFF.
2. Conversion from immediate-release carbidopa/levodopa to extended-release carbidopa/levodopa capsules is one method used to maximize ON condition and allow for a slight reduction in dose frequency.
3. Augmentation of a patient's carbidopa/levodopa regimen with a catechol-*O*-methyl transferase (COMT) inhibitor, monoamine-oxidase B (MAO-B) inhibitor, dopamine agonist, or adenosine receptor antagonist can aid in reduced OFF time per day. The newest therapies with evidence for this indication include opicapone, safinamide, and istradefylline.
4. On-demand therapies for rapid ON time include subcutaneous apomorphine as well as inhaled levodopa. The selection of which agent to choose should be patient specific.

features of PD primarily work to enhance dopamine levels and transmission. Some of the most common classes of medications in the treatment of PD include anticholinergics, dopamine agonists, monoamine oxidase B (MAO-B) inhibitors, catechol-*O*-methyl transferase (COMT) inhibitors, and levodopa. Additional agents used in the treatment of PD include istradefylline, an adenosine receptor antagonist, and amantadine, an NMDA receptor antagonist.

Because of the progressive nature of the disease along with its pathophysiology, almost every patient with PD will eventually require treatment with exogenous dopamine in the form of levodopa and will experience motor complications.[6] Examples of motor complications in the form of motor fluctuations include end-of-dose wearing OFF, delayed ON or no ON response, dyskinesias, and unpredictable OFF episodes.[7–9] A variety of management strategies to treat motor fluctuations, specifically end-of-dose wearing OFF and unpredictable OFF episodes, will be explored through a series of hypothetical patient cases. Dyskinesias, extra involuntary movements, is a common motor fluctuation that will not be explored in this article.

Case 1

A 73-year-old with a 5-year history of PD presented for a routine 3-month follow-up to the movement disorder clinic. At the time of the visit, the chief complaint included an increase in OFF time per day. The symptoms that emerge first in the OFF condition include reduced speech volume, slowed movements, and slowed thinking. The patient had initially been treated with rasagiline 1 mg daily as monotherapy and is currently on carbidopa/levodopa IR 25/100 mg, 1.5 tablets 4 times per day and remains on rasagiline 1 mg daily. Upon further evaluation it is noted that the transition to OFF condition occurs about 30 minutes prior to the next dose of carbidopa/levodopa.

End-of-Dose Wearing Off

In the scenario, the patient is experiencing predictable wearing OFF from their carbidopa/levodopa. Predictable wearing OFF tends to be one of the earliest types of motor fluctuations that arise in patients with PD.[9] This is due in part to the progressive shortening of the response to levodopa as the nigrostriatal neurons continue to lose the ability to synthesize and store dopamine.[10] Several strategies that exist to treat end-of-dose wearing OFF include a reduction in dose of levodopa administered with increased frequency, a change in levodopa formulation, or addition of another agent that can prolong the duration of action of levodopa, such as a COMT inhibitor.

Carbidopa/Levodopa Formulations and Place in Therapy

Mechanistically, levodopa crosses the blood-brain barrier, where it is converted to dopamine by striatal enzymes. To reduce the risk of adverse effects and increase its efficacy, levodopa is commonly administered with a decarboxylase inhibitor, such as carbidopa or, less commonly, benserazide (only approved in Canada and the United Kingdom). Generally, about 75 mg of carbidopa is needed per day to inhibit peripheral decarboxylation of levodopa, but it is not uncommon for patients with advanced disease to receive higher doses of carbidopa.[11]

The various formulations of carbidopa/levodopa that are approved by the US Food and Drug Administration (FDA) for use in the United States include carbidopa/levodopa (immediate release, Sinemet), carbidopa/levodopa extended-release tablet (Sinement CR), carbidopa/levodopa extended-release capsule (Rytary), quarter scored carbidopa/levodopa (Dhivy), and the intrajejunal formulation (Duopa). A subcutaneous formulation of foscarbidopa/foslevodopa is pending FDA approval. Features of the currently FDA-approved products can be found in Table 1. Of these available formulations, conversion to the extended-release capsule (Rytary) product from the immediate-release (IR) formulation is a common step taken in clinical practice when patients begin to experience motor fluctuation, and it is supported by clinical guidelines.[12] The phase 3 clinical trial for IPX066 (now the FDA-approved Rytary) specifically compared carbidopa/levodopa IR to the oral extended-release (ER) capsule

TABLE 1: Formulations of Carbidopa/Levodopa Available in the United States[13–16,18,19,58]

Form of Levodopa (Carbidopa)	Brand Name	Doses Available (Carbidopa/Levodopa)	Specifics About Formulation	Cost (Average Wholesale Price)
Carbidopa/levodopa immediate release	Sinemet	10/100 mg 25/100 mg 25/250 mg	• Most common formulation used in clinical practice	$0.71–$0.77 $0.23–$1.18 $0.86–$1.11
Carbidopa/levodopa immediate release (oral disintegrating tablet)		10/100 mg 25/100 mg 25/250 mg	• Immediate release formulation that may be preferrable if a patient cannot swallow pills	$1.22 $1.38 $1.75
Carbidopa/levodopa extended-release tablet	Sinement CR (brand name has been discontinued)	25/100 mg 50/200 mg	• Onset of effect varies and can take up to 2 h to start working • Use in practice is limited to bedtime dosing to prevent morning akinesia	$0.93–$0.99 $1.74–$1.90
Carbidopa/levodopa extended-release capsule	Rytary	23.75/95 mg 36.25/145 mg 48.75/195 mg 61.25/245 mg	• Similar onset of effect to the immediate release carbidopa/levodopa but longer duration of action • May open the capsule and sprinkle in applesauce if a patient has trouble swallowing • Brand name only	$4.99 $4.99 $4.99 $6.27
Carbidopa/levodopa immediate release (quarter scored tablet)	Dhivy	25/100 mg	• Tablet is scored in fours to allow for more specific dosing • Approved in 2021, brand name only	$3.90
Carbidopa/levodopa enteral suspension	Duopa	4.63 mg/20 mg per mL	• Requires J-tube placement • Allows for 16 h of continuous delivery as well as bolus doses • Patient removes the pump prior to bedtime	$2.62

formulation. Patients who were included in the study had to experience at least 2.5 hours of OFF time per day at baseline.[13] Patients first underwent optimization of carbidopa/levodopa IR for the first 3 weeks of the trial, followed by a 6-week open-label period for conversion to the ER capsule. Patients were then randomized to 13 weeks of double-blind treatment with either the IR-optimized regimen or the ER regimen. There was a statistically significant reduction in OFF time in those who received treatment with the ER carbidopa/levodopa capsule by 1.17 hours per day. In addition, the dosing frequency of the ER capsule product was a mean of 3.6 times per day compared with 5.0 times per day for the IR formulation.

Converting from IR carbidopa/levodopa to ER carbidopa/levodopa capsules is not an exact science, partly because of pharmacokinetic differences between the 2 formulations. The ER capsule formulation consists of a combination of IR and ER beads to allow for quick onset of effect and longer duration of action with minimal peak-to-trough fluctuations.[14] Levodopa plasma concentrations from ER reach the 50% C_{max} at approximately the same rate as IR; however, the levodopa plasma concentration remains above 50% C_{max} for nearly 4 hours with ER compared with 1.4 hours with IR.[15] This illustrates what is seen in clinical practice, a nearly identical onset of effect with ER carbidopa/levodopa compared with IR carbidopa/levodopa, but a longer duration of action with less peak-to-trough difference.

Like the IR products, the ER capsule consists of carbidopa/levodopa in a 1:4 ratio, but in differing strengths from those available as IR. Whereas IR carbidopa/levodopa comes in the ratios 10/100 mg, 25/100 mg, and 25/250 mg, the ER product is available as 23.75/95 mg, 36.25/145 mg, 48.75/195 mg, and 61.25/245 mg. The prescribing information

provides a dosing conversion between the two products.[16] In clinical practice, a strategy that is used to help convert between the formulations is to double the total daily dose of levodopa given and reduce the frequency of administration by one with the ER capsule formulation (eg, 4 times daily to 3 times daily). A nationwide survey of health care providers found this strategy to be more commonly employed rather than the use of the dose conversion table, which is the case in the author's clinical practice as well.[17]

Returning to case 1, the patient has been taking 1.5 tablets of carbidopa/levodopa IR 25/100 mg 4 times per day, for a total daily dose of levodopa IR 600 mg/day. Adjusting according to common practice, this patient would require levodopa ER 1200 mg/day divided between 3 doses per day, or approximately 400 mg per dose. This would be best accomplished by taking 2 of the 48.75/195 mg capsules 3 times per day or 3 capsules of 36.25/145 mg 3 times per day. Further adjustment would be based on symptoms and response to this initial regimen. Either a phone or in-person follow-up within 2 weeks would best advise the impact on this regimen change, as well as need for further adjustments.

It is important to note why the strategy for motor fluctuation may include conversion to the ER capsule formulation but does not include use of the carbidopa/levodopa ER tablet product. Studies have found erratic absorption with the ER tablet formulations, along with variable levodopa plasma concentrations.[18,19] Additionally, the ER tablet product has a delayed onset of effect that ranges from 60 to 180 minutes. Based on the available evidence, clinical guidelines do not recommend this strategy in the treatment of motor fluctuation.[12] In the author's clinical practice, the use of the ER tablet has been reserved to a dose before bedtime. When given at bedtime, the need for a fast onset of effect is negated because of the patient being asleep. This strategy allows for the patient to have some level of ON condition, which can be particularly helpful for nighttime awakenings to use the restroom or to ease the ability to turn in bed from side to side.

Case 2

A 78-year-old with a 7-year history of Parkinson disease presents to the movement disorder clinic with a chief complaint of increasing OFF time throughout the day. The OFF time is relatively predictable and generally begins to occur about 15 minutes prior to the next carbidopa/levodopa dose. The patient had been converted from carbidopa/levodopa IR to the ER capsule but did not notice improvement and therefore did not want to continue to pay more for the brand-name product. The current regimen includes carbidopa/levodopa 25/100 mg tablets, taking 2 tablets 4 times a day and a carbidopa/levodopa ER tablet 50/200 mg at bedtime, and amantadine 100 mg twice daily for dyskinesias. The patient denies having current issues with dyskinesias since starting amantadine and with prior adjustment of carbidopa/levodopa IR.

Other Options for Motor Fluctuation

In this case 2, the conversion from IR carbidopa/levodopa to the ER capsule occurred previously but because of a lack of perceived benefit and cost, this patient preferred the IR formulation. This case is a great example to expand upon what agents could be added to the current PD medication regimen to extend ON time. During the last 10 years, multiple agents have been approved for this indication, so some key considerations for these various agents will be explored further.

MAO-B: Safinamide

Safinamide was FDA approved in March 2017 as an adjunctive therapy to carbidopa/levodopa in the treatment of PD OFF episodes. Safinamide is a highly selective, reversible MAO-B inhibitor that also blocks voltage-dependent sodium and calcium channels and inhibits glutamate release. Interestingly, safinamide has the same mechanism of action as zonisamide, which is used off-label for parkinsonism and is available for this indication in Japan.[20] The selectivity of safinamide for MAO-B mitigates the need for any dietary restrictions that may exist with MAO-A inhibition. Even when given at a single dose of 10 mg/kg, no MAO-A inhibition was exhibited.[20]

Clinical trials explored the use of safinamide as an adjunctive agent to both dopamine agonist therapy and levodopa in early disease.[21,22] In patient case 2, the use of safinamide could be considered as an add-on to levodopa therapy because the patient has more advanced PD characterized by motor fluctuation. One of the clinical trials that investigated the efficacy of safinamide in patients with PD and at least 1.5 hours of OFF time per day found that patients randomized to receive safinamide had a significant improvement in ON time, achieving 1.42 more hours of ON time per day compared with 0.57 more hours in those who received placebo.[23] This ON time increase occurred without troublesome dyskinesia, which the patient in case 2 has a history of experiencing. Similarly, another phase 3 clinical trial investigated ON time without troublesome dyskinesia. Those randomized to receive safinamide experienced an increase of 1.36 hours of ON time compared with 0.97 hours in the placebo group.[24] Individuals randomized to receive safinamide 100 mg/day experienced a significant improvement in the MDS-UDPRS subscale score for activities of daily living compared with the placebo group. Interestingly, safinamide therapy has also been associated with improvement in pain, sleep, and mood, theorized to be due to its impact on glutamate, which is unique to

safinamide compared with the other MAO-B inhibitors, rasagiline and selegiline.[25–27] Clinical guidelines denote safinamide as an "efficacious" agent in the treatment of motor fluctuations.[12] If safinamide were to be added to this patient's regimen, it is recommended to start with 50 mg daily for 2 weeks and then to increase to 100 mg daily thereafter.[28]

Adenosine Receptor Antagonist: Istradefylline

An alternative add-on agent for this patient in case 2 to consider is istradefylline, an adenosine A_{2A} receptor antagonist. Although it does not work directly on dopamine, istradefylline antagonism of adenosine A_{2A} receptors is thought to indirectly prolong the activity of dopamine in PD.[29,30] Istradefylline is currently approved in the United States for patients treated with carbidopa/levodopa who are experiencing OFF time based upon results from four 12-week placebo-controlled phase 3 clinical trials.[31]

One of the first clinical trials for istradefylline evaluated the change in OFF time during 12 weeks in patients treated with levodopa with at least 3 hours of OFF time total per day at baseline. Placebo-corrected reduction in daily OFF time from baseline to end point was 0.7 hours, without any difference in ON time with troublesome dyskinesia between the groups.[32] Patients with a diagnosis of PD responsive to levodopa and at least 2 hours of wearing OFF per day were eligible for participation in a double-blind randomized clinical trial evaluating the reduction in OFF time between those who received istradefylline 40 mg compared with placebo. This study found a reduction in total daily OFF time of 1.8 hours in the istradefylline group compared with 0.6 hours in the placebo.[33] Reduction in OFF time was further demonstrated in the other phase 3 trials.

Clinical guidelines denote istradefylline as a "likely efficacious" agent in the treatment of motor fluctuations.[12] It is recommended to start istradefylline at 20 mg once daily and increase to 40 mg once daily as tolerated.[32,34,35] Given our patient case, istradefylline is another option that could be added to the treatment regimen, noting there is less evidence to support efficacy compared with safinamide.

COMT Inhibitor: Opicapone

COMT inhibitors reduce peripheral conversion of levodopa to dopamine and thereby increase the amount of levodopa that is bioavailable.[37] The place in therapy for COMT inhibitors is to extend the duration of the effects of levodopa. Prior to 2019, the only COMT inhibitors available in the United States included tolcapone and entacapone. One of the biggest limitations with the use of tolcapone is its black box warning for hepatotoxicity, which limits its use to those who have failed therapy with entacapone.[38] Entacapone does not have this warning, but it has a shorter half-life, requiring dosing with each dose of levodopa. Additionally, the total daily increase in ON condition that occurs with entacapone averages a mean of 0.6 hours per day.[39]

Opicapone is a third-generation COMT inhibitor that has a high binding affinity and slow dissociation constant to the COMT enzyme.[40] Its efficacy was established through the phase 3 clinical trials BIPARK 1 and BIPARK 2.[41,42] These trials included patients with PD with at least 1.5 hours of OFF time per day who were levodopa responsive. BIPARK 1 randomized patients to treatment with opicapone (5, 25, or 50 mg once per day), placebo, or entacapone (200 mg with each levodopa dose). The primary end point was the change from baseline to study end in absolute time in OFF condition per day. Upon the end of BIPARK 1, individuals randomized to placebo experienced a reduction in OFF condition by 56 minutes, 96.3 minutes in the entacapone group, 91.3 minutes in the 5-mg opicapone group, 85.9 minutes in the 25-mg opicapone group, and 116.9 minutes in the opicapone 50 mg group. Treatment with opicapone 50 mg was found to be superior to placebo and not inferior to entacapone in this study. Similarly, BIPARK 2 evaluated the change in absolute OFF time per day from baseline. Participants in BIPARK 2 were randomized to treatment with placebo, 25 mg of opicapone, or 50 mg of opicapone. Those who received 50 mg of opicapone had a significant reduction in OFF time compared with placebo, of 54.3 minutes per day.[42] Pooled analysis of these 2 double-blind trials and their open-label phases found a significant reduction in OFF time compared with placebo, with the 50 mg of opicapone resulting in a mean of 58.1 minutes per day.[43] Increases in ON time occurred without a significant increase in bothersome dyskinesias.

Given our patient case 2, opicapone would be another appropriate option to consider adding to the treatment regimen to reduce OFF time. The recommended dose for opicapone is 50 mg once daily, to be administered at bedtime.[44] There is no further dose titration necessary.

Summary of New Adjunctive Agents

Safinamide, istradefylline, and opicapone are all reasonable adjunctive options in our patient case, with clinical guidelines providing a stronger level of evidence for safinamide and opicapone compared with istradefylline. All three treatment options allow for convenient once-a-day dosing and have demonstrated significant increases in ON time without bothersome dyskinesias.[45] The expected decrease in OFF time per day tends to be close to 1 hour per day. The cost and coverage of these agents and patient-specific factors (such as previous/current medications) will most likely determine which agent may be trialed first because

TABLE 2: Opicapone, istradefylline, and safinamide[28,36,44,60–62]

Medication/ Brand Name	Mechanism of Action	Dose Availability, mg	Adverse Effects (Reported >10%)	Clinical Pearls	Cost (Average Wholesale Price)
Opicapone/Ongentys	COMT inhibitor	25 50	Dyskinesias	• Administered once nightly • Patients may experience constipation, dry mouth, and weight loss	$26.81
Istradefylline/Nourianz	Adenosine receptor antagonist	20 40	Dyskinesias	• Nondopaminergice therapy option • Approved as a monotherapy in Japan • Patients may experience insomnia	$72.10
Safinamide/Xadago	MAO-B inhibitor	50 100	Dyskinesias	• In addition to its MAO-B inhibition, also blocks voltage-dependent sodium and calcium channels and inhibits glutamate release • Patients may experience nausea	$45.58

all three are still brand name only and there has been no head-to-head trial completed to compare each agent. Table 2 provides a summary of these agents.

Case 3

A 63-year-old with a 6-year history of PD reports unpredictable OFF episodes that occur about 2 times per day most days of the week. The patient denied end-of-dose wearing OFF with the current medication regimen and denied any bothersome dyskinesias. The current medication regimen includes 2 capsules of carbidopa/levodopa ER 48.75/195 mg 4 times a day, safinamide 100 mg daily, escitalopram 10 mg daily, and as-needed carbidopa/levodopa IR 25/100 mg for unpredictable OFF episodes. The as-needed carbidopa/levodopa IR tends to result in excessive fatigue and unpredictable response. This patient is interested in on-demand therapy options for when there are unpredictable wearing off episodes.

Apomorphine

The first on-demand therapy available for PD in the United States was apomorphine administered subcutaneously, which was approved in 2004 and is now available as a generic formulation. Apomorphine is a dopamine receptor D1 and D2 agonist with poor oral bioavailability, hence the need for nonoral administration. The phase 3 clinical trials that led to its approval for the acute treatment of intermittent OFF episodes demonstrated significant improvement in the motor response score measured by the MDS-UPDRS compared with placebo at different time intervals after administration.[46–48] The overall time to ON response ranges from 10 to 20 minutes generally. Despite its reliable and fast onset of effect, there are some specific instructions when initiating the medication. Medical supervision is recommended for initial dosing.[49] To determine the target dose of apomorphine, patients are to present in OFF condition prior to injecting the first dose. The first dose given is 1 mg with close monitoring of blood pressure every 20 minutes for the first hour.[49] If the patient responds to and tolerates the initial test dose, then that is the target dose given for intermittent off episodes. If the dose does not lead to an adequate response, the patient may then receive 2 mg after 2 hours from the initial dose with the same blood pressure monitoring in between. This assessment continues every 2 hours until an effective and tolerated dose is found for the patient.[49] In addition to this assessment, patients who are to be initiated on apomorphine subcutaneous are recommended to take trimethobenzamide at least 3 days prior to first starting therapy because of the high incidence of nausea and vomiting with the medication.[50] Unfortunately, as of 2021 in the United States there has been a shortage of trimethobenzamide, eliminating the ability to pretreat patients.[51] As a result, the titration may be reduced and slowed down as patients tolerate. It is important to note that other commonly used antiemetics are contraindicated with apomorphine because of severe hypotension (5-HT3 antagonists) or disease state worsening (D-2 antagonists).

A subligual dosage form of apomorphine was approved in 2020 for treatment of OFF episodes in PD but was subsequently removed from the market in 2023. Premedication for nausea was not required with this dosage form. Pharmacokinetically, the sublingual form did have a slightly longer onset of effect with a lower peak drug concentration compared with the subcutaneous formulation.[49,52,53] In the

TABLE 3: On-demand therapies for Parkinson disease[45–49,55–59]

Medication/ Brand Name	Route of Administration	Time to Onset	Clinical Pearls	Cost (Average Wholesale Price)
Levodopa/Inbrija	Inhalation	10–30 min	• Capsule of levodopa is placed into the inhalation device similar to other dry powder inhalers • Most common adverse effect is cough	$23.04
Apomorphine/Apokyn	Subcutaneous injection	10–20 min	• Requires in-clinic initiation for close monitoring specifically for hypotension • Most rapid and predictable onset of effect • Recent generic formulation available	$591.31

phase 3 clinical trial, the change in motor score from the MDS-UPDRS scale before dose to after dose (primary outcome) significantly improved in the apomorphine group compared with placebo.[54] Most patients experienced an ON response within 30 minutes of taking the sublingual formulation. Despite good response and ease of use, the most common adverse effects with the sublingual form included lip swelling, oropharyngeal swelling, and oral mucosa erythema, resulting in nearly 20% of patients discontinuing therapy. The sublingual film also took about 3 minutes to dissolve, which may be longer than patients expect.

Levodopa: Inhaled

In 2018 an inhaled formulation of levodopa was approved for the intermittent treatment of OFF episodes in patients with PD. The inhalation formulation allows for better plasma bioavailability of levodopa by absorption through the pulmonary alveoli. In the phase 3 clinical trials, treatment with inhaled levodopa compared with placebo resulted in a significant improvement in the motor score of the MDS-UPDRS scale within 30 minutes after the dose was taken.[55,56] Overall time to ON response ranges from about 10 to 30 minutes after inhaling the dose in most patients. The most common adverse effects with use of the inhaled levodopa include cough and other upper respiratory tract effects, and it is not recommended in patients with underlying respiratory conditions. To administer, patients place one 42-mg capsule of levodopa into the inhalation device and inhale. After inhaling the contents of one capsule, the second 42-mg capsule is to be inhaled in the same manner. The two 42-mg capsules constitute one dose.[57] The dose can be repeated up to five times in a 24-hour period.

Summary of On-Demand Agents and the Patient Case

Overall, subcutaneous apomorphine along with inhaled levodopa result in relatively rapid ON condition, achieved within 30 minutes upon dosing. The subcutaneous apomorphine formulation renders the fastest and most predictable ON condition but is limited by the dosage form itself (many patients not wanting to inject a medication) and the need for medical supervision during initial dose titration. Table 3 provides a summary of these agents. Based on clinical experience, the inhaled levodopa formulation tends to be well tolerated and the preferred option by patients seen in clinic and would be a very reasonable option for our patient in case 3.

Conclusion

The treatment of OFF condition in Parkinson disease involves several different therapeutic options, especially given the number of agents recently approved for this indication. Specific factors to consider include the type of motor fluctuation the patient is experiencing, current medication, any optimization needed of the current medication regimen, and patient-specific factors, such as other chronic disease states and types of motor and nonmotor symptoms of PD. Although the cases presented highlight some specific options, it is important to note that many of the agents described can be used in combination with one another. In addition, all of the medications described in this article are only available as brand name products. Accessibility and overall cost are factors to consider in devising therapy options. Even with possible high out-of-pocket cost, insurance coverage varies, as does patient medication assistance programs. It is always a good idea to check the manufacturer's site for access options. All of these considerations demonstrate how the optimization of a patient's PD medication regimen becomes as much of an art as a science.

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