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REVIEW

Non-Oral Drug Delivery in Parkinson's Disease: Current Applications and Future

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ABSTRACT

Parkinson's disease (PD) is a type of movement disorder that affects the ability to perform daily activities. It is considered that 1 million people in the U.S. and more than 10 million people worldwide live with PD. It is a chronic and progressive disease, so symptoms worsen over the time. Patients experience motor symptoms such as tremors, stiffness and slow motion, and non-motor symptoms such as sleep problems, constipation, anxiety, depression and fatigue. Dopaminergic drugs are critical for treating motor symptoms in PD. Levodopa (L-DOPA) is the "gold standard" medication for the control of motor symptoms. Because of the progression of the disease, the effectiveness of oral L-DOPA decreases over time and motor fluctuations such as "delayed ON", "no ON" and unpredictable "ON-OFF" periods appear. These motor fluctuations affect the quality of life of the patient at a high rate and the patient has problems in fulfilling his daily morning routines. Gastrointestinal (GI) problems, as the common non-motor symptom, are the most important cause of motor fluctuations that occur because of inadequate oral treatment with the progression of PD. When oral treatments are not sufficient, non-oral treatments that are not affected by GI problems are required. In this review, the treatment strategies, developed and approved non-oral drug delivery systems in the early and advanced stages of PD are emphasized.

Keywords: Parkinson's disease, oral and non-oral treatment, motor and non-motor fluctuations

INTRODUCTION

Parkinson's disease (PD) is the most common neurodegenerative movement disorder that can affect the ability to perform daily activities.[1] It is considered that 1 million people in the U.S. and more than 10 million people worldwide have PD. PD is usually diagnosed in people over the age of 55. Although it is rare, it can also be seen in the young population between the ages of 21-45. The disease is called late-onset, when diagnosed in older people, and young-onset, when diagnosed in the young population.[2]

PD is a chronic and progressive disease. Motor and non-motor symptoms are seen in these patients. However, it is characterized by motor symptoms associated with movement. These symptoms are rhythmic shaking tremors, stiffness or rigidity of the muscles and slowness of the movement (bradykinesia). Movements are controlled by neurons in the brain and messages are transmitted to each other and to the rest of the body by chemicals called neurotransmitters. Dopamine, a neurotransmitter that control movement, is produced in *substantia nigra* area of the brain. In PD, 70-80% of dopamine-producing cells disrupt by stages and are lost, which called neurodegeneration. The damage to neurons causes low levels of dopamine in the part of the brain that controls balance and movement. When neurons do not pass on brain messages properly, their movements have not been controlled smoothly and the motor symptoms of PD appear. In addition to motor symptoms, non-motor symptoms related to PD can occur in patients. Non-motor symptoms are sleep problems, constipation, depression, anxiety, and fatigue. For many of these non-motor symptoms, definitive clinicopathological correlations are still not fully understood.[3] Dopaminergic drugs are critical for treating motor symptoms in PD. Levodopa (L-DOPA) is known as the "gold standard" for the control of motor symptoms in PD. Because of the progression of PD, effectiveness of oral L-DOPA decreases over time.[4] It has been reported that in 5-10 years, patients treated L-DOPA will develop motor fluctuations and dyskinesias in 70-80%.[5] The fluctuations in motor functions

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are due to ON responses (good antiparkinsonian effect) and OFF responses (the symptoms are not efficiently controlled) seen just before the next dose of L-DOPA. In the ON period, patients can fully move and function independently, and the patient is unable to function such as move, talk, smile as easily during the OFF period. These motor fluctuations can occur diversely. These are foreseeable end-of-dose "wearing OFF" phenomena, peripheral problems such as "delayed ON" or "no ON", and unpredictable "ON-OFF" periods. The delayed effect of oral medications causes an early morning OFF period.[6,7] This condition affects quality of life of the patients at a high rate and the patient has problems in fulfilling his daily morning routines. The results of an international multicenter study of EUROPAR, a partner of the European Parkinson's Disease Association, show that the incidence of OFF period is 60% even in patients undergoing optimized PD therapy.[8] L-DOPA dose is usually increased to manage these problems. However, increasing L-DOPA dose can cause involuntary movements or painful dyskinesia. Gastrointestinal (GI) problems, as a common non-motor symptom, are the most important cause of motor fluctuations that occur because of inadequate oral treatment with the progression of PD. Dysphagia, gastric dysfunction, colonic dysmotility, small-intestine motility, and delayed gastric emptying (GE) can be considered GI problems. When oral therapies are not insufficient, alternative drug delivery systems that are not affected by GI problems are necessary, which are known as non-oral treatments. Guidelines published in 2017 at the National Institute for Health and Care Excellence mention that non-oral treatments will be safe, important and effective for PD treatment.[9,10] In this review, importance of non-oral therapy in PD treatment is emphasized. It also includes available non-oral drug delivery systems and current studies of non-oral formulations.

METHODS

We used the websites of the American Parkinson Disease Association and the European Parkinson Disease Association for this review. Additionally, references for this review have been identified through PubMed, ScienceDirect and Google Academic using the terms "Parkinson's disease", "Parkinson's disease treatment strategy" and "Non-oral treatment of Parkinson's disease". We primarily selected articles published between 2000 and 2020. Only publications in English were evaluated. We evaluated more than 200 citations, of which 81 are included in this review.

Current oral treatment options for Parkinson's disease

There is no definite cure for PD, but the medicines used in treatments can provide important symptomatic control of the motor symptoms. Current pharmaceutical strategies for the control of symptoms are L-DOPA, catechol-*O*-methyl transferase (COMT) inhibitors, dopamine agonists, monoamine oxidase B (MAO-B) inhibitors, anticholinergic, and amantadine medications.[10]

L-DOPA is a medicine used since 1970 to treat PD and is still most effective for symptomatic treatment. It is effective in the early stages of PD but remains effective as PD progresses without intolerance developing over time. L-DOPA is routinely used along with a DOPA-decarboxylase inhibitor to reduce some treatment complications, prolong half-life, and increase L-DOPA availability to the brain.[11] However, after long-term use of L-DOPA oral formulations, problems such as motor and non-motor fluctuations and L-DOPA-induced dyskinesia can be observed because of pharmacokinetic properties of L-DOPA. Patients do not experience any fluctuations in motor or non-motor symptoms during the first years of L-DOPA use. Patients begin to aware of these fluctuations after 2-5 years of L-DOPA use. In this way, as the disease progresses, patients must make frequent adjustments to the dosage regimen and they should use L-DOPA more frequently due to the shortened effect time and reduced effect.[12] Increasing the dose and frequency of L-DOPA to control of motor symptoms may provide some improvement, but involuntary movements and painful dyskinesia may occur due to the high plasma concentration of L-DOPA. Dyskinesia can cause the problems in walking and balance; therefore, patients may have difficulties in social life. Additionally, in the later stages of PD, patients become completely dependent on care, and those caring for their care has a heavy social responsibility, both socially and economically.[13,14]

Since motor fluctuations greatly affect the course of the disease, clinicians occasionally have difficulty managing the disease. After 5 years of L-DOPA treatment, approximately 50% of patients experience wearing off, and this rate rises to about 80% after 10 years.[15] Clinicians should choose the appropriate PD medicines to manage symptoms effectively and improve the patient's quality of life. The most important reason for fluctuations in the use of oral PD medications are GI dysfunctions such as slow GE, irregular jejunal absorption, and competition with dietary amino acids in the areas of absorption.[16,17]

COMT inhibitors are drugs that inhibit the enzyme COMT that acts on dopamine breakdown and extend the duration of L-DOPA activity. Doctors use them along with L-DOPA to treat the motor symptoms of PD.[18] Because they prolong L-DOPA duration of action by increasing half-life and delivery to the brain. In some patients, COMT inhibitors provide control of motor symptoms by reducing off-time compared with standard L-DOPA/DOPA decarboxylase inhibitor combinations.[19] Tablet formulations of COMT inhibitors are available on the market. Although they are able to improve motor function in some patients, they are not prescribed alone because they offer a limited effect on PD symptoms. Entacapone and tolcapone, approved COMT inhibitors, are reversible COMT inhibitors approved for treating PD. A third COMT inhibitor, opicapone, is available in Europe but has not yet been approved by the Food and Drug Administration (FDA). Each of these COMT inhibitors has problems in terms of pharmacokinetics, pharmacodynamics, clinical efficacy or safety. Additionally, their elimination half-lifes are approximately 2-3 hours.[20]

The most common adverse effects associated with the addition of COMT inhibitors to carbidopa/L-DOPA treatment are strengthening the dopaminergic effects of drugs, such as nausea, dyskinesia, orthostatic hypotension, sleep disorders, hallucinations, and vomiting. L-DOPA dose adjustment must avoid these events. Dark yellow or orange urine discoloration is related to the colour of the COMT inhibitors and their metabolites. Entacapone from COMT inhibitors is preferred as the first-line treatment in patients with PD. Because tolcapone causes hepatotoxicity. The descriptions of acute, fatal fulminant hepatitis and potentially fatal neurological reactions in association with tolcapone led to the suspension of its marketing authorization in Europe and Canada. In many other countries, use of the drug is restricted to patients, who are not responding to other therapies. If tolcapone is used in PD treatment, proper monitoring of liver function, and liver enzymes is required during the first six to eight months of the treatment.[21,22]

MAO-B inhibitors have been used for treating PD as both early monotherapy and combined therapy in patients with the more advanced disease.[23] Selegiline and rasagiline are selective MAO-B inhibitors approved for PD treatment.[24] Both selegiline and rasagiline were originally developed as antidepressants. However, low and medium doses of selegiline required to provide an irreversible MAO-B inhibition have not had antidepressant activity. The most important differences between these two active substances are their metabolism, their interaction with cytochrome (CYP) P450 enzymes and their molecular biological/genetic level properties.[25] Amphetamine metabolites occur because of the metabolism of selegiline with CYP enzymes. These metabolites can occur after oral use and can cause sleep problems in patients.[24]

The oral bioavailability of selegiline is about 10%. This low bioavailability has led to the development of different non-oral drug delivery systems such as transdermal, buccal, and nasal.[26,27] Another MAO-B inhibitor is rasagiline and because of the metabolism of rasagiline, unwanted metabolites such as amphetamine-like metabolites do not form.[18] Studies have shown that amphetamine-like metabolites occur only in the plasma of patients with PD during the use of selegiline, and not during chronic rasagiline therapy.[28,29] Additionally, rasagiline administered orally is rapidly absorbed from GI tract and reaches the highest plasma concentrations within an hour. Rasagiline's oral bioavailability is about 36% due to its high hepatic first-pass metabolism.[30]

"Cheese reaction", which is a serious side effect, occurs especially when non-selective MAO inhibitors are administered with certain foods such as cheese and drugs such as decongestants. Because of this reaction, hypertensive crisis, palpitations, tachycardia, blurred vision, arrhythmias, and other sympathomimetic problems can be seen. The "cheese reaction" occurs particularly, when older MAO inhibitors are administered with biogenic amine-like substances such as decongestants or high dietary tyramine (more than 500 mg *per* day). Although there are clinical pharmacology and safety data showing that rasagiline and selegiline are selective MAO-B inhibitors, concerns remain regarding interactions with tyramine and the potential for hypertensive crisis. Despite being rare, cases of the "cheese reaction" have been informed during treatment with selegiline. It has been stated that normal dietary tyramine for both selegiline and rasagiline does not cause clinically meaningful interactions, but taking more than 150 mg tyramine *per* day may increase the risk.[25] In the study of Goren et al.[29], rasagiline at the recommended therapeutic dose of 1 mg/day provides a selective MAO-B inhibition. Simultaneously, it has also been noted that, when rasagiline is used at doses >2 mg/day, its selectivity for MAO-B decreases and tyramine sensitivity increases.[29]

Dopamine agonists demonstrate antiparkinsonian effects by directly acting on dopamine receptors and mimicking the endogenous neurotransmitter. Oral L-DOPA/DOPA decarboxylase inhibitor application is inevitably necessary with the advance of PD. In the long term, chronic administration of oral L-DOPA formulations in a fixed combination with inhibitors of the main metabolizing L-DOPA enzymes results in the onset of so-called motor complications. When the disease progresses, the duration of L-DOPA response shortens in addition to the short plasma L-DOPA half-life.[31] L-DOPA converts to dopamine in both the center nervous system and the periphery. To increase the bioavailability of L-DOPA and decrease its side effects, it is often administered along with peripheral decarboxylase inhibitors (such as carbidopa and benserazide). Dopamine decarboxylase inhibitors prevent the conversion of L-DOPA to dopamine in the periphery, allowing for more L-DOPA to cross the brain-blood barrier.[32]

Compared to L-DOPA, dopamine receptor agonists do not require the enzymatic conversion to an active metabolite, and do not have potentially toxic metabolites. However, they do not compete with other substances for their active transport across the blood and blood-brain barrier, and are not depended on the functional capacity of nigrostriatal neurons.[18] Dopamine agonists are classified as ergot or non-ergot types, and these active agents have essential differences associated with receptor affinities. Bromocriptine and cabergoline, as ergot derivatives, are dopamine agonists and they are not commonly used for treating PD. Ropinirole and pramipexole rotigotine are non-ergot-derived dopamine agonists, which are approved for PD therapy.[33] Apomorphine is the most potent dopamine agonist, but it effectively stimulates both D1 and D2 receptors like dopamine. However, due to some limitations, apomorphine cannot be used as an oral drug.[34]

Anticholinergic agents recently used to treat PD are benztropine and trihexyphenidyl. Since these drugs non-selectively block cholinergic receptors in the body, some side effects are seen. There are some hesitations about the use of these drugs for this reason. When selective cholinergic receptor antagonists were tried, significant benefits could not be obtained in PD treatment. Anticholinergics can alleviate dystonia and tremors caused by wearing off. However, it has no significant effect on other PD symptoms.[35]

Dysfunctions of gastrointestinal system in patients with PD

Dysphagia

Chewing and swallowing functions require regularly contracting and relaxing of many muscles. Therefore, it is inevitable that dysphagia is common in patients with PD. Dyspgahia is a problem that reduces quality of life and obstructs intake of the medication and increases the risk of aspiration, which is the cause of death of most patients in PD. PD-related dysphagia is not fully understood. Nevertheless, dopaminergic and non-dopaminergic mechanisms are effective in the development of dysphagia in PD.[36]

Lately, results of the studies disclosed that the dysphagia prevalence based on subjective conclusions, in patients with PD is 35% and rises to 82% by taking objective measures of swallowing dysfunction into account.[37] Aydogdu et al.[35] evaluated the dysphagia prevalence with the Videofluoroscopic Swallowing Study (VFSS) using the guidelines of the United Kingdom Parkinson's Disease Brain Bank. In this study, VFSS evaluation was performed on 23 patients with PD and 16 of the total sample were diagnosed with dysphagia.[35] Some clinical predictors should be considered when evaluating a patient with PD for the presence of dysphagia. For example; in patients with PD, weight loss without any reason or a body mass index below 20 is highly indicative of dysphagia. It is stated that 20% of patients develop malnutrition during PD. Another predictor of dysphagia and aspiration pneumonia is sialorrhea or drooling.[37,38]

Drooling

Drooling has many negative effects on quality of life, such as social embarrassment, decreased oral hygiene, bad breath, increased oral bacteria, difficulty speaking and eating, and increased risk of aspiration pneumonia.[39] There are no standard description and criterion for the diagnosis of drooling in patients with PD. For this reason, the prevalence forecast varies. Leibner et al.[37] conducted a questionnaire study on the drooling problem with 58 patients with PD and 51 healthy volunteers. In the end of the study, when patients with PD and control groups were compared, the rate of drooling was 59% and 14%, respectively.[37] Müller et al.[38] managed a study to examine the emergence and severity of autonomic and sensory symptoms in 207 newly diagnosed, untreated patients with PD and 175 healthy volunteers. The most obvious difference was observed in drooling, which was present in 42% of patients with PD but just 6% of the control group.

Gastric emptying

Disrupted GE (gastroparesis) is a common problem in patients with PD. In gastroparesis, patients experience symptoms such as abdominal discomfort or postprandial bloating, nausea, early satiety and weight loss.[9] It is thought that the cause of delayed and motor fluctuations in PD is delayed GE.[39]

Tanaka et al.[40] conducted a study with three groups. These groups were 20 patients with PD with newly diagnosed, untreated; treated with L-DOPA for a long time, advanced-stage 40 patients with PD; 20 healthy volunteers. The half-emptyting time ($T_{1/2}$) of healthy volunteers, newly diagnosed untreated and long-treated patients were found to be 86 min, 122 min, and 125 min, respectively. Goetze et al.[41] conducted a study with 36 patients with PD (divided into two as mild and advance) and 22 healthy volunteers. Because of this study, 97% of patients with PD had delayed GE. $T_{1/2}$ was found to be significantly longer in patients with PD compared in the control group. (169 *vs*. 107 min). Delayed GE was associated with degree of the disease. GE was found 149 and 196 min for patients with mild and advanced PD, respectively.[41] Unger et al.[42] subjected 20 healthy volunteers, 21 drug-naive and early-stage patients with PD and 18 patients with PD treated with dopaminergic medicines to 13C octanoate breath test to determine the duration of GE. Because of the study, it was observed that GE test (1/2) differs significantly between the groups. GE test (1/2) was found in control, drug-naive, early-stage patients with PD and treated patients with PD, 123.3 min ± 16.6, 166.6 min ± 32.4, and 203.6 min ± 46.8, respectively.[42] Most of these studies reported significantly increased the GE test in the PD group compared with the controls.

Small intestinal bacterial overgrowth (SIBO)

SIBO and changing gut microbiota raise doubts about the effectiveness of oral drug therapy in PD.[41] Recent studies showed that incidence of SIBO is high in PD. Additionally, GI symptoms and worsening of motor functions in PD have been reported to be related to SIBO.[43] Fasano et al.[44] showed that patients with PD and SIBO have more serious motor fluctuations (off time, delayed on-time, and non-on-time) than those without SIBO.

Colonic dysmotility

One of the most important GI problems observed in PD is decreased bowel movement. However, many PD drugs, such as anticholinergics and dopamine agonists, have been shown to cause constipation.[39]

In the study by Cheon et al.[45], the rate of constipation in patients with PD is 65.8%. In a survey study, the rates of difficulty in defecation in patients with PD and control group were reported as 59% and 20.9%, respectively. In the same study, the rate of laxative prescribing was reported as 29.9% and 9.5%, respectively.

Non-oral treatment necessity in PD treatment

Although orally administered L-DOPA is considered as "gold standard" drug for the control of motor symptoms in PD, the duration of benefit is seen to decreases in use long-term at an oral dose of L-DOPA.[4] Patients begin experiencing fluctuations in motor function in the later stages of PD. Due to the late effects of oral medications, the early morning OFF-periods are the most challenging situation in PD. This problem can complicate the patient's daily morning routines and seriously affect their quality of life.[7] As the disease progresses, the most important reason for oral treatment failure and motor fluctuations are the above-mentioned GI problems. Dysfunctions in the GI system occur at all levels of PD and this cause motor fluctuations in the advanced stages of PD, which make management of the disease difficult.[46] Especially, dysphagia may induce silent

aspiration and delayed GE. Problems such as delayed "on" and non "on" responses may arise due to gastroparesis in PD's oral dopaminergic treatment.[7,16] GI problems, such as gastroparesis, which occur in 70-100% of patients, can decrease the effectiveness of oral medications by delaying their absorption and delivery into the bloodstream.[16] Delayed ON and even dose failure, which causes motor fluctuations, may occur because of inadequate levels of medication plasma levels.[47,48] Besides, it has been stated in recent studies that the pathological process of PD can be managed and even started by the intestinal microbiota through the intestinal-brain axis.[49,50] Additionally, studies have shown that bacterial metabolites that may affect the enteric nervous system differ between patients with PD and healthy control groups.[51] At the same time, it has been indicated that previous studies have that some PD drugs may change the microbiota content. The increasing recognition of multilevel GI dysfunction in patients with PD has contributed to the development of non-oral methods for treating PD's motor and non-motor symptoms.[46]

Current studies on non-oral formulations

The liquid intranasal rotigotine is formulated of a pharmaceutically satisfactory acid addition salt of rotigotine and α-cyclodextrin. α-Cyclodextrin is used to predominantly stabilize rotigotine hydrochloride used. A formulation for intranasal use of rotigotine has been developed for therapy in PD and restless leg syndrome. The formulation underwent two phase 2 studies to assess efficacy, safety, and tolerability in a randomized, double-blind, placebo-controlled, and proof-of-concept manner. However, the results of these studies did not show improvement in secondary outcome measures such as a change in Unified Parkinson's Disease Rating Scale III (UPDRS III) administration administration and "OFF" reversals. Development of the drug was discontinued.[52]

Priano et al.[53] completed a pilot study on a new preparation of apomorphine, which was included in microemulsion and administration *via* the transdermal route (APO-MTD). Twenty-one patients were treated and the results obtained showed that APO-MTD delivered an average of 5.1 h of therapeutic plasma levels, improved the UPDRS III scores, and reduced the overall length of "OFF" periods. However, as promising as this treatment may seem, because of the time taken of 1 h to reach therapeutic concentrations, APO-MTD may not be the "ideal" treatment for the rapid relief of the "OFF" periods suffered by patients with PD.

The sublingual formulation of the D2-D3 agonist piribedil, S90049, was designed to abort "OFF" episodes in PD. A phase 2, double-blind, randomized, and placebo-controlled study showed superiority of S90049 in UPDRS III post-application in advanced-stage patients with PD. Additionally, the switch from "OFF" to "ON" was significantly greater in patients using S90049 inhalation than in placebo. Despite these results, no further activity has been reported since 2010.[54]

Sintov et al.[55] have suggested that transdermal L-DOPA administration can be effective to provide continuous dopaminergic stimulation. Considering that L-DOPA is insoluble in most solvents and has limited permeability through the skin, a modern self-assembling nanomicellar system with 2% L-DOPA and 1% carbidopa has been developed. Because of *in vitro* tests and *in vivo* studies in rabbits, it has been observed that transdermal permeability and systemic absorption of L-DOPA from the skin increased significantly through this formulation developed.

Non-oral formulations are required because of high liver metabolism and poor oral bioavailability of selegiline. Accordingly, the buccal film formulation with the poly(lactide-co-glycolide) (PLGA) nanospheres of the selegiline was developed. By evaluation of *in vitro* and *in vivo* studies, buccal films prepared with selegiline-loaded nanospheres have been observed to show great properties such as good physical properties, sufficient bioadhesion, and controlled drug release. Besides, thanks to the formulation prepared, it was seen that a higher amount of selegiline could be administered through the buccal mucosa. With this study, it is supported that buccal administration of the selegiline is an advantageous and promising approach that can overcome the problems limiting the successful delivery of this drug.[56]

Mishra et al.[24] developed a nanolipid carrier (NLC) formulation with selegiline hydrochloride to be administered nasally, considering that the nasal route is a convenient way to target the drug directly to the brain. NLC formulation loaded with selegiline hydrochloride showed 93 ± 5.25% entrapment efficiency and 51.96% loading capacity. It has been shown that with the optimized NLC formulation, 70% release can be achieved within 10 h, and then the drug release continues for up to 22 h (97%). The drug was found to improve behavioral parameters in rotenone-induced rats.

Ravi et al.[57] have developed a nasal thermosensitive gel formulation to provide effective treatment of PD by considering the low oral bioavailability of rasagiline mesylate. Because of pharmacokinetic studies in rabbits, *in situ* gels were found to provide a significant increase in the bioavailability of rasagiline mesylate.

Çelik et al.[58] have developed buccal mucoadhesive tablets to increase the low bioavailability of piribedil and provide a controlled release treatment for PD. Generally, buccal tablets prepared with hydroxypropyl methylcellulose can provide the necessary controlled release and physical properties. Because of the study, it was concluded that buccal mucoadhesive tablets provide various advantages such as controlled-release compared to traditional oral dosage forms. It is thought that side effects can be reduced because of the high bioavailability with lower doses to provide the desired effect.

The use of drugs targeted to the brain continuously and safely in PD is critical in the treating of this disease. In a study, surface-modified biodegradable PEG-PLGA nanoparticles were prepared with lactoferrin (Lf) to target rotigotine intranasally to the brain for PD treatment. When all the results of the study were examined, Lf nanoparticles were shown to be a suitable carrier for targeting rotigotine to the brain intranasally in PD treatment.[59]

Developed non-oral PD formulations

Levodopa/carbidopa intestinal gel (Duopa™) (LCIG)

Although L-DOPA is the gold standard in PD treatment, because of its short plasma half-life, oral L-DOPA treatment cannot effectively stimulate receptors. Motor fluctuations are seen due to insufficient plasma level.[60] LCIG formulation has been developed to be used to provide a continuous effect by keeping the plasma level of L-DOPA constant.[61] With the help of this pump, small doses of L-DOPA/carbidopa are administered into the small intestine at regular intervals, by passing the stomach. LCIG allows safe titration of L-DOPA to high doses, even more than 2000 mg/day and leads to more stable L-DOPA plasma concentrations.[61] Through this formulation, irregular absorption of L-DOPA caused by prolonged GE time in patients with PD is prevented.[61] In a study, when evaluating the effectiveness of the LCIG formulation against L-DOPA-carbidopa tablets, it was reported that LCIG significantly reduced "OFF" times and increased "ON" time without troubling dyskinesias. Because of the study, percentages of the patients, who were reported as "better" for dyskinesia, tremor, and gait disturbance called motor symptoms, were 80%, 55%, 65%, and 85%, respectively. Percentages reported for non-motor symptoms, pain, sleep disorders, depression, and incontinence were 50%, 50%, 42.5%, and 32.5%, respectively. Studies have shown that LCIG formulation is a promising alternative for advanced patients with PD with motor complications.[62]

Intrajejunal TriGel infusion (LECIG)

TriGel is a novel formulation obtained by adding entacapone to LCIG. Entacapone reduces conversion of L-DOPA to 3-O-methyldopa by blocking the second-largest pathway of L-DOPA. Thus, the plasma concentration of L-DOPA increases.[63] In a clinical study, LCIG and LECIG treatments were compared. Because of this study, dose-adjusted L-DOPA exposure was found to be significantly higher in the LECIG formulation compared to LCIG. It was observed that 3 patients had a 20% increase in systemic exposure to L-DOPA and a 40% or higher increase in six patients, and 2 patients could not achieve the target systemic exposure.[64] It is thought that the combination of opicapone, a newly developed COMT inhibitor, and LCIG can provide a similar effect.[65]

Inhaled levodopa powder (Inbrija®)

L-DOPA inhalation powder (Inbrija®) is a dry powder formulation administered orally with an inhaler, enabling rapid drug absorption in the pulmonary system. It is manufactured by Acorda Therapeutics and has been approved by FDA to treat the symptoms of Parkinson's patients during "OFF" periods.[66] Each capsule contains 42 mg spray-dried L-DOPA powder, 1,2-dipalmitoyl-snglycero-3-phosphocholine, and sodium chloride. The dry powder particles (5-10 μm diameter) are homogeneous, low in density, and highly porous for aerosolizability and lung deposition. Inbrija® was developed to achieve a rapid effect by providing a consistent and rapid increase in the concentration of the drug in the bloodstream. Pulmonary administration provides rapid absorption of L-DOPA due to its large surface area and low metabolic activity, so delayed "in" period or dose failures can be avoided.[66] Because of a study to determine the pharmacokinetics and tolerability of the formulation, T_{max} was 15 min in patients who are administered inhaler L-DOPA powder, but after oral administration, T_{max} ranged from 20 min to 90 min. However, no changes in lung function parameters were observed in patients and no patient complained of cough or shortness of breath.[67,68]

Rotigotine patch

The transdermal patch formulation of rotigotine (Neupro®), a dopamine agonist, has been developed for use alone in the early stages of PD or in addition to L-DOPA in the advanced stage of the disease. Rotigotin transdermal patch has been approved in EU, China, and Japan as a combination therapy with monotherapy and L-DOPA for early PD treatment. With the developed transdermal patch formulation, stable rotigotin plasma levels could be achieved for 1-2 days with a single daily administration.[69] A double-blind, placebo-controlled, and randomized study demonstrated that rotigotin patch can well manage both motor function and sleep problems in patients with PD with motor dysfunction, when waking up in the morning.[70] Additionally, other important effects of rotigotine patch on non-motor symptoms include pain, mood, and anhedonia associated with dopamine fluctuations.[71] Compared with rotigotine patch and other conventional oral dopamine agonists, impulse control disorder was reported to be less common with the use of rotigotine patch. It has been reported that the most common side effects after the application of the rotigotin patch are skin reactions in the application area and some neuropsychiatric problems.[71,72]

Subcutaneous rotigotine-polyoxazoline

We provided continuous dopaminergic stimulation by preparing a subcutaneous formulation of rotigotine with polyoxazolines.[73] *In vivo* studies using rat models with 6-hydroxydopamine lesions have shown that rotigotine-polyoxazoline slow-release conjugate relieves motor symptoms by repeated dosing and provides a long rotigotin half-life. With these promising results, a slow-release conjugate of rotigotine has FDA confirmation to enter phase 1 study (NCT02579473) with anew patients with PD.[73] Olanow et al.[74] evaluated the safety, tolerability, and pharmacokinetics of polymer-conjugated rotigotine in patients with PD with a multicentre open-label, multiple incremental, and dose-spaced cohort studies. Because of this study, it has been observed that, when the polymer-conjugated rotigotine is subcutaneously administered once a week, relatively constant plasma rotigotine levels can be achieved, which are safe and well-tolerated.

Subcutaneous apomorphine

Subcutaneous apomorphine has been developed to manage unpredictable and predictable "OFF" periods, in patients with PD well. The subcutaneous apomorphine has been developed in two different formulations. These are intermittent injection of apomorphine and a continuous infusion of apomorphine with a removable infusion pump without surgery. It is specified that it

is a very suitable formulation to prevent delayed or failed "ON" situations caused by GE and L-DOPA absorption problems and to alleviate early dystonia or akinesia quickly and safely. It has been reported that a consistent antiparkinsonian response with subcutaneous apomorphine was obtained and no significant circadian changes were observed during this response. The effect of subcutaneous apomorphine injection on "ON" time was evaluated by a multicentre and open-label phase IV study in patients with PD with morning akinesia. In this study, firstly, the normal morning dose of oral L-DOPA was applied to the patients and "ON" times were recorded. Then, "ON" times of the patients were recorded again for a week using apomorphine injection instead of oral L-DOPA. Because of the study, it was observed that apomorphine injection shortened 37 min the patients' become "ON" status by compared to oral L-DOPA. With several open-label clinical trials, apomorphine infusion significantly reduced OFF time by up to 85% compared with baseline and increase ON time by an average of 5.5 h daily in patients with PD.[75,76]

Inhaled apomorphine (VR040)

In PD, it has been observed that "OFF" periods can be managed with subcutaneous apomorphine, but some patients may experience difficulty in application because it requires the injection. For this reason, it is thought that inhaled apomorphine may be useful. To determine optimal efficacy, safety, and tolerability for inhaled apomorphine in patients with PD, randomized, double-blind, active, and placebo parallel-group, and increased dose titration studies were conducted in 16 centers in 3 countries. Because of this study, the meantime to "ON" in 33 patients in the OFF period was found to be 8.1 min for inhaled apomorphine and 13.1 min for placebo. Additionally, the proportion of those who became "open" within 40 min in patients who received inhaled apomorphine and placebo (except "partially open") was found to be 60.0% and 26.7%, respectively. In the double-blind phase 2 study, tolerability, safety, and effectiveness of VR040 were evaluated. It was reported that development of a UPDRS III in 47 patients was 26.8 points for inhaled apomorphine and 14.9 for placebo.[77,78]

Sublingual apomorphine (APL-130277)

APL-130277 is a film strip in clinical development that is investigated for treating OFF periods. It consists of a thin bilayered film designed to improve apomorphine delivery, while optimizing tissue compatibility and film disintegration. The first layer consists of apomorphine and is designed to provide stability, rapid drug diffusion and enhanced bioavailability. The second layer is a buffer layer that is designed to increase drug permeability and neutralize acid formation following drug absorption. As a result, it is designed as a "turning ON" medication to acutely manage OFF episodes by rapidly delivering apomorphine from the oral cavity without any mucosal irritation. Hauser et al.[79] conducted a phase 2, open-label, proof-of-concept study to assess tolerability, safety, and efficacy, and to determine the effective doses.

Buccal selegiline (Zydis™ ZELAPAR)

Non-oral alternative formulations have been explored because of the low oral bioavailability of selegiline, high rate of first-pass effects, and conversion to undesired metabolites in the liver. One of these factors is the tablet formulation prepared for application to buccal mucosa the Zydis™ technology.[80] Because of pharmacokinetic studies, Zydis™ selegiline can inhibit MAO-B at one-eighth of the traditional oral dose and reduce amphetamine metabolites by 80-90%. Because of phase 4 studies, it was seen that ZELAPAR was preferred by patients because it was well tolerated and provides ease of use.[25,81] Waters et al.[81] evaluated the safety and efficacy of zydis selegiline in patients with PD with motor fluctuations during L-DOPA therapy with a short-term clinical study. Because of the study, it was seen that an orodispersible tablet of selegiline as an additional treatment to L-DOPA in patients with PD with motor fluctuation problems was effective and safe.

CONCLUSION

Current therapy options for PD remain focused on the symptomatic improvement of motor features related predominantly to the loss of dopaminergic neurons in *substantia nigra*, but do not address the root cause of the disease. Improvements in trial design must evaluate candidate drugs more appropriately, perhaps with the introduction of validated clinical markers. Physicians need practical guidance both to help patients make a judgment on what drug to use and when to initiate it. This remains very much an individual decision and will need to take account of many factors, including the patient's age and co-morbidity and the physician's own interpretation of the data available and the information presented here. Oral dopaminergic treatments were mainly focused on the management of PD symptoms. However, it has been thought and investigated that GI problems in patients with PD can significantly affect the effectiveness of oral treatments. As a result, it has been observed that GI problems such as dysphagia, delayed GE, SIBO, and changes in colon motility complicate oral treatment in PD and cause delayed "in" or early morning "OFF" fluctuations in patients. For this reason, non-oral drug delivery systems have been studied to manage PD symptoms effectively.

We seek to bring further clarity to the non-oral treatment options for patients at different stages of PD. The therapies included in this review have all been shown to result in significant improvements of both motor and non-motor symptoms, but each therapy also has many characteristic advantages and drawbacks that need to be matched with the patient's symptomatology.

The costs related to all non-oral drug delivery systems are significant, and further cost reductions are required to increase access to these therapies. Moreover, there is a need for further development of the non-oral continuous drug delivery techniques-both to increase their ease of use and to reduce the relatively frequent device-related adverse effects. In addition to changing the existing drug administration systems,

new methods of administration are required by examining the current studies.

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Ethics

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Authorship Contributions

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