Expert Opinion

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Advances in the delivery of treatments for Parkinson's disease

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Innovative drug delivery in Parkinson's disease (PD) has the potential to reduce or avoid many side effects of current treatment, such as wearing-off type fluctuations, dyskinesia, on-off phenomena or bouts of motor freezing. The traditional orally administered formulations of L-dihydroxyphenylalanine combined with a peripheral aromatic acid decarboxylase inhibitor remain the mainstay of treatments for PD. However, such combination therapies have been further formulated to extend their duration of action by including a catechol-*O*-methyltransferase inhibitor. Preventing the breakdown of dopamine has also been achieved by monoamine oxidase-B inhibition; this approach now having been formulated for sublingual use (Zelapar®, Valeant Pharmaceuticals). An alternative approach bypasses the oral route of administration and instead relies on continuous duodenal infusion (Duodopa®, Solvay, NeoPharma AB) for better therapeutic effect. The clinical use of dopamine agonists as antiparkinsonian drugs now incorporates a variety of delivery techniques. For example, apomorphine, which relies on parenteral administration for maximum bioavailability, may be delivered via rectal, intranasal, sublingual and subcutaneous (e.g., Apokyn®, Mylan Bertek) routes. Meanwhile, rotigotine and lisuride have both been formulated for delivery via skin patches. Finally, the authors examine more experimental delivery techniques, including the delivery of genes via viral vectors or liposomes, intracranial transplant of a variety of cells and of L-dihydroxyphenylalanine by prodrug-dispensing liposomes or pulmonary delivery (AIR®, Alkermes). The advent and application of these varied technologies will help encourage patient-specific means of treatment for PD.

Keywords: L-DOPA, levodopa, MPTP, RPE, selegiline

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1. Introduction

Parkinson's disease (PD) is classically described as an unrelenting and irreversible degeneration of the dopaminergic cells of the substantia nigra pars compacta, leading to a loss of the neurotransmitter dopamine within the striatum [1]. The resulting expression of symptoms during the later stages of cell loss includes the well-known triad of rigidity, bradykinesia and resting tremor. Although it is now appreciated that PD is a more complex disorder involving pathology in addition to that observed in the nigrostriatal pathway [2], most therapies address the primary issue of the replacement/enhancement of dopamine.

2. Opportunities for novel means of drug delivery in Parkinson's disease: reducing motor complications

The 1960s heralded the dawn of the first truly successful therapy for PD. The discovery that treating patients with the precursor to dopamine, L-dihydroxyphenylalanine (L-DOPA) could alleviate symptoms [3] was a huge leap forward. Currently

available formulations of L-DOPA (e.g., Sinemet®, Merck; Madopar®, Roche) contain L-DOPA combined with a peripheral aromatic acid decarboxylase inhibitor to decrease metabolism of L-DOPA, thus enhancing increases in brain dopamine and reducing peripheral side effects such as nausea. However, following the introduction of L-DOPA, it soon became apparent that these treatments were associated with the development of many debilitating side effects. These include motor complications such as fluctuations in motor response and the onset of abnormal involuntary movements.

Motor fluctuations may take the form of a predictable decrease in the duration of action following L-DOPA administration, called 'wearing off', and a patient may require more frequent doses of L-DOPA than at earlier stages of the disease to obtain consistent relief of symptoms. Sometimes this may occur suddenly and unpredictably. In these instances patients may benefit from the delivery of a fast-acting therapeutic to restore mobility.

Abnormal involuntary movements may also occur secondary to chronic dopamine replacement therapy; L-DOPA-induced dyskinesia (LID) [4]. Furthermore, patients can switch from an 'on' and mobile state, often associated with LID, to being stiff and immobile or 'off'; this is known as 'on-off' motor fluctuations. In such situations, the benefit of therapy is often, at best, marginal. As will be discussed below, the mechanism of these side effects are probably central and due to intermittent stimulation of dopamine receptors, thus the delivery of drugs in a way that reduces the expression, or attenuates the evolution of motor complications, would be extremely valuable.

In addition, PD patients may experience a lack of response to L-DOPA due to poor L-DOPA absorption. The compund crosses the wall of the small intestine and the blood–brain barrier via a saturable carrier-mediated transporter. Competition for this transporter between dietary amino acids and L-DOPA can result in delayed switching on or failure of a dose of L-DOPA to have any benefit [5]. Other factors that affect L-DOPA absorption include slow or erratic gastric emptying, which may occur secondary to concurrently used anticholinergics and food [6], as well as age and PD itself. All of these factors combined can result in an important contribution of peripheral pharmacokinetics to the chance of erratic and unpredictable responses to L-DOPA. Thus, the delivery of drugs in a way that bypasses gastrointestinal factors may reduce variability of L-DOPA delivery to the brain and thus improve antiparkinsonian efficacy and reduce motor fluctuations.

A critical need in the development of novel treatments for PD is to provide the most efficacious relief of parkinsonian symptoms while preventing, or at least reducing, the incidence of side effects, particularly motor complications such as fluctuations or LID. The challenges presented to the development of better treatments are how to best preserve the, so far, unmatched ability of L-DOPA to alleviate symptoms without evoking LID and other motor complications, or to find an alternative therapy (e.g., a dopamine receptor agonist, non-dopaminergic drug, surgical intervention, gene therapy, or a combination of the above) that may be similarly efficacious to L-DOPA but not share its complications. Given that L-DOPA remains the gold standard in the symptomatic treatment of PD, an understanding of why existing L-DOPA therapy can predispose to side effects is desirable and highlights how delivery could be controlled to provide better therapy.

3. Mechanisms of motor complications in Parkinson's disease

Although not yet fully understood, much progress has been made towards a better understanding of the pathophysiology of L-DOPA-induced motor complications in PD [7-9]. Current concepts suggest that pulsatile stimulation of dopamine receptors within the parkinsonian brain, due to a combination of progressive nigrostriatal neurodegeneration, peripheral pharmacokinetics and central pharmacodynamics of L-DOPA, underlies motor fluctuations [10-13].

Loss of dopaminergic neurons is a key factor in the development of motor complications. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned, dopamine-denervated primates exhibit many of the cardinal symptoms and biochemical hallmarks of PD. Animals with full lesions, representative of advanced PD, have extensive dopamine depletion and hunched and akinetic postures [14]. LID is readily developed by such animals, sometimes becoming apparent with as little as once- or twice-daily oral administration of a therapeutically relevant dose of L-DOPA over the course of a few days. Monkeys with an intact dopamine system are in fact capable of developing LID in response to chronic L-DOPA administration [15]. However, they require extended periods of treatment or much higher doses in order to elicit the effect. Therefore, the more advanced the disease state, the greater the extent of dopamine denervation and the greater the chance that dopamine replacement therapy will result in unwanted side effects. L-DOPA more readily induces LID following the loss of dopaminergic terminals because it is more likely to lead to intermittent stimulation of dopamine receptors. Thus, as the degeneration of dopamine-containing cells advances during PD, the remaining neurons are progressively less able to provide physiological, continuous dopamine release as required for tonic stimulation of receptors. Although dopamine agonists can also provoke a dyskinetic response in MPTP primates, compounds with a longer duration of action can provide more tonic dopamine receptor stimulation and consequently have less propensity to cause dyskinesia. Accordingly, dopamine-depleted animals in which either L-DOPA or a dopamine agonist are administered via constant infusion, compared with acute oral or parenteral administration, show greatly reduced levels of drug-induced dyskinesia (e.g., [10]).

Although it is likely that continuous dopamine receptor stimulation is desirable, there are other factors that appear to be important in predicting the onset of motor complications. The relative affinity of the drug for each of the different

dopamine receptors is also an important consideration [16]. Drugs that act principally at the D2 class of receptor, such as ropinirole, pramipexole or bromocriptine, cause less dyskinesia than L-DOPA or those acting at both D1 and D2 sites [17-21]. Furthermore, apomorphine and pergolide, which activate both D1 and D2 receptors, both lead to heightened levels of motor complications following repeated treatment in MPTP-treated marmosets. Indeed, this occurs in spite of the half-life of pergolide (21 h) being significantly longer than that of apomorphine (45 min) [22].

4. Traditional means of extending the value of dopamine replacement therapy

Controlled release formulations of L-DOPA have been used for some time in advanced PD in an attempt to extend the duration of action of L-DOPA. With the half-life of L-DOPA averaging only 1.3 h, formulations such as Madopar HBS (in Europe) and Sinemet CR have been shown to induce fewer fluctuations in plasma L-DOPA concentrations than standard forms of the drugs [23]. However, the bioavailability of Sinemet CR is only 71%, as compared with 99% for the standard preparation. Therefore, an average 30% increase in the dose of the L-DOPA/carbidopa combination is required to elicit the same relief of symptoms with a risk of exacerbating dyskinesia, particularly later in the day [24]. In clinical practice, switching patients between Sinemet CR and regular Sinemet does not usually give any additional advantage in terms of wearing-off problems. In addition, these preparations also typically have a longer latency to benefit, therefore, patients may experience 'delayed-on' problems; especially if doses are not overlapping (i.e., the effect wears off before the next dose).

The identification of pulsatility in L-DOPA levels as a factor contributing to the emergence of motor complications has led to the suggestion that controlled release formulations of L-DOPA may be a potential means of preventing the development of LID in early PD. Such a controlled release approach may be considered an alternative to dopamine agonists in providing an effective *de novo* therapy. It would theoretically have less propensity to provoke dyskinesia than traditional formulations of L-DOPA, although it would retain the apparently more sustained antiparkinsonian actions of L-DOPA, in comparison with agonists. However, in a more recent study [25] it appears that *de novo* controlled release L-DOPA is not associated with the development of less LID than regular L-DOPA. This is probably because even with these controlled release delivery methods there are still fluctuations sufficient to lead to pulsatile stimulation and LID.

Other pre-existing antiparkinsonian therapies that rely on the oral route of administration include many of the dopamine agonists. Table 1 describes a selection of commonly used drugs of this class. Early use of dopamine agonists can delay the use of L-DOPA therapy, which may be a critical factor in delaying the onset of motor complications [26,27]. In addition, some dopamine agonists have less potential to induce motor complications because of the long half-life, which prevents pulsatile dopamine receptor stimulation, and, in some cases, the pharmacology can also offer benefits, in terms of reducing motor complications, by avoiding D1 stimulation [17-21]. In addition, dopamine agonists bypass the peripheral pharmacokinetic problems inherent with L-DOPA [28]. However, dopamine agonists are often less effective antiparkinsonian agents than L-DOPA and eventually most patients will require L-DOPA therapy. In addition, tolerability of dopamine agonists may be a problem in elderly patients due to the risk of exacerbating behavioural or psychotic problems. The recent finding suggesting that ergot-related dopamine agonists pergolide and cabergoline may be associated with cardiac valvulopathy and pulmonary fibrosis may also limit the use of these dopamine agonists [29,30].

One method of maintaining more steady-state and long-lasting dopamine concentrations within the brain has been to inhibit catechol-*O*-methyl transferase, an enzyme responsible for both the peripheral metabolism of L-DOPA and removing dopamine from the synaptic cleft. There are currently two catechol-*O*-methyl transferase inhibitors available, tolcapone and entacapone. Tolcapone was associated with hepatotoxicity and was withdrawn in many countries, or only permitted to be used with strict monitoring controls in others. However, regulatory monitoring is currently being reviewed and tolcapone may become more readily available once again. Although randomised comparative studies have not been performed, it is a common clinical impression that tolcapone may be more efficacious than entacapone in controlling motor fluctuations [31]. This may relate to the purely peripheral effects of entacapone on the degradation of L-DOPA as compared with the additional central effects of tolcapone on dopamine metabolism [32,33].

Entacapone has so far not demonstrated any liver toxicity and is an efficacious means of enhancing central dopamine levels [34]. Entacapone is used as an adjunct therapy that reduces wearing off symptoms. When administered in several frequent daily doses, the addition of entacapone to L-DOPA decreases the daily fluctuations in plasma L-DOPA by $\leq 40\%$ [35] and extends on-time by 1 – 2 h. The short half-life of entacapone (1 h) means that each 200-mg dose has to be coadministered with L-DOPA.

Selegiline is an irreversible and selective inhibitor of monoamine oxidase type B (MAO-B). The MAO-B enzyme primarily catalyses the metabolism of dopamine in the brain. The potential for selegiline to provide neuroprotection in early PD was investigated in the Deprenyl and Tocopherol Antioxidative Therapy for Parkinson's Disease (DATATOP) studies [36-38]. However, the ability of selegiline to significantly slow disease progression compared with placebo was lost after 2 years. The symptomatic effects of selegiline were also confounding factors in these studies as selegiline-mediated inhibition of MAO-B provides a longer duration of dopamine in the synapse. Several early clinical studies demonstrated that

Table 1. Traditional drugs and delivery methods for Parkinson's disease compounds.

Active ingredient	Dosage	Trade name (manufacturer)	Formulation	Details	Development stage	Ref.
L-DOPA/ benserazide or carbidopa	L-DOPA/ benserazide or carbidopa 50/12.5 – 200/50 mg	Various, including Prolopa® and Madopar® (Roche), Sinemet® (Merck)	Oral	Basic L-DOPA formulations; capsules, tablets, soluble and controlled release formulations.	Approved/ marketed	[202,203]
Ropinirole	0.25 – 5 mg	Requip® (GlaxoSmithKline)	Oral	D2/D3 agonist	Approved/ marketed	[17,204]
Pergolide		Permax® (Eli Lilly, Amarin)	Oral	D1/D2/D3 agonist	Approved/ marketed	[107]
Pramipexole	0.125 – 1.5 mg	Mirapex® (Boehringer Ingelheim, Pfizer)	Oral	D2/D3 agonist	Approved/ marketed	[205]
Cabergoline	0.5 mg	Dostinex® (Cabaser, North America; Pharmacia, Europe)	Oral	D2/D3 agonist Long half-life, potential for once-daily administration	Approved/ marketed	[206]
Selegiline	5 mg	Eldepryl® (Somerset Pharmaceuticals), Deprenyl	Oral	Monoamine oxidase-B inhibitor	Approved/ marketed	[207]

L-DOPA: L-Dihydroxyphenylalanine.

selegiline (5 – 10 mg/day) had a mild effect on PD patients with wearing-off motor fluctuations [39,40]. However, selegiline is metabolised in the liver to produce amphetamine metabolites that have been suggested to be associated with possible increased mortality [41]. This has lead to a decline in the use of selegiline in many countries.

5. Novel antiparkinsonian therapeutics: form and delivery

Many therapies have been developed that build on the considerable experience gained from decades of clinical use of existing drugs in PD. Thus, improvements in the antiparkinsonian efficacy of L-DOPA have been achieved by reducing the pulsatility of dopamine replacement. In addition, alternative methods of delivery, such as via buccal or subcutaneous routes, enhance the efficacy of dopaminergic agents, either L-DOPA or dopamine agonists, by improving the speed of onset and increased bioavailability. These new advances are summarised in Table 2.

5.1 Enterally absorbed agents

5.1.1 Combination L-dihydroxyphenylalanine/ carbidopa/entacapone

A new formulation has been developed with L-DOPA/carbidopa and entacapone combined into a single tablet (Stalevo®; Novartis/Orion). The aim of this single tablet is to reduce the number of tablets the patient has to take. Stalevo is undergoing clinical studies as an add-on therapy for wearing-off symptoms [42,43]. In addition, the use of Stalevo as a monotherapy to prevent the onset of motor complications by delivering continuous dopaminergic stimulation is currently undergoing study. Thus, in nonhuman primates, L-DOPA/carbidopa/entacapone, if given *de novo* four times daily, is associated with the development of less LID than L-DOPA/carbidopa [44]. This finding raises the possibility that this novel formulation has the potential to be an alternative to dopamine agonists in the avoidance of the development of LID. Clinical trials to address this are currently under way. The potential advantage of Stalevo over the currently available dopamine agonists is that it will probably exhibit better efficacy in alleviating parkinsonian symptoms. However, the relatively short duration of action of L-DOPA, even with the addition of entacapone, requires the patient to take each dose of Stalevo every 3 – 4 h in order to maintain a steady level of L-DOPA; compliance with this regimen may prove difficult. Comparative studies with dopamine agonists as a monotherapy will be required to determine if Stalevo is more effective at preventing long-term motor complications.

5.1.2 Ropinirole controlled release

Ropinirole is a mixed D2/D3 agonist that is efficacious in the treatment of both early PD as a monotherapy [45,46] and as a means of delaying the onset of motor complications [19]. The potential for ropinirole to delay disease progression is currently under investigation [47]. In addition, ropinirole can be used as an adjunct to L-DOPA therapy to reduce motor complications [48,49]. The half-life of ropinirole is 5.8 h, thus requiring three doses or more per day. In practice, patients often use four or five doses for maximal benefit. To improve

duration of action, ropinirole OCR (Requip® CR, GlaxoSmithKline) controlled release formulation has been developed and is currently undergoing Phase III clinical trials. Ropinirole OCR uses SkyePharma's Geomatrix® drug delivery system, which constitutes a multi-layered tablet that controls the dissolution and absorption of the drug in the body. Thus, ropinirole OCR aims to provide consistent dopaminergic stimulation through the steady slower release of ropinirole and also to assist patient convenience and compliance by formulating it for a once-daily treatment. The relative advantage of ropinirole CR over cabergoline, which also only requires once-daily dosing is not yet known. However, the potential side-effect profiles may differ in terms of ergot-related side effects experienced with cabergoline [50-52].

5.2 Buccally absorbed drugs

5.2.1 L-dihydroxyphenylalanine, carbidopa orally disintegrating tablets (Parcopa®)

The RapiTab technology has been employed to prepare a means of delivering L-DOPA in an orally dissolving tablet with a minty taste, Parcopa® (Schwarz Pharma) [201]. The RapiTab technology is based on the DuraSolv® technology (Cima Labs). The benefits of this technology are not realised when the onset of the effects are rapid, indeed the latency of onset of antiparkinsonian actions are similar to traditional oral formulations of L-DOPA. However, the potential value of this product lies in its convenience and ease of use. They are more durable than many orally dissolving formulations and are taken without the need for drinking water. They may be of special value in patients who have difficulty swallowing in ensuring that they can easily access their medication.

5.2.2 Zydis selegiline (Zelpar®)

A new transmucosal preparation of selegiline (zydis selegiline) is now available (Valeant Pharmaceuticals). Zydis® technology from Cardinal Health constitutes a freeze-dried tablet that dissolves quickly on the tongue and, by buccal delivery, potentially offers a convenient and fast-acting route resulting in more reliable levels of selegiline [53]. However, the plasma concentration of selegiline is similar with both regular and transmucosal preparations [53]. This delivery mechanism bypasses first-pass hepatic metabolism and reduces the production of theoretically toxic, amphetamine-like metabolites. A single, double-blind, randomised, placebo-controlled trial has shown that selegiline (2.5 mg/day) significantly reduced total daily off-time in PD patients, with predictable wearing-off, by 2.2 h compared with 0.6 h for placebo. The average number of dyskinesia-free 'on-hours' for the zydis selegiline patients increased by 1.8 h [54]. The main adverse effects were dizziness, hallucinations, headache and dyskinesia; although there was no significant difference between placebo and zydis selegiline. So far, there have been no studies comparing the efficacy of regular and zydis selegiline. Although the pharmacological advantages with the zydis preparation of selegiline are minimal, ease of use may be an advantage to PD patients. The potential benefit of zydis selegiline will also need to be compared with another MAO-B inhibitor, rasagiline (Teva), recently licensed in Europe as an add-on therapy in the treatment of wearing-off in PD. Rasagiline is 10- to 15-fold more potent than selegiline and is not associated with a potential for amphetamine-like metabolites [55]. Clinical studies have shown that in PD patients with on-off fluctuations, rasagiline 0.5 mg/day and 1 mg/day reduced total daily off-time by 1.41 and 1.85 h, respectively [56]. Preclinical data also suggest a potential neuroprotective action of rasagiline [57] that may be reflected in the findings of the TVP-1012 (rasagiline) in the Early Monotherapy for Parkinson's Disease Out-Patients (TEMPO) study. This study found that early stage PD patients who commence treatment with rasagiline as an adjunctive therapy are associated with better outcome at 1 year, than those patients who delay the start of treatment [58]. Although a case is building for a neuroprotective action of rasagiline, equally plausible explanations could underlie the findings of TEMPO so far.

5.2.3 Duodopa®

As discussed above, delays in gastric emptying and protein-rich meals all slow the time to onset of L-DOPA. Particularly in advanced stages of PD, patients with swallowing difficulty may have further problems with orally administered medication. There have been several attempts at delivering L-DOPA, in various preparations, directly into the duodenum as a way of avoiding the stomach and so improving absorption [59-61]. As a potential solution to these problems, Duodopa® (Solvay, NeoPharma AB) is a novel technology combining a gel suspension of L-DOPA and carbidopa infused directly into the duodenum. The drug combination is suspended in a methylcellulose matrix, which improves L-DOPA solubility thus enabling higher than normal concentrations to be achieved. A computer-controlled pump that is worn outside the body regulates the release of the gel and this, in turn, can be programmed and monitored remotely by a clinician via an integrated mobile phone. Plasma levels of L-DOPA obtained using delivery by Duodopa have been shown to be much more constant and stable than those obtained with standard oral preparations of L-DOPA [61]. In advanced patients in whom symptoms were being treated by multiple oral antiparkinsonian drugs, open-label studies have shown an improvement in on-time with Duodopa with no exacerbation of motor complications [61,62]. Although this treatment option is a viable choice for advanced cases of PD, technical issues may limit widespread use.

5.3 Parenterally administered drugs

5.3.1 Apomorphine

Apomorphine, the mixed dopamine D1/D2 agonist, has been used extensively in Europe for many years as an antiparkinsonian agent and has recently been licensed in the US. Apomorphine is administered parenterally as it undergoes extensive first-pass metabolism and, as such, has a rapid onset of action.

Table 2. Novel delivery of Parkinson's disease compounds .

Active ingredient	Dosage	Trade name (manufacturer)	Formulation	Details	Development stage	Ref.
L-DOPA/ carbidopa/ entacapone	L-DOPA/ carbidopa 200 mg; entacapone 50/12.5, 100/25, 150/37.5 mg	Stalevo® (Novartis/Orion)	Oral	Triple formulation of L-DOPA/ carbidopa with entacapone (Comtess/Comtan). Increases on-time and evokes fewer motor complications	Approved/ marketed	[208]
L-DOPA/ carbidopa	L-DOPA/ carbidopa 20/5 mg/ml	Duodopa® (Solvay, Neopharma AB)	Duodenal infusion	Gel suspension of drug infused directly into the duodenum. Indicated for advanced patients with uncontrollable motor complications	Approved/ marketed, limited distribution	[61,62, 108,109]
L-DOPA/ carbidopa	L-DOPA/ carbidopa 100/25, 100/10, 250/25 mg	Parcopa® (Schwarz Pharma)	Oral	RapiTab® technology orally disintegrating tablets	Approved/ marketed	[110,209]
L-DOPA	-	AIR® (Alkermes)	Pulmonary	AIR® technology for the delivery of small and large molecules to the lung, allowing rapid onset of action and the potential for prolonged release	Preclinical	[90,210]
L-DOPA	-	-	Liposomes	Administration of liposomal formulation of prodrug (+)-1b ([(*O*,*O*-diacetyl)-L-DOPA-methylester]-succinyldiamide) via encapsulation in unilamellar liposomes of dimiristoylphosphatidylcholine and cholesterol	Preclinical	[89]
Selegiline	1.25 mg	Zelapar® (Valeant Pharmaceuticals)	Sublingual	Monoamine oxidase-B inhibitor Zydis technology, using a freeze-dried tablet that dissolves quickly on the tongue, can enhance drug absorption and improve patient compliance	Phase III	[111,211]
Selegiline	Unknown	(Somerset Pharmaceuticals)	Transcutaneous patch	Unknown	Unknown	[112]
Apomorphine	100 mg/day	Apokyn® (Mylan Bertek)	Subcutaneous injection	D1/D2 agonist Formulated for delivery via a metered dose injector pen. Approved for the treatment of acute parkinsonian hypomobility	Approved/ marketed	[68,212]
Apomorphine	10 mg/ml	APO-go® Pen (Britannia Pharmaceuticals)	Subcutaneous injection	D1/D2 agonist APO-go pen 10 mg/ml solution for injection	Approved/ marketed	[213]
Apomorphine	10 mg/ml	(Nastech)	Intranasal	D1/D2 agonist	Phase II	[214]
Apomorphine	10 – 30 mg	Apomorphine (Cardinal Health)	Sublingual	D1/D2 agonist Zydis technology, using a freeze-dried tablet that dissolves quickly on the tongue, can enhance drug absorption and improve patient compliance	Approved/ marketed	[215]

BDNF: Brain-derived neurotrophic factor; GAD: Glutamic acid decarboxylase; GDNF: Glial cell line-derived neurotrophic factor; L-DOPA: L-dihydroxyphenylalanine; MPTP: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; TH: Tyrosine hydroxylase.

Table 2. Novel delivery of Parkinson's disease compounds (continued).

Active ingredient	Dosage	Trade name (manufacturer)	Formulation	Details	Development stage	Ref.
Apomorphine	98 mg/rod	ProNeura™ (Titan Pharmaceuticals)	Subcutaneous implantation of nonerodable ethylene vinyl acetate rods	D1/D2 agonist An invasive experimental approach that nonetheless has demonstrated that continuous delivery of apomorphine is not associated with the development of motor complication in the MPTP-lesioned monkey	Preclinical	[10]
Rotigotine	-	Neupro® (Schwarz Pharma, Aderis)	Transcutaneous patch	D2 agonist Rotigotine transdermal system with the active ingredient rotigotine is a new dopamine receptor agonist applied once daily to the skin as a transdermal patch. Rotigotine is released continuously over 24 h	Phase III	[113,114,216]
Rotigotine	2 – 5 mg	(Schwarz Pharma, Aderis)	Intranasal	D2 agonist Rotigotine formulated as a nasal spray has entered Phase I development. Rotigotine nasal spray will be evaluated in patients with Parkinson's disease to treat acute symptoms	Phase I	
Ropinirole	-	Requip® CR (GlaxoSmithKline, SkyePharma)	Oral	D3/weak D2 agonist Geomatrix® once-daily controlled release formulation	Phase III	[217]
Lisuride	-	(Prestwick Pharmaceuticals, Schering AG)	Transcutaneous patch	D2/D1 agonist Lisuride, developed by Schering AG, is a dopamine agonist targeted for the treatment of Parkinson's disease. Problems with psychosis	Phase II	[218]
Retinal pigment cells	-	Spheramine® (Titan Pharmaceuticals, Schering AG)	Striatal implant	Human retinal pigment epithelial cells on microcarrier beads that produce L-DOPA	Phase I/II	[93]
GDNF	-	-	Intracranial injection	Herpes simplex virus	Preclinical	[96]
GDNF	-	-	Intracranial injection	Retroviral vector/astrocytes	Preclinical	[97]
BDNF (neuron-specific enolase promoter)	-	-	Intracranial injection	Adeno-associated virus	Preclinical	[102]
GDNF	-	-	Intracranial injection	Lentiviral vector	Preclinical	[98]
GDNF	-	-	Intracranial injection	Adenoviral vector	Preclinical	[99]
GDNF	-	-	Intracranial injection	Adeno-associated virus	Preclinical	[100]
GAD	-	-	Intracranial injection	Adeno-associated virus	Phase I/IIa	[104]

BDNF: Brain-derived neurotrophic factor; GAD: Glutamic acid decarboxylase; GDNF: Glial cell line-derived neurotrophic factor; L-DOPA: L-dihydroxyphenylalanine; MPTP: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; TH: Tyrosine hydroxylase.

Table 2. Novel delivery of Parkinson's disease compounds (continued).

Active ingredient	Dosage	Trade name (manufacturer)	Formulation	Details	Development stage	Ref.
TH/GTP cyclohydrolase	-	-	Intracranial injection	Adeno-associated virus	Preclinical	[103]
Sonic hedgehog, Gli-1	-	-	Intracranial injection	Adeno-associated virus	Preclinical	[101]
TH	-	-	Intravenous	Liposomes	Preclinical	[105,106]

BDNF: Brain-derived neurotrophic factor; GAD: Glutamic acid decarboxylase; GDNF: Glial cell line-derived neurotrophic factor; L-DOPA: L-dihydroxyphenylalanine; MPTP: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; TH: Tyrosine hydroxylase.

The rapid time to onset makes apomorphine ideal for use as an adjunctive rescue therapy in instances of acute parkinsonian hypomobility, freezing, or in instances of severe on-off fluctuations [63-65]. Although as efficacious as L-DOPA at ameliorating parkinsonian symptoms, apomorphine has a very short half-life (~ 45 min) and, as such, requires frequent administration. Patients requiring several injections daily can be converted to continuous infusion of apomorphine over 10 – 12 h. Several preparations of apomorphine are available for intermittent subcutaneous injection. Apokyn® (Mylan Bertek) and Apo-go® (Britannia Pharmaceuticals) are measured-dose injector pens that can be applied most commonly to the upper arm, thigh or abdomen and offer the patient the choice of rapid self-medication during an off-period. The main side effect of apomorphine is the development of skin nodules at the injection site. This can be minimised by rotating the injection site, ensuring strict aseptic technique; diluting the apomorphine 1:1 with normal saline; massage; or local skin ultrasound. Apomorphine is also pro-emetic, and thus 3 days prior to starting use the patient is usually given trimethobenzamide or domperidone.

Continuous subcutaneous infusions of apomorphine are an effective means of alleviating LID, partly due to continuous dopaminergic stimulation, but also because the doses of oral L-DOPA can be reduced [66-69]. Indeed, Katzenschlager *et al.* [69] tested subcutaneous apomorphine at a mean dose of 75.2 mg/day, and found a marked reduction in dyskinesia on continuous subcutaneous apomorphine therapy that was matched by a reduction in dyskinesia during subsequent challenge with L-DOPA. These findings lend weight to the concept that replacement of short-acting oral antiparkinsonian medication with a more continuous stimulation of dopamine receptor may ameliorate, to some extent, the mechanisms underlying drug-induced dyskinesia in PD, a concept termed depriming. Intravenous apomorphine has been proposed as an alternative to subcutaneous administration, but serious side effects have been encountered, including vascular thrombosis and deposition of apomorphine crystals within the cardiovascular system [70].

Other parenteral routes for apomorphine delivery have been explored to bypass the need for injections; these include intranasal [71,72], sublingual [73-77] and rectal [78,79] preparations. Of these, the sublingual route has been most expansively and successfully developed. Like that used by selegiline, Zydis technology is used to allow rapid absorption directly into the systemic circulation. In one trial, Hughes *et al.* [73] found that sublingual apomorphine (57 mg) in 10 PD patients was effective. The mean time to onset was 25 min and the mean duration of action was 118 min. One potential problem reported, as with all such routes where the site of administration cannot be infinitely varied, was the occurrence of stomatitis at higher dosages.

5.3.2 Rotigotine

Rotigotine (Neupro®, Schwarz Pharma), a fast-acting D2-like receptor selective agonist that, like the lisuride formulation described in Section 5.3.3, has been prepared as a silicone-based transdermal patch that is replaced every 24 h. Two key studies examined the efficacy, safety and incidence of side effects following the use of rotigotine patch in either early- [80] or late-stage [81] PD. In early-stage patients, who had not yet received any form of dopaminergic therapy, rotigotine (4.5 – 18 mg/day) was administered in a double-blind fashion. Over 8 – 11 weeks of treatment in this latter trial, there was no reports of desensitisation as a consequence of the constant dopamine administration. At higher doses, relief of parkinsonism, as measured by changes in Total Unified Parkinson's Disease Rating Scale (UPDRS) score, was comparable to that following administration of the dopamine agonists pramipexole and ropinirole. The principal side effects were, again, similar in type and intensity to those experienced by other early-stage PD patients on *de novo* dopamine agonist treatments and included somnolence, nausea and vomiting [80]. In late-stage patients, the potential applications for rotigotine therapy are somewhat different with parkinsonian symptoms being so severe as to require the use of L-DOPA. As such, all patients receiving rotigotine in the reported trials are 'primed' for motor complications. Having had their dose of L-DOPA titrated as low as possible, patients then receiving rotigotine had a significant improvement in their off-time compared with placebo. There was no change in the UPDRS score, suggesting that rotigotine was able to adequately compensate for the decrease in L-DOPA dosing. Most importantly, adverse

effects due to rotigotine were reported as mild and the amount of dyskinesia associated with on-time was decreased. These data would suggest that the transdermal patch represents an exciting and potentially effective complement to existing therapies. Of special interest, perhaps, in addition to any potential therapeutic benefits, is the opportunity to use this drug to test the hypothesis that continuous dopaminergic stimulation from the initiation of PD therapy will limit the development of motor complications. In the case of rotigotine, there are no published data, so far, from chronically-treated, drug-naive, MPTP-treated primates, thus making the answer to this question even more keenly anticipated. In addition to pharmacological advantages, it has also been suggested that a once-daily patch would have significant lifestyle advantages for patients. These have probably been overstated. With respect to late-stage patients, it is unlikely that a patch will dramatically reduce the number of oral medications taken per day. In earlier patients, where patch monotherapy may be a therapeutic option, lifestyle factors may actually act against the uptake of rotigotine usage. Such patients with mild symptoms may instead prefer to use orally administered agonists in preference to a patch that would not be consistent with an active lifestyle (e.g., it is not clear how swimming or showering after sporting activities may interfere with drug delivery).

5.3.3 *Lisuride patch*

Lisuride is not a novel addition to the class of dopamine agonists [82], but it should not be overlooked; indeed as a mixed D1/D2 agonist it is of a similar breed to apomorphine and as such is an excellent therapy for alleviating parkinsonian symptoms. Continuous subcutaneous infusion of lisuride as an adjunctive treatment with L-DOPA in PD patients has been applied experimentally since the late 1980s [83-85]. An improvement in motor performance was seen in most patients; however, adverse effects were common, especially psychiatric effects, leading to treatment withdrawal in most cases [86]. In fact, increased incidence of psychotic events in patients taking lisuride has to date been a serious limiting factor. The potential benefits of lisuride are hoped to be preserved in a new patch formulation under development by Prestwick and Schering AG. Eight PD patients with on-off motor complications were treated with lisuride patches in addition to their pre-existing antiparkinsonian drug regimen for up to 8 days [87]. Lisuride patch application significantly improved antiparkinsonian relief compared with baseline and only transient skin irritations in four patients were observed. A clinical trial to further assess the efficacy of lisuride patches and the incidence of dyskinesia and other motor complications is currently being conducted.

6. Future therapies and delivery technologies

Three approaches, based on liposomes, sustained release and pulmonary delivery, respectively, have recently been described preclinically and have the potential to enhance the delivery of dopamine-replacement therapy in PD. First, dopamine-containing liposomes, after stereotactic implantation in the striatum, can produce both behavioural recovery and enhanced striatal dopamine levels in a rat model of PD [88]. However, it is unlikely that the additional benefit given by such an approach will ever be significantly better than that achieved via less invasive methods of providing continuous dopamine receptor stimulation. Second, and more excitingly with respect to the development of novel therapeutics, are the findings that liposomes containing a precursor of L-DOPA, (+)-1b ([(*O*,*O*-diacetyl)-L-DOPA-methylester]-succinyldiamide), can be administered systemically, by injection, and dramatically elevate striatal extracellular dopamine levels more effectively than equimolar L-DOPA, again in a rat model of PD [89]. Such a delivery mechanism may provide an alternative to subcutaneous apomorphine in a small proportion of late-stage patients. However, it is unlikely to provide significant benefit over orally administered, or patch-delivered L-DOPA or dopamine agonists. In the MPTP primate, the ProNeura delivery system, based upon ethylene vinyl acetate rods (Titan Pharmaceuticals), has been used to deliver apomorphine in a nonpulsatile manner. Such a delivery system, when implanted subcutaneously, has demonstrated an ability to alleviate parkinsonism with a low propensity to lead the development of dyskinesia, in previously untreated animals [10]. Third, pulmonary delivery of L-DOPA using the AIR® technology (Alkermes) has demonstrated the ability to enhance the pharmacokinetics of L-DOPA, at least with respect to providing a rapid onset, cutting latency times by one-third [90]. This approach could realistically provide an alternative to apomorphine injections as a means of dealing with sudden off or freezing bouts. However, it may lead to fluctuations in dopamine receptor stimulation, at least as dramatic as those with oral L-DOPA. Instead, this would probably be employed judiciously, as rescue therapy, rather than front-line therapy.

The prospect of being able to directly replace, or stimulate regrowth indirectly of damaged and lost cells within the parkinsonian brain is highly attractive and may represent the best and most novel delivery of therapy for PD. The first strategy involves transplanting cells derived from stem cells, of various sources, that are predifferentiated to become dopamine-producing cells. These cells will ideally be capable, not only of supplementing lost dopamine but also to release that dopamine in a manner physiologically akin to that of the original tissue. In such a way, the problems associated with pulsatile and improper receptor stimulation that impair current therapeutics could be avoided. The first double-blind, placebo-controlled, randomised study of fetal tissue transplantation for the treatment of patients with advanced PD found improvements in early-onset PD in the absence of pharmacological treatment [91]. However, in more advanced, older patients, no improvement was derived from the implant despite evidence that the graft had survived. Moreover, as much as 56% of patients suffered from dyskinesia after a 12-h drug-free period [92]. It has been

hypothesised, amongst other things, that the cause of these off-state dyskinesias may relate to the specific type of dopamine neuron, and that a pure transplant of nigrostriatal neurons of the A9 nigrostriatal variety would solve this problem. However, the technical challenges associated with producing such cells are great. Given the slow rate of progress to date in controlling the phenotype of stem cells and the low yields of those few types with the desired phenotypes, it is unlikely that such issues will be resolved satisfactorily to deliver therapies within a 5- to 10-year time frame. Pharmacological means of delivering continuous dopaminergic stimulation are more viable and promising. However, an existing area of cell-based therapies that is largely overlooked and may be more likely to succeed, is one based on the transplantation of non-dopaminergic cells. Thus, our understanding of basal ganglia function in PD suggests that the inhibition of the subthalamic nucleus would have good antiparkinsonian benefit (indeed, this is a rationale underlying subthalamic deep-brain stimulation). GABAergic cells have proven much easier to produce than dopaminergic cells and this may be applicable to such a transplantation strategy.

A pragmatic approach to the problem of cell-based therapies has been to ignore some of the complex cell biology issues surrounding how best to make perfect nigrostriatal-like cells. Instead, it is envisaged that other cells could be transplanted and survive to produce and release dopamine or L-DOPA. This approach has been applied to the use of human retinal epithelial pigment cells, which produce L-DOPA [93,94]. Spheramine® technology (Titan Pharmaceuticals, Schering AG) are microcarriers that can be linked to cells, and are intended to increase the ability of the cells to which they are attached to survive in the hostile environment of the nonimmunosuppressed brain. Retinal epithelial pigment cells linked to Spheramine microcarriers were recently evaluated in advanced PD patients following unilateral stereotactic implantation. Six patients were assessed at baseline and at 6 months following transplantation, at which time their UPDRS score off-treatment had improved by 34% [95]. Interestingly, unlike the mesencephalic transplants, no off-state dyskinesias have been observed with this approach.

In addition to cell and tissue transplants, viral vector technology has progressed much in recent times and although much of the activity is in academic centres awaiting translation into therapeutics, the first clinical studies are ongoing. Recent uses of viral vectors have included means of:

- introducing growth factors, such as glial cell line-derived neurotrophic factor [96-100], sonic hedgehog [101] and brain-derived neurotrophic factor [102]
- enhancing endogenous L-DOPA synthesis (e.g., delivering tyrosine hydroxylase and GTP-cyclohydrolase) [103]
- changing the phenotype of the subthalamic nucleus from an excitatory one into an inhibitory one, glutamic acid decarboxylase [104]

In a similar way, the delivery of genes via nonviral vectors (e.g., liposomes administered intravenously) is undoubtedly an area where much excitement will be generated and hopes built in the coming years. As an example of the potential value of this approach, pegylated immunoliposome delivery of the tyrosine hydroxylase gene has already been shown to alleviate behavioural deficits in rodent models of PD [105,106].

As with stem-cell based approaches, the underlying science behind these approaches is excellent and innovative. However, it is far from clear that they represent realistic opportunities for delivering widely applicable therapies within a 5- to 10-year time frame. Furthermore, the approaches targeting the enhancement of dopaminergic function seem unlikely to provide significant benefits over pharmacological approaches to the same problem while providing significant technical disadvantages. Viral approaches, such as the delivery of growth factors or glutamic acid decarboxylase to the subthalamic nucleus, for which it has proven difficult to discover small molecule mimetics do, however, offer hope of providing otherwise inaccessible benefit.

7. Expert opinion

Advances in understanding the complications of dopamine replacement therapy have led to an appreciation of the opportunities for novel modes of drug delivery in PD. Products to meet these opportunities are already being realised. At present, these products are likely to be based around novel means of delivering drugs similar to those that have been used for many years. All these new approaches have undoubted benefits, although this may have been overstated in many instances. For example, will the use of a patch or a controlled release formulation of dopamine agonist that provides minimal extra therapeutic benefit, while reducing the daily intake of tablets from 10 to 7, really impact on the quality of life of that patient? It is likely, therefore, that there would be minimal economic benefit in terms of healthcare costs. Instead, if the substantial technical challenges can be overcome, the advent of novel cell- and gene-based approaches has great potential to impact on the therapeutic landscape in PD. However, the interaction between cell biologists, who are expert in stem cell function, and neurobiologists, expert in basal ganglia function in PD, has not been sufficient to extend these activities much beyond a dopaminocentric approach. As this is being accomplished, a small proportion of the gene and cell delivery approaches in development are being truly innovative and provide a possibility for a radically different future for PD therapeutics.

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