Expert Opinion

informa healthcare

New drug delivery strategies for improved Parkinson's disease therapy

Antonio Di Stefano[†], Piera Sozio, Antonio Iannitelli & Laura Serafina Cerasa
'G. d'Annunzio' University, School of Pharmacy, Department of Drug Sciences, Via dei Vestini 31, 66100 Chieti, Italy

Increasing interest has been addressed toward the introduction of new therapeutic approaches to obtaining continuous dopaminergic stimulation (CDS). The goal of this therapeutic strategy is to reduce the occurrence and severity of L-DOPA (LD)-associated motor fluctuations and dyskinesia, and provide good long-term safety and tolerability. CDS can be achieved by the administration of oral dopamine (DA) agonists with a long half-life, transdermal or subcutaneous delivery of DA agonists, or intestinal LD infusion. To allow higher concentrations of LD to reach the brain and to reduce peripheral side effects, the therapeutic approach provides the concomitant administration of LD, carbidopa and entacapone that have been developed in tablet form, standard LD/carbidopa, LD/benserazide, LD/entacapone, LD/tolcapone associations or long-acting controlled release formulations, LD/carbidopa and LD/benserazide. Alternatively to solid formulations, LD/carbidopa liquid forms have been developed. Furthermore, the authors examine a series of new LD codrugs and non-dopaminergic drugs for Parkinson's disease treatment, together with a variety of experimental delivery strategies including transdermal therapeutic systems, liposomes, solid lipid nanoparticles and biocompatible microparticles. This review provides an overview of progress in anti-Parkinson therapy, mainly focused on delivery strategies and codrug approach for treatment of this neurological disorder.

Keywords: anti-Parkinson, codrugs, dendrimers, nanoparticles, transdermal delivery

Expert Opin. Drug Deliv. (2009) ***6****(4):389-404*

1. Introduction

Parkinson's disease (PD) is a progressive disabling neurodegenerative movement disorder pathologically characterised by depletion of melanised dopaminergic neurons in the nigrostriatal region coupled with the presence of intracytoplasmatic proteinaceous inclusions of fibrillar α-synuclein (Lewy bodies) and a reduction of dopamine (DA) striatal availability [1]. PD is manifested clinically by bradykinesia, postural instability, rigidity and tremor, and a number of patients also suffer from anxiety, depression, autonomic disturbances and dementia. There is no cure for PD, as currently available therapies can neither arrest nor reverse the progression of the disease [2].

2. L-DOPA therapy

Several drugs that boost the levels of DA or mimic its effects are available for treating PD, but none has surpassed the clinical efficacy of its biological precursor L-DOPA (LD) [3]. Since its introduction in the late 1960s, this drug, which counteracts Parkinsonian motor symptoms by restoring the nigrostriatal DA

10.1517/17425240902870405 © 2009 Informa UK Ltd ISSN 1742-5247

deficiency, still remains the key compound of pharmacotherapy to which all other therapies are compared.

2.1 Traditional LD-based therapies

LD has a short half-life (about 60 min) due to its rapid and extensive decarboxylation to DA and methylation to 3-O-methyldopa by dopa decarboxylase (DDC) and catechol-O-methyltransferase (COMT), respectively [4]. During LD treatment of early stage PD, the clinical effects of the drug last for many hours (the so called 'honeymoon period' of LD), no significant return/deterioration of symptoms occurs, and there is no dyskinesia, since the presynaptic dopaminergic neurons are still able to store the exogenous LD for its subsequent slow release into the synaptic cleft [5]. Along with the therapeutic benefits of LD, however, significant nausea and vomiting occur when DDC converts LD into DA peripherally. The discovery of peripheral LD decarboxylase inhibitors (DDCIs) in the mid-1970s made it possible to counteract these side effects, with the inhibition of DDC greatly reducing the gastrointestinal side effects and extending LD half-life to about 90 min: current LD formulations containing DDCI include LD/carbidopa, Sinemet® (Merck Sharp & Dohme, USA), LD/Benserazide, Madopar® (Roche, Switzerland). Unfortunately, while administration of LD/DDCI is useful in minimising the peripheral side effects of LD (nausea, emesis, arrhythmia and hypotension), it does not slow down the progression of the disease and the emergence of motor complications. A number of studies have suggested that these complications might be reduced by identifying a way to attenuate peaks and marked fluctuations of LD plasma levels [6-8]. A 30% reduction in daily fluctuations of plasma LD, as well as about 1 h decreased 'off time', were obtained with the concomitant administration of LD, carbidopa and entacapone, which are characterised by similar pharmacokinetic properties [9-17]. The latter, a COMT inhibitor, was developed during the 1990s to be used as an adjunct to LD/DDCI in the treatment of PD, and is currently in widespread clinical use (Comtan®, Novartis, Switzerland; Comtess®, Orion, Finland). Another such COMT inhibitor developed in the same period, tolcapone (Tasmar®, Valeant, Finland), is appropriate only in restricted indications, because of its hepatotoxicity [18,19]. With the aim to reduce the number of tablets patients have to take, a concomitant administration of LD, carbidopa and entacapone has been developed in tablet form (Stalevo®, Novartis/Orion) for the treatment of PD patients manifesting motor complications. Clinical evidences suggest that treatment with LD/DDCI and entacapone significantly increases time with less symptoms and affords better functionality [20].

In addition to standard LD/carbidopa, LD/benserazide, LD/entacapone, LD/tolcapone associations, two long-acting controlled release formulations, LD/carbidopa (Sinemet CR®, Merck Sharp & Dohme, USA) and LD/benserazide (Madopar HBS®, Roche, Switzerland), have been developed to achieve smooth plasma concentration levels. Clinical studies have compared standard and long-acting controlled release formulations in stable PD patients and those with motor fluctuations: although long-acting formulations seem to reduce the amount of 'off' time and permitted lower daily doses for control of motor complications than those required with standard formulations, conflicting results indicate that controlled release formulations had a longer lag time to peak plasma level, required higher total LD dosage intake, and failed to postpone or reduce long-term LD treatment problems [18,21-26]. As an alternative to solid formulations, LD/carbidopa liquid forms have been developed. The ingestion of small doses of LD/carbidopa in liquid form can shorten the time to reach peak concentration and thus hasten onset of the effect ameliorating the 'on' time without worsening the dyskinesia, but has no effect on plasma LD variability or motor response fluctuations [27-29].

2.2 Continuous LD delivery approach

While administration of LD/DDCI to lessen LD-induced nausea and vomiting can be addressed as described above, there remains the fact that after a good initial response, chronic LD treatment for several years can lead to a variety of motor complications that can be more disabling than the disease itself: patients experience a decrease in the duration of drug effect ('wearing-off' phenomenon) and, as the number of functioning DA neurons decreases in the central nervous system (CNS), the patient becomes more sensitive to LD plasma level fluctuations (on/off effects) [30-37]. It is thought that the most important factors in the onset of these complications are the non-physiological pulsatile stimulation of post-synaptic DA receptors by LD together with the progressive loss of DA-containing neurons and consequent alteration of DA turnover [38]. The goal of current treatment concept is to provide continuous dopaminergic stimulation (CDS) based on fractionation of LD daily dose, oral ingestion of liquid LD, and use of continuous i.v. or duodenal LD infusions [39-43]. The goal of this therapy is to reduce the occurrence and severity of LD-associated motor fluctuations and dyskinesia, and provide good long-term safety and tolerability [44]. Due to its unfavourable physicochemical properties continuous i.v. LD infusion resulted in cumbersome infusion systems that hardly meet patient's compliance. Continuous intraintestinal infusion of LD methyl ester, a more soluble LD prodrug requiring less volume of infusate, provided significant reduction in 'off' time and dyskinesia in comparison to administration of standard oral LD formulation over prolonged periods of time, as confirmed in a placebo-controlled double-blind cross-over study [45-50]. Micronised LD/carbidopa (20 mg/5 mg per mL) suspensions utilising a methylcellulose gel (Duodopa®, Solvay Belgium) demonstrated sufficient physical and chemical stability for continuous long-term enteric (duodenal/jejunal) delivery via a portable pump [51-53]. While clinical evidence indicates that duodenal infusions of very low doses of drug ameliorate plasma LD fluctuations and dyskinesia, yielding a satisfactory therapeutic

Table 1. Traditional and innovative LD-based therapies.

Drug	Dosage	Trade name (manufacturer)	Details	Ref.
LD/benserazide	100/25 mg	Madopar (Roche)	Oral Capsules	
LD/benserazide	200/50 mg	Madopar (Roche)	Oral Breakable tablets	
LD/benserazide	100/25 mg	Madopar HBS (Roche)	Oral Controlled release formulation Tablets	
LD/benserazide	100/25 mg	Madopar (Roche)	Oral Tablets dispersible	
LD/carbidopa	100/25 mg 100/10 mg 250/25 mg	Sinemet (Merck)	Oral Tablets	
LD/carbidopa	100/25 mg 200/50 mg	Sinemet CR (Merck)	Oral Controlled release formulation Tablets	
LD/carbidopa	20 mg/5 mL	Duodopa (Solvay, Neopharma AB)	Suspension of micronised LD/carbidopa in a microcrystalline methylcellulose gel for enteral delivery. Indicated for patients affected by PD with highly fluctuating motor function. Duodenal infusion.	[51]
LD/carbidopa	100/25 mg 100/10 mg 250/25 mg	Parcopa (Schwarz Pharma)	Orally disintegrating tablets based on RapiTab® technology to deliver the drugs without the need for water. Oral disintegrating tablets	[175]
LD/carbidopa/ entacapone	50/12.5/200 mg 100/25/200 mg 150/37.5/200 mg 200/50/200 mg	Stalevo (Orion/Novartis)	Combination of LD, carbidopa and entacapone in an unique tablet providing a better patient compliance and a reduction of motor complications. Oral film coated tablets	[176]
LD methylester/ carbidopa	125/12.5 mg 100/25 mg	V1512 (Vernalis)	Formulation of water soluble LD prodrug (LD methylester) and Carbidopa in effervescent tablets. LD methylester is less susceptible to impaired gut motility and quickly pass through to the small intestine assisted by gravity. Oral effervescent tablets	[177,178]
Levodopa	0.1/0.25/0.50 g	Dopar (Merck)	Oral tablets	
LD methyl ester HCl	1 g of granulate = 717.71 mg LD methyl ester HCl	Levomet (Chiesi Farmaceutici)	Water soluble prodrug of LD Oral granulate	
LD dimeric prodrugs	–		LD prodrugs encapsulated in unilamellar liposomes of DMPC and CHL.	[161-163]
LD dendrimers	–		LD dendritic prodrugs.	[167]
LD alkyl esters			Water soluble alkyl esters of LD. Intranasal.	[173]
LD/bioactive lipid	–	AMR103 (Amarin)	Single chemical entity from LD conjugation to a bioactive lipid (Targeted lipid transport technology). Preclinical study.	[179]
LD	–	AIR (Alkermes)	AIR technology for the drug delivery to the lung. Pulmonary. Preclinical study.	[180]

Table 2. Traditional drugs and novel delivery systems for the treatment of PD.

Drug	Dosage	Trade name (manufacturer)	Formulation	Details	Ref.
COMT inhibitors					
Tolcapone	100/200 mg	Tasmar (Valeant Pharmaceuticals)	Oral film-coated tablets	Potential hepatotoxicity	[181]
Entacapone	200 mg	Comtan/Comtess (Novartis/Orion)	Oral film-coated tablets		[182]
MAO-B inhibitors					
Selegiline	5 mg	Eldepryl (Somerset Pharmaceuticals)	Oral capsules		[183]
Selegiline	1.25 mg	Zelapar (Valeant Pharmaceuticals)	Sublingual disintegrating tablets	Freeze-dried tablets (Zydis® technology) for buccal delivery of selegiline hydrochloride. Once placed on the tongue, tablet dissolves in seconds without the need for water. The formulation allows lower levels of selegiline byproducts, once a day administration and improved patient compliance.	[184]
Rasagiline	0.5 – 1 mg	Azilect (Teva Pharmaceuticals)	Oral tablets		[185]
Safinamide		(Merck Serono)		Add-on therapy in subject with early idiopathic PD. Phase III	[186]
Ergoline DA receptor agonists					
Bromocriptine	2.5 mg	Parlodel (Novartis)	Oral snap tabs		
Bromocriptine	5 mg	Parlodel (Novartis)	Oral capsules		
Bromocriptine	–			Bromocriptine encapsulated in solid lipid nanoparticles of tristearin/tricaprin.	[164]
Pergolide	0.05/0.25/1 mg	Permax (Elililly/Amarin)	Oral tablets		
Cabergoline	1 – 2 mg	Cabaser (Pharnacia & Upjohn)	Oral tablets		
Lisuride	0.2/0.5/1 mg	Dopergin (Schering)	Oral tablets		
Lisuride	2.5 µg/h (10 cm^2) 5 µg/h (20 cm^2)	Nenad TDS (Axxonis)	Transdermal patches	Lisuride Transdermal Delivery System (TDS) available as 10 and 20 cm^2 patches provide CDS through stable plasma concentrations and are indicated as add-on therapy for PD. Phase III	[187]
Lisuride	–	Nenad sc (Axxonis)	Subcutaneous powder for solution for subcutaneous infusion	Continuous subcutaneous infusion of Lisuride delivered by a programmable mini pump intended to treat late-stage patients when standard combination therapy with LD and DA agonists proves no longer effective. Phase III	[187]

Table 2. Traditional drugs and novel delivery systems for the treatment of PD (continued).

Drug	Dosage	Trade name (manufacturer)	Formulation	Details	Ref.
Di-hidroergocriptina	5 mg	Daverium (Marvecs Pharma)	Oral capsules		
Di-hidroergocriptine	10 mg	Daverium (Marvecs Pharma)	Oral tablets		
Non-ergoline dopamine receptor agonists					
Pramipexole	0.125/0.25/0.5 1/1.5 mg	Mirapex (Boehringer Ingelheim Pharmaceuticals)	Oral tablets		[188]
Ropinirole	0.25/0.5/1/2/3/4/5 mg	Requip (GlaxoSmithkline)	Oral tablets		[189]
Ropinirole	2/4/8 mg	Requip XL (GlaxoSmithkline)	Oral extended-release tablets	Three-layered tablet with a central slow release containing ropinirole core and two outer layers controlling the drug release. The formulation allows once daily administration and is indicated for the treatment of idiopathic PD.	[110]
Rotigotine	2 mg/24 h 4 mg/24 h 6 mg/24 h 8 mg/24 h	Neupro (Schwarz Pharma)	Transdermal patches	Silicone-based, matrix type, lipid-soluble patch designed for the continuous transdermal delivery of rotigotine. Recalled in the US on April 2008 due to rotigotine crystallisation in the patches.	[149]
Rotigotine	–	(Aderis Pharmac. Schwarz Pharma)	Nasal spray	Rotigotine formulated as a nasal spray for the acute treatment of off symptoms in subjects with advanced stage idiopathic PD. Phase II	[190]
Apomorphine	10 mg/mL	Apokyn (Vernalis Pharmaceuticals)	Subcutaneous injection	Apomorphine hydrochloride formulation for the subcutaneous injection of the drug via a metered dose pen. Indicated for the treatment of off episodes in patients with advanced PD.	[96]
Apomorphine	10 mg/mL	Apo-go Pen (Britannia Pharmaceuticals)	Subcutaneous injection	Apomorphine solution available in the form of a pre-filled multiple dose pen device for intermittent subcutaneous injections.	[97]
Apomorphine	5 mg/mL	Apo-go PFS (Britannia Pharmaceuticals)	Continuous infusion	Apomorphine solution available in the form of pre-filled syringe (PFS) for continuous infusion achieved by means of a portable pump (Crono Apo-go).	[97]
Apomorphine	10 mg/mL	Apo-go Ampoules (Britannia Pharmaceuticals)	Subcutaneous injection	Continuous infusion by means of a portable pump is achieved by mixing a diluted solution manually using APO-go drawn from an ampoule.	
Apomorphine	5 mg/mL	Apo-go PFS (BritanniaPharmaceuticals)	Continuous infusion	Apomorphine solution available in the form of pre-filled syringe (PFS) for continuous infusion achieved by means of a portable pump (Crono Apo-go).	[97]

Table 2. Traditional drugs and novel delivery systems for the treatment of PD (continued).

Drug	Dosage	Trade name (manufacturer)	Formulation	Details	Ref.
Apomorphine	10 mg/mL	Apo-go Ampoules (BritanniaPharmaceuticals)	Subcutaneous injection	Continuous infusion by means of a portable pump is achieved by mixing a diluted solution manually using APO-go drawn from an ampoule.	[97]
Apomorphine	-	Apomorphine nasal (Britannia Pharmaceuticals)	Nasal Powder	Apomorphine powder formulation (Lyonase technology) for nasal delivery of the drug. Results from phase II clinical trials showed that the nasal powder formulation had a clinical effect equivalent to subcutaneous apomorphine. Phase III	[191]
Apomorphine	-	Apomorphine sublingual (AmarinCorporation)	Sublingual	Sublingual formulation of apomorphine for the treatment of off episodes in patients with advanced Parkinson's disease. Phase I	[192]
Apomorphine	-	VR040 (Vectura Group plc)	Pulmonary Dry powder	Formulation of apomorphine hydrochloride as dry powder for pulmonary administration via Aspirair® powder inhaler. Phase II	[105]
NMDA receptor antagonist					
Amantadine	100 mg	Symmetrel (Endo Pharmac.)	Oral tablets		[193]
Amantadine	50 mg/5 mL	Symmetrel (Endo Pharmac.)	Oral syrup		[193]
Anticholinergics					
Biperiden	2 mg	Akineton (Par Pharmaceutical)	Oral tablets		
Biperiden	4 mg	Akineton (Par Pharmaceutical)	Oral controlled release tablets		
Biperiden	2.3 mg/1 mL	Akineton (Par Pharmaceutical)	Oral solution		
Biperiden	5 mg/1 mL	Akineton (Par Pharmaceutical)	Parenteral solution injection		
Trihexyphenidyl	2 mg	Artane (Wyethlederle)	Oral tablets		
Trihexyphenidyl	2 mg/5 mL	Artane (Wyethlederle)	Oral elixir		
Trihexyphenidyl	5 mg	Artane Retard (Wyethlederle)	Oral prolonged release capsules		
Metixene	5 mg	Tremaril (Lpbist.Farmaceutico)	Oral tablets		
Benztropine	0.5/1/2 mg	Cogentin (Par Pharmaceutical)	Oral tablets		
Orphenadrine	50 mg	Disipal (Yamanouchi Pharma)	Oral tablets		
Orphenadrine	40 mg/2 mL	Disipal vials (Yamanouchi Pharma)	Parenteral		
Bornaprina	4 mg	Sormodren (Teofarma)	Oral tablets		

window in advanced PD patients, this delivery method has obvious disadvantages, as it requires surgical placement of visible percutaneous endoscopic gastrostomy and demands chronic post-operative maintenance [54-57]. In addition to i.v. and enteric infusion, many other administration routes have been considered as a way to provide continuous delivery of LD to the striatum: these enclose transdermal patches [58], transdermal iontophoretic delivery of zwitterionic LD [59] and subcutaneous implantation of polymeric systems releasing LD [60], but to date none of these approaches has been tested in PD patients.

3. LD and DA prodrugs

Intravenous administration of LD was found to increase its plasma levels and to improve its pharmacokinetic profile, reducing the frequency of motor fluctuation with significant improvement in mobility [61]. Furthermore, i.v. co-administration of LD with carbidopa significantly increased the plasma LD half-life, and the area under the plasma LD concentration (AUC) versus time profile [62]. Since i.v. infusion is inconvenient for routine clinical use, several approaches have been attempted to enhance LD bioavailability and minimise its side effects, but it has not been easy to produce a controlled release LD preparation that maintains adequate plasma levels more effectively [63-66]. For this reason, efforts have been made to ameliorate the dissolution, absorption and metabolism problems of LD, with considerable attention devoted to the production of prodrugs with better pharmacological and pharmacokinetic properties than LD.

In efforts to resolve dissolution and absorption problems of LD, several derivatives have been studied with the aim of enhancing LD chemical stability and water or lipid solubility, and diminishing its susceptibility to enzymatic degradation. In order to address the metabolism problems of LD and improve bioavailability, the prodrug approach appears to be quite promising [67-74]. For example, LD has been modified to yield two esters that are highly soluble prodrugs, a methyl (Levomet®, Chiesi Pharmaceuticals, Italy) or an ethyl ester (Etilevodopa, TV-1203, Teva Pharmaceutical, Israel) [75]. The ethyl ester, which is currently in Phase III clinical trials, could be given subcutaneously or intramuscularly to effect rapid reversal of akinesia and rigidity; the drug has been well tolerated with only minor and negligible side effects [76]. Similarly, in recent years a codrug approach has been used for LD delivery to the CNS. In particular the 'mutual prodrug' strategies offer improved delivery when it is desirable to have two drugs reach a site simultaneously. The dual acting codrugs are absorbed well and can release the parent drugs at the desired site of action with improved delivery properties [77-80]. Several dual acting codrugs, in which LD and DA are linked covalently to antioxidant molecules, induce sustained release of drug in rat striatum and seem to protect against the oxidative stress deriving from auto-oxidation of DA. These multifunctional codrugs, obtained by joining LD with (R)-α-lipoic acid (LA) and glutathione (GSH), were synthesised to overcome the pro-oxidant effect associated with LD therapy. Treatment with LD-sulphur-containing antioxidant codrugs seems to provide a new therapeutic strategy for PD by improving the dissolution profile, gastrointestinal absorption, nigrostriatal bioavailability and metabolism problems of LD [81,82].

4. DA receptor agonists

The beneficial effects of LD for the treatment of PD have stimulated much research in the design of DA receptor agonists with potential clinical use. DA receptor agonists can be divided into two major classes: the ergot derivatives, such as bromocriptine (BK), pergolide, lisuride and cabergoline, and the non-ergot derivatives, such as ropinirole, pramipexole, apomorphine, rotigotine and piribedil. Among these, apomorphine has been formulated and licensed for subcutaneous administration and ropinirole is available as immediate and controlled release tablets, and therefore will be discussed in more detail below; whereas lisuride and rotigotine, formulated and licensed as transdermal therapeutic systems (TTS), will be discussed in the pertinent paragraph. DA agonists may be used alone to delay the need for LD, or may be used with LD to increase their effectiveness. Some studies have suggested that these agents may be neuroprotective [83-86]. The adverse effects of DA agonists are similar to those experienced with LD, furthermore some side effects are thought to be shared among all DA agonists, such as excessive somnolence, cardiac valvulopathy and repetitive behaviour, while others could be considered class-specific, as reported by Jain and Water [87]. In particular all ergots are associated with rare episodes of pulmonary and retroperitoneal fibrosis, peripheral vascular effects, as well as leg swelling [88].

4.1 Apomorphine

Apomorphine is a short-acting non-ergoline DA agonist that exerts its anti-Parkinsonian effect by direct stimulation of striatal pre-synaptic and post-synaptic DA D_1 and D_2 receptors [89,90]. Depending on the parenteral administration route, its plasma half-life is approximately 40 min, with a range of 30 – 60 min. Due to extensive apomorphine inactivation during hepatic first-pass metabolism, many routes of administration have been explored, but currently only subcutaneous administration is used in clinical practice [91]. Although it is associated with a high frequency of nausea, orthostatic hypotension, yawning and drowsiness, apomorphine is considered a 'rapid rescue' agent for the management of motor fluctuations, especially for those patients who experience a few short-lasting, disabling 'off' periods each day. Moreover, apomorphine can readily improve early morning hypomobility, enabling patients to perform ordinary tasks such as dressing, bathing and eating [92-95]. Apomorphine is useful for the acute and long-term treatment of 'off' episodes because of its rapid onset of action (within 5 – 15 min) following subcutaneous injection via a specially designed syringe (a multi-dose

injector pen) in the abdomen, thigh or upper arm (Apokyn®, Mylan Bertek Pharmaceuticals; APO-go®, Britannia Pharmaceuticals, UK). Since the clinical effect of one single dose lasts approximately 40 – 90 min, therapeutic strategy should combine co-administration of apomorphine and oral anti-Parkinson drugs soon before or during an 'off' episode, so the delayed onset of the oral medication may overlap the waning apomorphine effect [92,96-98].

Continuous subcutaneous apomorphine infusions as an add-on to LD or as a monotherapy may be an alternative for patients with advanced PD and severe motor fluctuations. Continuous subcutaneous infusions by means of a portable pump (Crono APO-go®, Britannia Pharmaceuticals, UK) are considered effective in alleviating LD-induced dyskinesia and in reducing long 'off' periods poorly controlled by conventional oral drug treatment due to more physiological CDS and because the doses of oral LD can be reduced [99-103].

Patients should receive prophylactic anti-emetic treatment (trimethobenzamide or domperidone) three days before initiating apomorphine therapy, to counteract the apomorphine-induced nausea and vomiting. Furthermore, as skin nodules develop at the injection site, patients/carers should receive instructions on the correct drug injection procedure and the importance of periodically changing the injection site [104].

As an alternative to injectable formulations, apomorphine hydrochloride dry powder have been developed for pulmonary (VR_{040}, Vectura Group plc; development stage phase II) and nasal delivery (Apomorphine nasal, Lyonase technology, Britannia Pharmaceuticals; phase III) [105,106].

4.2 Ropinirole

Ropinirole is a non-ergoline pre- and post-dopaminergic agonist highly selective for D_2-receptors, which has been approved for use in mono and combination therapy for PD. After oral administration, the bioavailability is nearly 50% and the metabolic elimination mainly hepatic [107,108]. Due to its relatively short half-life (approximately 6 h), the drug should be taken three times a day to ensure stable plasma concentrations [109]. Ropinirole has also been formulated and approved as extended release tablets (RequipXL®, GlaxoSmithKline, UK) that improve the duration of action, thus allowing once-a-day administration and hopefully facilitating good compliance. The incidence of motor complications appears to be lower with this formulation, while the adverse effects are comparable to those of other currently used dopaminergic agonists: nausea, ataxia, dizziness, somnolence, postural hypotension and fatigue [110-112].

5. Anti-cholinergics

Anti-cholinergic drugs (trihexyphenidyl, benztropine, procyclidine and orphenadrine), all specific for muscarinic receptors, act by restoring the equilibria between striatal DA and acetylcholine activity. Although anti-cholinergics are believed to be specifically effective against tremor in the early stage of tremor-predominant PD, a recent review (Cochrane Database Systems Review) does not strongly support the suggestion that these drugs have potentially better effects on tremor than on other outcome measures [113,114].

The major factor limiting the use of these drugs is their anti-cholinergic side effects: confusion, drowsiness, agitation and hallucinations, together with urinary retention, blurred vision, constipation and tachycardia are common, especially in elderly patients. Effects on cognitive function and increased susceptibility to dementia have also been documented. Furthermore, abrupt withdrawal leads to precipitation of acute Parkinsonian symptoms [115,116].

6. COMT inhibitors

COMT inhibitors, examples of which include entacapone and tolcapone, are used mainly in combination with LD. These agents do not uncommonly provoke sleep disturbances, orthostatic hypotension, dyskinesia, confusion and insomnia. Although tolcapone is efficacious in the control of motor fluctuations [117], there have been increasing concerns about its safety, in particular its potential hepatotoxicity, and thus its use has been restricted in many countries [118]. In contrast, entacapone has not been associated with changes in liver function, and provides a valuable therapeutic tool for the management of PD-related motor fluctuations [119].

7. Monoamine oxidases-B inhibitors

Since the 1970s, selective monoamine oxidases-B (MAO-B) inhibitors, which do not induce the hypertensive response to oral tyramine (the so-called 'cheese effect'), have been found to be of therapeutic benefit in PD. The central MAO-B inhibition is able to enhance striatal dopaminergic activity, thereby improving PD motor symptoms by slowing down the catabolism of DA without significantly affecting MAO-A activity [120-123].

Selective MAO-B inhibitors currently available are selegiline and rasagiline. Selegiline is a propargyl amphetamine derivative that has low bioavailability (~ 10%) and undergoes extensive first-pass hepatic metabolism to three pharmacologically active metabolites: desmethylselegiline, L-methamphetamine and L-amphetamine [124]. In an effort to improve selegiline's bioavailability, a selegiline tablet designed for oral disintegration and buccal adsorption (oral disintegrating tablet [ODT], Zelapar®, Valeant Pharmaceuticals, USA) has been formulated; by avoiding first-pass metabolism, it increases selegiline delivery and reduces amphetamine metabolite plasma concentration. Since the new formulation consists of freeze-dried tablets (Zydis® technology, USA) that disintegrate in the mouth without the need for water, they can be useful in Parkinsonian patients who have difficulty swallowing. The pre-gastric route also has the advantage of making it possible to reduce the selegiline dosage: the 10 mg conventional tablets and 1.25 mg ODTs produce similar plasma selegiline

concentrations [125-129]. Presently, selegiline is indicated as adjunctive treatment for Parkinsonian patients manifesting motor complications who are undergoing LD therapy. The adverse effects associated with selegiline ODT are dizziness and dyskinesia, hallucinations, headache and dyspepsia.

Alternatively to selegiline, rasagiline (Azilect®, Teva Pharmaceuticals, Israel) is a second generation MAO-B inhibitor that undergoes first pass metabolism to inactive aminoindan, and thus oral administration of the drug is devoid of potentially neurotoxic amphetamine metabolites [130]. Rasagiline has been demonstrated to be efficacious as monotherapy of early-stage disease and as adjunctive therapy in LD-treated patients with motor fluctuations [131-133]. Many evidences suggest that rasagiline might have an active role in slowing down the progression of PD because its molecular structure incorporating a N-propargyl-R-amidoindan ring capable of potentially neuroprotective effects [134,135]. Results from the ADAGIO study, the first large scale, randomised, double-blind, placebo controlled, delayed start study examining rasagiline potential disease-modifying effects in 1,176 patients with early, untreated Parkinson's disease, showed that patients who took rasagiline 1 mg tablets once daily upon entry into the trial demonstrated a significant improvement compared to those who initiated the drug 9 months later, and are consistent with a disease-modifying effect [136,137].

8. Other drugs

8.1 Amantadine

Amantadine, an antiviral agent, has been found to be effective in PD treatment, particularly in reducing dyskinesia through its anti-glutamate action, as noted in pharmacological studies [138]. It can promote the release of DA, prevent its re-uptake and bolster its synthesis, although its mechanism of action is still unclear and its effects are short-lived. Its CNS effects include restlessness, depression, confusion and hallucinations. In a recent work, More *et al.* proposed a new GSH-targeted prodrug in which a bioreversible bond links amantadine to GSH [78]. The new compound showed affinity for the GSH transporter to the blood–brain barrier (BBB) and has been proposed for pharmacological evaluation as an anti-Parkinson agent.

9. Delivery strategies in anti-Parkinson therapies

9.1 Transdermal therapeutic systems

An innovative delivery strategy for treating PD is a skin patch, or transdermal therapeutic system (TTS), which offers considerable advantages over parenteral or oral administration of anti-Parkinson therapy: patch use could enhance plasma concentration, reduce gastrointestinal variations and avoid first-pass metabolism, as well as simplifying the daily dosing schedule and ensuring a short plasma elimination half-life of the drug after patch removal. Furthermore, there are indications that patient compliance may be increased with TTS treatment [139].

9.1.1 Transdermal rotigotine

Rotigotine is a non-ergoline agonist of DA D_1-D_3 receptors with beneficial effects in the treatment of PD [140]. The (S)-enantiomer of rotigotine has been formulated as a new silicone-based, matrix type, lipid-soluble patch (Neupro®, Schwarz Pharma AG, Germany) and approved as monotherapy for the treatment of early-stage idiopathic PD in the US, or as an adjunct to LD across all disease stages in the EU. The three strengths available – 2, 4 and 6 mg/24 h – with a respective release surface area of 10, 20 and 30 cm^2, are designed for the continuous delivery of rotigotine over a 24 h period. This rotigotine transdermal system significantly improved 'off' time in subjects with early PD and, in combination with LD, in patients in the advanced stage of the disease. It was safe and well tolerated, showing the side effects typical of a DA receptor agonist [141-148]. Skin reactions such as erythema, pruritus and dermatitis are occasional, and should be avoided by changing the application site daily.

The rotigotine transdermal system has recently been recalled in the US due to the formation of visible snowflake-like rotigotine crystals on the patch surface that compromise the drug absorption and efficacy [149]. The manufacturer has revised the recommended storage conditions (now advising a storage temperature between 2 and 8 °C), a measure intended to reduce the occurrence of crystallisation of the active substance.

More recently, data from experimental studies on 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned animal models of PD have shed light on the potential neuroprotective effects of rotigotine [150,151].

9.1.2 Transdermal lisuride

Lisuride, a potent dopaminergic (D_1 and D_2) iso-ergoline agonist characterised by low bioavailability (10 – 20%) and short half-life after oral administration (approximately 2 h), has been available for almost 20 years for the treatment of PD in daily amounts of 1.5 – 4.5 mg divided into three doses [152,153]. Recently, Axxonis Pharma has submitted a European marketing authorisation application for lisuride parenteral forms (Nenad® from Axxonis, Germany; transdermal patch and subcutaneous infusion) developed to provide CDS and to minimise the psychiatric complications usually noticed during long-term lisuride administration [154]. The 10 and 20 cm^2 patches release 2.5 and 5.0 µg lisuride per hour, respectively, and are indicated as add-on therapy for PD. The patch was safe and well tolerated with typical adverse events (nausea, emesis, dizziness, orthostatic hypotension) of dopaminergic agents and local reversible skin reactions at the application site [155]. The lisuride formulation for subcutaneous infusion comes as a soluble powder; a programmable mini-pump delivers the drug so that stable personalised drug levels can be achieved and is indicated for the treatment of patients with advanced stage PD associated with severe motor fluctuations. Its efficacy and safety were demonstrated in several clinical studies over the last two decades, in

which subcutaneous infusion of lisuride showed significant therapeutic efficacy for 'off' and hypermobility states and a significant reduction in motor fluctuations, comparable to that achieved with apomorphine subcutaneous infusion [156-160].

9.2 Upcoming advanced drug delivery strategies and technologies

A great contribution to improving therapies for neurodegenerative diseases is expected with the application of nanotechnology to the pharmaceutical sciences. Targeted and localised delivery limiting severe side effects, such as psychiatric disturbances and dyskinesias deriving from the distribution of any anti-Parkinsonian drug in healthy tissues are key challenges in PD therapy. In recent years there has been increasing interest in developing drug delivery systems able to target pharmacologically active molecules in close proximity to their site of action. Among these, liposomes, polymeric or lipidic micro- and nanoparticles, polymeric micelles and the more recent dendrimers seem to be the most effective in providing tools to interact with biological systems at molecular level with a high degree of specificity, to provide neuroprotection and to facilitate the delivery of drugs and small molecules across the BBB.

Recently, several LD dimeric prodrugs have been encapsulated in unilamellar liposomes of dimiristoylphosphatidylcholine (DMPC) and cholesterol (CHOL), and their striatal LD and DA concentrations after i.p. administration in rats monitored by *in vivo* microdialysis, using the high performance liquid chromatography coupled with electrochemical detection (HPLC-EC) method. These formulations showed about 2.5-fold increases in basal DA levels and a sustained delivery of DA in dialysate rat striatum, suggesting that liposomal formulation significantly increases LD and DA concentrations with respect to equimolar administration of LD itself or free prodrugs [161-163].

Solid lipid nanoparticles (SLN) of tristearin/tricaprin were able to encapsulate high quantities of BK, to enhance its stability and to foster controlled BK release, thus improving the pharmacokinetic properties of the drug. Both free and BK nanostructured lipidic carriers have been assayed in 6-hydroxydopamine (6-OHDA) hemi-Parkinsonian rats; these formulations had more rapid time of onset, provided smooth plasma levels, attenuated akinesia and prolonged the half-life of the drug [164].

Dendrimers are artificial hyperbranched and monodisperse three-dimensional molecules and have defined molecular weights and host–guest entrapment properties [165]. Since dendrimers are synthesised from branched monomer units in a stepwise manner, it is possible to conduct a precise control on molecule size, shape, dimension, density, polarity, flexibility and solubility by choosing different building/branching units and surface functional groups [166]. Recently the synthesis of novel dendritic LD prodrugs (first, second and third generation) have been reported. LD has been chemically converted into a cascade structure to form a well-defined dendritic architecture with better water solubility, less sensitivity to light degradation than LD and a precise mechanism of LD release *in vitro* [167].

Nasal administration of pharmacologically active molecules enables their preferential absorption to the CNS, bypassing the limitations of the BBB because of the unique connections that the olfactory and trigeminal nerves provide between the brain and external environment. Possible mechanisms of transport of active molecules may involve axonal transport from the olfactory neurons of the olfactory epithelium to the olfactory bulb and extracellular transport routes involving bulk flow and diffusion within perineuronal channels and perivascular spaces or lymphatic channels directly connected to cerebrospinal fluid [168-172]. With the aim of overcoming the low bioavailability of oral LD formulations, several water soluble alkyl esters of LD have been synthesised as prodrug candidates for nasal administration. The butyl ester prodrug administered nasally in rats improved CNS bioavailability, compared to the same substance in an equimolar i.v. dose, without producing significant quantities of DA in the peripheral circulation [173].

LD has also been formulated in aerodynamic, biocompatible microparticles for deep pulmonary administration (Alkermes AIR), in an effort to avoid the variable bioavailability and poor pharmacokinetics of oral formulations. The pulmonary route allows the particles to deliver the active principle rapidly to the systemic circulation, avoiding the problems of erratic absorption and extensive metabolism associated with standard LD formulations. The pharmacokinetic, neurochemical and behavioural characteristics of LD administered using oral and pulmonary formulations have been evaluated in a 6-OHDA-treated rat model of PD: a more rapid time of onset and a three to fivefold dose reduction were achieved when LD was administered by the pulmonary route [174]. Unfortunately, micro- and nanosized drug delivery systems are still affected by poor stability in biological fluids, rapid enzymatic degradation and unfavourable pharmacokinetic properties. It is hoped that once the absorption, distribution, metabolism, excretion and toxicity of such systems in humans are well understood, their clinical application will no longer be limited.

10. Expert opinion

One of the great successes of neuropharmacological therapy has been the introduction of LD in PD treatment. LD, which can be considered as a prodrug of DA, still remains the most clinically effective drug for treatment of PD, despite the fact that several new therapeutic approaches have been introduced in clinical practice. Substitution therapy with LD is, however, associated with a number of acute problems. The peripheral conversion of LD by DDC to DA is responsible for the typical gastrointestinal (nausea, emesis) and cardiovascular (arrhythmia, hypotension) side effects. Currently, the main challenge in improving LD for PD treatment is to alleviate or eliminate the motor complications

caused or worsened by marked LD plasma level fluctuations. Another issue is the theoretical concern that cytotoxic metabolites generated by the drug's oxidative metabolism might accelerate neuronal degeneration and disease progression. Taken together, these problems limit the long-term value of LD therapy.

In the alternative, a large number of neurosurgical procedures for advanced PD can markedly improve motor performance, but the risk of intracranial haemorrhages and hardware complications have to be taken into consideration when weighing possible benefits and the patient's quality of life.

Unfortunately, neither current surgical therapies, nor pharmacological ones, can arrest or reverse the progression of the disease. However, there is good reason to hope that effective new treatments for PD will not be long in coming. The impressive amount of information on PD pathogenesis gained in recent years has fuelled numerous developments, while the extensive range of agents and procedures investigated offers immense potential for preventing and eventually curing this condition. These studies include efforts to develop controlled release LD formulations to alleviate the motor complications caused by LD haematic levels variability. Also, alternatives or adjuncts to LD therapy offer great potential. Novel therapeutic strategies include formulations linking dopaminergic drugs with neuroprotective agents, increasing LD striatal levels and offering sustained release of the drug without any fluctuation in brain concentration. In addition, recent strategies to increase drug delivery to the brain using microspheres, nanocapsules and BBB shuttles for carrier-mediated LD transport have proved beneficial in pharmacological animal models, increasing hopes for the development of other effective standards of care for this illness.

Acknowledgements

We thank Sheila Beatty for linguistic revision of the manuscript.

Declaration of interest

The authors state no conflict of interest and have received no payment in the preparation of this manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Abou-Sleiman PM, Muqit MMK, Wood NW, et al. Expanding insights of mitochondrial dysfunction in Parkinson's disease. Nat Rev Neurosci 2006;7:207-19
2. Singh N, Pillay V, Choonara YE. Advances in the treatment of Parkinson's disease. Prog Neurobiol 2007;81:29-44
3. LeWitt PA. Levodopa for the treatment of Parkinson's Disease. N Engl J Med 2008;359:2468-76

• **This review provides a discussion of mechanism, benefits and problems related to LD therapy from a clinical point of view.**

4. Lyytinen J, Kaakkola S, Gordin A, et al. Entacapone and selegiline with L-dopa in patients with Parkinson's disease: an interaction study. Parkinsonism Relat Disord 2000;6:215-22
5. Müller T. Dopaminergic substitution in Parkinson's Disease. Expert Opin Pharmacother 2002;2:1393-403
6. Goetz CG. New strategies with dopaminergic drugs: modified formulations of levodopa and novel agonists. Exp Neurol 1997;144:17-20
7. Gundert-Remy U, Hildebrand R, Stiehl A, et al. Intestinal absorption of levodopa in man. Eur J Clin Pharmacol 1983;25:69-72
8. Fahn S. Parkinson Study Group. Does levodopa slow or hasten the rate of progression of Parkinson's Disease? J Neurol 2005;252:37-42
9. Gordin A, Kaakkola S, Teräväinen H. Clinical advantages of COMT inhibition with entacapone - a review. J Neural Transm 2004;111:1343-63
10. Kuoppamäki M, Korpela K, Marttila R, et al. Comparison of pharmacokinetic profile of levodopa throughout the day between levodopa/carbidopa/entacapone and levodopa/carbidopa when administered four or five times daily. Eur J Clin Pharmacol 2009: published on line 20 February 2009, doi:10.1007/s00228-009-0622-y
11. Müller T, Erdmann C, Muhlack S, et al. Entacapone improves complex movement performance in patients with Parkinson's disease. J Clin Neurosci 2007;14:424-8
12. Onofrj M, Thomas A, Vingerhoets F, et al. Combining entacapone with levodopa/DDCI improves clinical status and quality of life in Parkinson's Disease (PD) patients experiencing wearing-off, regardless of the dosing frequency: results of a large multicentre open-label study. J Neural Transm 2004;111:1053-63
13. Rinne UK, Larsen JP, Siden A, et al. Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. Nomecomt Study Group. Neurology 1998;51:1309-14
14. Kurth MC, Adler CH, Hilaire MS, et al. Tolcapone improves motor function and reduces levodopa requirement in patients with Parkinson's disease experiencing motor fluctuations: a multicenter, double-blind, randomized, placebo-controlled trial. Tolcapone Fluctuator Study Group I. Neurology 1997;48:81-7
15. Baas H, Beiske AG, Ghika J, et al. Catechol-O-methyltransferase inhibition with tolcapone reduces the 'wearing off' phenomenon and levodopa requirements in fluctuating parkinsonian patients. J Neurol Neurosurg Psychiatry 1997;63:421-8
16. Parkinson Study Group. Entacapone improves motor fluctuations in levodopa-treated Parkinson's disease patients. Parkinson Study Group. Ann Neurol 1997;42:747-55
17. Nutt JG, Woodward WR, Beckner RM, et al. Effect of peripheral catechol-O-methyltransferase inhibition on the pharmacokinetics and pharmacodynamics of levodopa in parkinsonian patients. Neurology 1994;44:913-9

18. Olanow CW, Watkins PB. Tolcapone: an efficacy and safety review. Clin Neuropharmacol 2007;30:287-94
19. Olanow CW, Jankovic J. Neuroprotective therapy in Parkinson's disease and motor complications: a search for a pathogenesis-targeted, disease-modifying strategy. Mov Disord 2005;20:3-10
20. Brooks DJ. Optimizing levodopa therapy for Parkinson's disease with levodopa/carbidopa/entacapone: implications from a clinical and patient perspective. Neuropsychiatr Dis Treat 2008;4:39-47
21. Ahlskog JE, Muenter MD, Mcmanis PG. Controlled-release Sinemet (CR-4): a double-blind crossover study in patients with fluctuating Parkinson's disease. Mayo Clin Proc 1988;63:867-86
22. Cedarbaum JM, Hoey M, Kutt H, et al. Controlled-release levodopa/carbidopa. III. Sinemet CR5 treatment response fluctuations in Parkinson's disease. Clin Neuropharmacol 1988;11:168-73
23. Cedarbaum JM, Breck L, Kutt H, et al. Controlled-release levodopa/carbidopa. II. Sinemet CR4 treatment of response fluctuations in Parkinson's disease. Neurology 1987;37:1607-12
24. Dupont E, Andersen A, Boas J, et al. Sustained-release Madopar HBS compared with standard Madopar in the long-term treatment of de novo parkinsonian patients. Acta Neurol Scand 1996;93:14-20
25. Block G, Liss C, Reines S, et al. Comparison of immediate-release and controlled release carbidopa/levodopa in Parkinson's disease: a multicenter 5-year study. The CR First Study Group. Eur Neurol 1997;37:23-7
26. Koller WC, Hutton JT, Tolosa E, et al. Immediate-release and controlled-release carbidopa/levodopa in PD: a 5-year randomized multicenter study. Neurology 1999;53:1012-9
27. Pappert EJ, Goetz CG, Niederman F, et al. Liquid levodopa/carbidopa produces significant improvement in motor function without dyskinesia exacerbation. Neurology 1996;47:493-5
28. Pappert EJ, Buhrfiend C, Lipton JW, et al. Levodopa stability in solution: time course, environmental effects, and practical recommendations for clinical use. Mov Disord 1996;11:24-6
29. Metman LV, Hoff J, Mouradian MM, et al. Fluctuations in plasma levodopa and motor responses with liquid and tablet levodopa/carbidopa. Mov Disord 1994;9:463-5
30. Marsden CD. Late levodopa failure – pathophysiology and management. Basel: Editiones Roche, 1993
31. Fahn S. Adverse effects of levodopa. Carnforth: Parthenon, 1992
32. Zappia M, Annesi G, Nicoletti G, et al. Sex differences in clinical and genetic determinants of levodopa peak-dose dyskinesias in Parkinson disease: an exploratory study. Arch Neurol 2005;62:601-5
33. Olanow CW, Agid Y, Mizuno Y, et al. Levodopa in the treatment of Parkinson's disease: current controversies. Mov Disord 2004;19:997-1005
34. Dewey JRB. Management of motor complications in Parkinson's disease. Neurology 2004;62:S3-7
35. Jankovic J. Motor fluctuations and dyskinesias in Parkinson's disease: clinical manifestations. Mov Disord 2005;20:S11-6
36. Jankovic J, Stacy M. Medical management of levodopa-associated motor complications in patients with Parkinson's Disease. CNS Drugs 2007;21:677-92
37. McColl CD, Reardon KA, Shiff M, et al. Motor response to levodopa and the evolution of motor fluctuations in the first decade of treatment of Parkinson's disease. Mov Disord 2002;17:1227-34
38. Thanvi BR, Lo TCN. Long term motor complications of levodopa: clinical features, mechanisms, and management strategies. Postgrad Med J 2004;80:452-8
39. Nyholm D. Pharmacokinetic optimization in the treatment of Parkinson's disease: an update. Clin Pharmacokinet 2006;45:109-36

• **An authoritative overview of the strategies for optimization of the treatment of PD, with a focus on pharmacokinetics of LD and DA agonists.**

40. Kurth MC. Using liquid levodopa in the treatment of Parkinson's disease: a practical guide. Drugs Aging 1997;10:332-40
41. Stocchi F, Vacca L, Ruggieri S, et al. Intermittent vs continuous levodopa administration in patients with advanced Parkinson disease: a clinical and pharmacokinetic study. Arch Neurol 2005;62:905-10
42. Nilsson D, Hansson LE, Johansson K, et al. Long-term intraduodenal infusion of a water based levodopa–carbidopa dispersion in very advanced Parkinson's disease. Acta Neurol Scand 1998;97:75-83
43. Gordon M, Markhamc J, Hartlein JM, et al. Intravenous levodopa administration in humans based on a two-compartment kinetic model. J Neurosci Methods 2007;159:300-7
44. Nyholm D. The rationale for continuous dopaminergic stimulation in advanced Parkinson's disease. Parkinsonism Relat Disord 2007;13:13-7
45. Stocchi F, Vacca L, Ruggieri S, et al. Infusion of levodopa methyl ester in patients with advanced PD: a clinical and pharmacokinetic study. Arch Neurol 2005;62:905-10
46. Kurlan R, Rubin AJ, Miller C, et al. Duodenal delivery of levodopa for on-off fluctuations in parkinsonism: preliminary observations. Ann Neurol 1986;20:262-5
47. Sage JI, Trooskin S, Sonsalla PK, et al. Long-term duodenal infusion of levodopa for motor fluctuations in parkinsonism. Ann Neurol 1988;24:87-9
48. Ruggieri S, Stocchi F, Carta A, et al. Jejunal delivery of levodopa methylester. Lancet 1989;8653:45-6
49. Syed N, Murphy J, Zimmerman T, et al. Ten years' experience with enteral levodopa infusions for motor fluctuations in Parkinson's disease. Mov Disord 1998;13:336-8
50. Kurth MC, Tetrud JW, Tanner CM, et al. Double-blind, placebo-controlled, crossover study of duodenal infusion of levodopa/carbidopa in Parkinson's disease patients with 'on-off' fluctuations. Neurology 1993;43:1698-703
51. Duodopa® website. Available from: www.duodopa.com [Last accessed 6 October 2008]
52. Nyholm D, Nilsson Remahl AI, Dizdar N, et al. Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease. Neurology 2005;64:216-23
53. Antonini A, Isaias IU, Canesi M, et al. Duodenal levodopa infusion for advanced Parkinson's disease: 12-month treatment outcome. Mov Disord 2007;22:1145-9
54. Samanta J, Hauser RA. Duodenal levodopa infusion for the treatment of Parkinson's

disease. Expert Opin Pharmacother 2007;8:657-64

55. Sage JL, Mchale DM, Sonsalla P, et al. Continuous levodopa infusions to treat complex dystonia in Parkinson's disease. Neurology 1989;39:888-91
56. Nyholm D, Askmark H, Gomes-Trolin C, et al. Optimizing Levodopa pharmacokinetics: intestinal infusion versus oral sustained-release tablets. Clin Neuropharmacol 2003;26:156-63
57. Nyholm D, Lewander T, Johansson A, et al. Enteral levodopa/carbidopa infusion in advanced Parkinson disease: long-term exposure. Clin Neuropharmacol 2008;31:63-73
58. Iwase H, Sudo J, Terui J, et al. Transdermal absorption of L-dopa from a new system composed of two separate layers of L-dopa and hydrogel in rats. Drug Dev Ind Pharm 2000;26:755-9
59. Kankkunen T, Huupponen I, Lahtinen K, et al. Improved stability and release control of levodopa and metaraminol using ion exchange fibers and transdermal iontophoresis. Eur J Pharm Sci 2002;16:273-80
60. Sabel BA, Dominiak P, Haeuser W, et al. Levodopa delivery from controlled-release polymer matrix: delivery of more than 600 days in vitro and 225 days of elevated plasma levels after subcutaneous implantation in rats. J Pharmacol Exp Ther 1990;255:914-22
61. Birkmayer W, Danielcyk W, Neumayer E, et al. L-dopa level in plasma, primary condition for the kinetic effect. J Neural Transm 1973;34:133-43
62. Leppert PS, Cortese M, Fix JA. The effects of carbidopa dose and time and route of administration on systemic L-Dopa levels in rats. Pharm Res 1988;5:587-91
63. Sasahara K, Nitanai T, Habara T, et al. Dosage form design for improvement of bioavailability of levodopa IV: possible causes of low bioavailability of oral levodopa in dogs. J Pharm Sci 1981;70:730-3
64. Hutton JH, Morris JL, Gustavo CR. Treatment of chronic Parkinson's disease with controlled-release carbidopa/levodopa. Neurology 1988;45:861-4
65. Bordor N, Sloan KB, Higuchi T, et al. Improved delivery through biological membranes 4: prodrugs of L-dopa. J Med Chem 1977;20:1435-45
66. Goole J, Vanderbist F, Amighi K. Development and evaluation of new multiple-unit levodopa sustained-release floating dosage forms. Int J Pharm 2007;334:35-41
67. Wang H, Lee J, Tsai M, et al. Synthesis and pharmacological activities of a novel tripeptide mimetic dopamine prodrug. Bioorg Med Chem Lett 1995;5:2195-98
68. Marrel C, Boss G, Van De Waterbeemd H, et al. L-Dopa esters as potential prodrugs. Eur J Med Chem 1985;20:459-65
69. Cooper DR, Marrel C, Van De Waterbeemd H, et al. L-Dopa methyl ester – a candidate for chronic systemic delivery of L-Dopa in Parkinson's disease. Clin Neuropharmacol 1984;7:89-8
70. Garzon-Aburbeh A, Poupaert JH, Claesen M, et al. A lymphotropic prodrug of L-dopa: synthesis, pharmacological properties, and pharmacokinetic behavior of 1,3-dihexadecanoyl-2-[(S)-2-amino-3-(3, 4-dihydroxyphenyl)prop anoyl] propane-1,2,3-triol. J Med Chem 1986;29:687-91
71. Cooper DR, Marrel C, Van De Waterbeemd H, et al. L-dopa esters as potential prodrugs: effect on brain concentration of dopamine metabolites in reserpinized mice. J Pharm Pharmacol 1987;39:809-18
72. Cooper DR, Marrel C, Van De Waterbeemd H, et al. L-dopa esters as potential prodrugs: behavioural activity in experimental models of Parkinson's disease. J Pharm Pharmacol 1987;39:627-35
73. Ihara M, Tsuchiya Y, Sawasaki Y, et al. New potential prodrug to improve the duration of L-dopa: L-3-(3-hydroxy-4-pivaloyloxyphenyl) alanine. J Pharm Sci 1989;78:525-29
74. Cingolani GM, Di Stefano A, Mosciatti B, et al. Synthesis of L-(+)-3-(3-hydroxy-4-pivaloyloxybenzyl)-2, 5-diketomorpholine as potential prodrug of L-dopa. Bioorg Med Chem Lett 2000;10:1385-8
75. Stocchi F, Ruggieri S, Carta A, et al. Intravenous boluses and continuous infusions of L-DOPA methyl ester in fluctuating patients with Parkinson's disease. Mov Disord 1992;7:249-56
76. Djaldetti R, Melamed E. Levodopa ethylester: a novel rescue therapy for response fluctuations in Parkinson's disease. Ann Neurol 1996;39:400-4
77. Singh G, Sharma PD. Mutual prodrugs: a recent trend in prodrug design. Indian J Pharm Sci 1994;56:69-79
78. More SS, Vince R. Design, synthesis and biological evaluation of glutathione peptidomimetics as components of anti-Parkinson prodrugs. J Med Chem 2008;51:4581-8
79. Rosini M, Andrisano V, Bartolini M, et al. Multi-target-directed drug design strategy: from a dual binding site acetylcholinesterase inhibitor to a trifunctional compound against Alzheimer's disease. J Med Chem 2007;50:6446-9
80. Sozio P, Iannitelli A, Cerasa LS, et al. New L-Dopa codrugs as potential antiparkinson agents. Arch Pharm 2008;341:412-7
81. Di Stefano A, Sozio P, Cocco A, et al. L-Dopa- and Dopamine-(R)-α-Lipoic acid conjugates as multifunctional codrugs with antioxidant properties. J Med Chem 2006;49:1486-93
82. Pinnen F, Cacciatore I, Cornacchia C, et al. Synthesis and study of L-Dopa-Glutathione codrugs as new anti-Parkinson agents with free radical scavenging properties. J Med Chem 2007;50:2506-15
83. Schapira AH. Dopamine agonists and neuroprotection in Parkinson's disease. Eur J Neurol 2002;9:7-14
84. Schapira AH. Neuroprotection and dopamine agonists. Neurology 2002;58:S9-S18
85. Schapira AH. Neuroprotection in PD a role for dopamine agonists? Neurology 2003;61:34-42
86. Schapira AH, Olanow CW. Rationale for the use of dopamine agonists as neuroprotective agents in Parkinson's disease. Ann Neurol 2003;53:149-57
87. Jain S, Water CH. Controversies of dopamine agonists: somnolence, cardiac valvulopathy and repetitive behaviors. Curr Drug Ther 2007;2:17-20
88. Stocchi F, Vacca L, Onofrj M. Are there clinically significant differences between dopamine agonists. Adv Neurol 2003;91:259-66
89. Menon R, Stacy M. Apomorphine in the treatment of Parkinson's disease.

Expert Opin Pharmacother 2007;8:1941-50

90. Ul HI, Lewitt PA, Fernandez HH. Apomorphine therapy in Parkinson's disease: a review. Expert Opin Pharmacother 2007;8:2799-809
91. Neef C, van Laar T. Pharmacokinetic–pharmacodynamic relationships of apomorphine in patients with Parkinson's disease. Clin Pharmacokinet 1999;37:257-71
92. Obering CD, Chen JJ, Swope DM. Update on apomorphine for the rapid treatment of hypomobility ('Off') episodes in Parkinson's Disease. Pharmacotherapy 2006;26:840-52
93. Kolls BJ, Stacy M. Apomorphine: a rapid rescue agent for the management of motor fluctuations in advanced Parkinson Disease. Clin Neuropharmacol 2006;29:292-301
94. Pahwa R, Koller WC, Trosch RM, et al. Subcutaneous apomorphine in patients with advanced Parkinson's disease: a dose-escalation study with randomized, double-blind, placebo-controlled crossover evaluation of a single dose. J Neurol Sci 2007;258:137-43
95. Trosch RM, Silver D, Bottini PB. Intermittent subcutaneous apomorphine therapy for 'off' episodes in Parkinson's disease: a 6-month open-label study. CNS Drugs 2008;22(6):519-27

- **An investigation on the long-term efficacy and safety of apomorphine administered via subcutaneous route in advanced PD patients.**

96. Apokyn website. Available from: www.apokyn.com/
97. Apo-go website. Available from: www.apo-go.co.uk/index.htm.
98. Stacya M, Silver D. Apomorphine for the acute treatment of 'off' episodes in Parkinson's disease. Parkinsonism Relat Disord 2008;14:85-92
99. Manson AJ, Turner K, Lees AJ. Apomorphine monotherapy in the treatment of refractory motor complications of Parkinson's Disease: long-term follow-up study of 64 patients. Mov Disord 2002;17:1235-41
100. Katzenschlager R, Hughes A, Evans A, et al. Continuous subcutaneous apomorphine therapy improves dyskinesias in Parkinson's Disease: a prospective study using single-dose challenges. Mov Disord 2005;20:151-7
101. García Ruiz PJ, Sesar Ignacio Á, Ares Pensado B, et al. Efficacy of long-term continuous subcutaneous apomorphine infusion in advanced Parkinson's Disease with motor fluctuations: a multicenter study. Mov Disord 2008;23:1130-6
102. Di Rosa AE, Epifanio A, Antonini A, et al. Continuous apomorphine infusion and neuropsychiatric disorders: a controlled study in patients with advanced Parkinson's disease. Neurol Sci 2003;24:174-5
103. Morgante L, Basile G, Epifanio A, et al. Continuous apomorphine infusion (CAI) and neuropsychiatric disorders in patients with advanced Parkinson's Disease: a follow-up of two years. Arch Gerontol Geriatr 2004;9:291-6
104. Bowron A. Practical considerations in the use of apomorphine injectable. Neurology 2004;62:S32-6
105. Vectura product pipeline and product profiles. Available from: www.vectura.com/vec/products/pipeline/profiles/
106. Britannia products in developments. Available from: www.britannia-pharm.co.uk/partnerships.shtml#Apo-nasal%20PD.
107. Jost WH, Angersbach D, Rascol O. Clinical studies with ropinirole in Parkinson's disease and RLS. J Neurol 2006;253:16-21
108. Jost WH, Angersbach D. Ropinirole, a non-ergoline dopamine agonist. CNS Drug Rev 2005;11:253-72
109. Hubble J, Koller WC, Atchison P, et al. Linear pharmacokinetic behavior of ropinirole during multiple dosing in patients with Parkinson's disease. J Clin Pharmacol 2000;40:641-6
110. RequipXL website. Available from: www.requipxl.com/
111. Pahwa R, Stacy MA, Factor SA, et al. Ropinirole 24-hour prolonged release. Randomized, controlled study in advanced Parkinson disease. Neurology 2007;68:1108-15

- **Evaluation of ropinirole 24-hour prolonged release as an adjunct to LD in patients with PD and motor fluctuations.**

112. Gallagher DA, Schrag A. Impact of newer pharmacological treatments on quality of life in patients with Parkinson's disease. CNS Drugs 2008;22:563-86
113. Lees A. Alternatives to levodopa in the initial treatment of early Parkinson's disease. Drugs Aging 2005;22:731-40
114. Katzenschlager R, Sampaio C, Costa J, et al. Anticholinergics for symptomatic management of Parkinson's disease. Cochrane Database Syst Rev 2003;3:CD003735
115. Comella CL. Therapy of Parkinson's Disease. New York: Mercel Dekker Inc, 1995
116. Movement Disorders Society Evidence-Based Review. Management of Parkinson's disease: an evidence-based review. Mov Disord 2002;7:1-166
117. Rajput AH, Martin W, Saint-Hilaire MH, et al. Tolcapone improves motor function in parkinsonian patients with the wearing off phenomenon: a double blind, placebo-controlled, multicenter trial. Neurology 1997;49:1066-71
118. Assal F, Spahr L, Hadengue A, et al. Tolcapone and fulminant hepatitis. Lancet 1998;352:958
119. Schrag A. Entacapone in the treatment of Parkinson's disease. Lancet Neurol 2005;4:366-70
120. Birkmayer W, Riederer P, Youdim MBH, et al. Potentiation of the anti-akinetic effect after L-Dopa treatment by an inhibitor of MAO-B, deprenil. J Neural Transm 1975;36:303-23
121. Birkmayer W, Riederer P, Ambrozi L, et al. Implications of combined treatment with Madopar and deprenil in Parkinson's disease; a long-term study. Lancet 1977;1:434-43
122. Lees AJ, Shaw KM, Kohout LIJ, et al. Deprenyl in Parkinson's disease. Lancet 1977;2:791-5
123. Reiderer P, Reynolds GP. Deprenyl is a selective inhibitor of brain MAO-B in the long-term treatment of Parkinson's disease. Br J Clin Pharmacol 1980;9:98-9
124. Reynolds GP, Riederer P, Sandler M, et al. Amphetamine and 2-phenylethylamine in post-mortem parkinsonian brain after (-)deprenyl administration. J Neural Transm 1978;43:271-7
125. Lew MF, Pahwa R, Leehey M, et al. Safety and efficacy of newly formulated selegiline orally disintegrating tablets as an adjunct to levodopa in the management of 'off' episodes in patients with Parkinson's disease. Curr Med Res Opin 2007;23:741-50
126. Ondo WG, Sethi KD, Kricorian G. Selegiline orally disintegrating tablets in patients with Parkinson disease

and 'wearing off' symptoms. Clin Neuropharmacol 2007;30:295-300

127. Waters CH, Sethi KD, Hause RA, et al. Zydis selegiline reduces off time in Parkinson's disease patients with motor fluctuations: a 3-month, randomized, placebo-controlled study. Mov Disord 2004;19:426-32
128. Clarke A, Brewer F, Johnson ES, et al. A new formulation of selegiline: improved bioavailability and selectivity for MAO-B inhibition. J Neural Transm 2003;110:1241-55
129. Clarke A, Johnson ES, Mallard N, et al. A new low-dose formulation of selegiline: clinical efficacy, patient preference and selectivity for MAO-B inhibition. J Neural Transm 2003;110:1257-71
130. Finberg JPM, Lamensdorf I, Commissiong JW, et al. Pharmacology and neuroprotective properties of rasagiline. J Neural Transm 1996;48:95-101
131. Parkinson Study Group. A controlled trial of rasagiline in early Parkinson disease. the TEMPO Study. Arch Neurol 2002;59:1937-43
132. Rascol O, Brooks DJ, Melamed E, et al. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. Lancet 2005;365:947-54
133. Parkinson Study Group. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations. The PRESTO Study. Arch Neurol 2005;62:241-8
134. Tatton W, Chalmers-Redman R, Tatton N. Neuroprotection by deprenyl and other propargylamines: glyceraldehyde-3-phosphate dehydrogenase rather than monoamine oxidase B. J Neural Transm 2003;110:509-15
135. Tatton WG, Chalmers-Redman RM, Ju WJ, et al. Propargylamines induce antiapoptotic new protein synthesis in serum- and nerve growth factor (NGF)-withdrawn, NGF-differentiated PC-12 cells. J Pharmacol Exp Ther 2002;301:753-64
136. Olanow CW, Hauser RA, Jankovic J, et al. A randomized, double-blind, placebo-controlled, delayed start study to assess rasagiline as a disease modifying therapy in Parkinson's Disease (The ADAGIO Study): rationale, design, and baseline characteristics. Mov Disord 2008;23:2194-201
137. Olanow CW, Rascol O. Early Rasagiline Treatment Slows UPDRS Decline in the ADAGIO Delayed Start Study. Salt Lake City, UT. 133rd Annual Meeting of the American Neurological Association, 2008
138. Stoof JC, Booij J, Drukarch B. Amantadine as a N-methyl-D-aspartic acid receptor antagonist: new possibilities for therapeutic application? Clin Neurol Neurosurg 1992;92:S4-6
139. Jenner P. A novel dopamine agonist for the transdermal treatment of Parkinson's disease. Neurology 2005;65:3-5
140. Belluzzi JD, Domino EF, May JM, et al. N-0923, a selective dopamine D2 receptor agonist, is efficacious in rat and monkey models of Parkinson's disease. Mov Disord 1994;9:147-54
141. LeWitt PA, Lyons KE, Pahwa R. Advanced Parkinson disease treated with rotigotine transdermal system PREFER Study. Neurology 2007;68:1262-7
142. Watts RL, Jankovic J, Waters C, et al. Randomized, blind, controlled trial of transdermal rotigotine in early Parkinson disease. Neurology 2007;68:272-6
143. Poewe WH, Rascol O, Quinn N, et al. The SP 515 Investigators, efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomized controlled trial. Lancet Neurol 2007;6:513-20
144. Babic T, Boothmann B, Polivka J, et al. Rotigotine transdermal patch enables rapid titration to effective doses in advanced-stage idiopathic Parkinson disease: subanalysis of a parallel group, open-label, dose-escalation study. Clin Neuropharmacol 2006;29:238-42
145. Metman LV, Gillespie M, Farmer C, et al. Continuous transdermal dopaminergic stimulation in advanced Parkinson's disease. Clin Neuropharmacol 2001;2:163-9
146. Hutton JT, Metman LV, Chase TN, et al. Transdermal dopaminergic D(2) receptor agonist therapy in Parkinson's disease with N-0923 TDS: a double-blind, placebo-controlled study. Mov Disord 2001;16:459-63
147. Jankovic J, Watts RL, Martin W, et al. Transdermal rotigotine: double-blind, placebo-controlled trial in Parkinson disease. Arch Neurol 2007;64:676-82
148. Gueldenpfennig WM, Poole KH, Sommerville KW, et al. Safety, tolerability, and efficacy of continuous transdermal dopaminergic stimulation with rotigotine patch in early-stage idiopathic Parkinson Disease. Clin Neuropharmacol 2005;28:106-10
149. Neupro website. Available from: www.neupro.com/Home/Home.asp [Last accessed 21 March 2008]
150. Scheller D, Chan P, Li Q, et al. Rotigotine treatment partially protects from MPTP toxicity in a progressive macaque model of Parkinson's disease. Exp Neurol 2007;203:415-22
151. Scheller D, Stichel-Gunkel C, Lübbert H, et al. Neuroprotective effects of rotigotine in the acute MPTP-lesioned mouse model of Parkinson's disease. Neurosci Lett 2008;432:30-4

- **Investigation on potential neuroprotective property of rotigotine in MPTP-lesioned animal**

152. Allain H, Deste´e A, Petit H, et al. Five-year follow-up of early lisuride and levodopa combination therapy versus levodopa monotherapy in de novo Parkinson's disease. Eur Neurol 2000;44:22-30
153. Hayashi R, Tako K, Mikashita H, et al. Efficacy of low-dose lisuride infusion in Parkinson's disease. Intern Med 1998;37:444-8
154. Heinz A, Suchy I, Klewin I, et al. Long-term observation of chronic subcutaneous administration of lisuride in the treatment of motor fluctuations in Parkinson's disease. J Neural Transm 1992;4:291-301
155. Woitalla D, Müller T, Benz S, et al. Transdermal lisuride delivery in the treatment of Parkinson's disease. J Neural Transm Suppl 2004;68:89-95
156. Baronti F, Mouradian MM, Davis TL, et al. Continuous lisuride effects on central dopaminergic mechanisms in Parkinson's disease. Ann Neurol 1992;32:776-81
157. Vaamonde J, Luquin MR, Obeso JA. Subcutaneous lisuride infusion in Parkinson's disease: response to chronic administration in 34 patients. Brain 1991;114:601-17
158. Stocchi F, Ruggieri S, Vacca L, et al. Prospective randomized trial of lisuride infusion versus oral levodopa in patients

with Parkinson's disease. Brain 2002;125:2058-66

159. Stocchi F, Bramante L, Monge A, et al. Apomorphine and lisuride infusion: a comparative chronic study. Adv Neurol 1993;60:653-5
160. Ruggieri S, Stocchi F, Carta A, et al. Comparison between L-dopa and lisuride intravenous infusions: a clinical study. Mov Disord 1988;3:313-9
161. Di Stefano A, Sozio P, Iannitelli A, et al. Maleic- and fumaric-diamides of (O,O-diacetyl)-L-Dopa-methylester as anti-Parkinson prodrugs in liposomal formulation. J Drug Target 2006;14:652-61
162. Cannazza G, Di Stefano A, Mosciatti B, et al. Detection of L-DOPA, Dopamine and its metabolites in rat striatum dialysates following peripheral administration of L-DOPA prodrugs by mean of HPLC-EC. J Pharm Biomed Anal 2005;36:1079-84
163. Di Stefano A, Carafa M, Sozio P, et al. Evaluation of rat striatal L-Dopa and DA concentration after intraperitoneal administration of L-Dopa prodrugs in liposomal formulations. J Control Release 2004;99:293-300
164. Esposito E, Fantin M, Marti M, et al. Solid lipid nanoparticles as delivery systems for Bromocriptine. Pharm Res 2008;25:1521-30
165. Tomalia DA, Baker H, Dewald J, et al. A new class of polymers: starburst-dendritic macromolecules. Polym J 1985;17:117-32
166. Tomalia DA, Naylor AM, Goddard WA. Starburst dendrimers: molecular-level control of size, shape, surface chemistry, topology, and flexibility from atoms to macroscopic matter. Angew Chem Int Ed Engl 1990;29:138-75
167. Tang S, Martinez LJ, Sharma MA, et al. Synthesis and characterization of water-soluble and photostable L-DOPA dendrimers. Org Lett 2006;8:4421-4
168. Illum L. Transport of drugs from the nasal cavity to the central nervous system. Eur J Pharm Sci 2000;11:1-18
169. Thorne RG, Pronk GJ, Padmanabhan V, et al. Delivery of insuline-like growth factor-I to the rat brain and spinal cord along olfactory and trigeminal pathways following intranasal administration. Neuroscience 2004;127:481-96
170. Sakane T, Akizuki M, Yoshida M, et al. Transport of cephalexin to the cerebrospinal fluid directly from the nasal cavity. J Pharm Pharmacol 1991;43:449-51
171. Sakane T, Akizuki M, Yamashita S, et al. The transport of drugs to the cerebrospinal fluid directly from the nasal cavity: the relation to the lipophilicity of the drug. Chem Pharm Bull 1991;39:2456-8
172. Kumar TA, David GFX, Sankaranarayanan A, et al. Pharmacokinetics of progesterone after its administration to ovariectomized rhesus monkeys by injection, infusion, or nasal spraying. Proc Natl Acad Sci 1982;79:4185-9
173. Kao HD, Traboulsi A, Itoh S, et al. Enhancement of the systemic and CNS specific delivery of L-Dopa by the nasal administration of its water soluble prodrugs. Pharm Res 2000;17:978-84
174. Bartus RT, Emerich D, Snodgrass-Belt P, et al. Pulmonary formulation of L-Dopa enhances its effectiveness in a rat model of Parkinson's disease. J Pharmacol Exp Ther 2004;310:828-35
175. Schwarz Pharma press release for Parcopa® aprroval from PDA. Available from: www.schwarzpharma.com/sp/n2345/Press_Release__August_30_2004
176. Stalevo website. Available from: www.stalevo.com
177. Information on V1512. Available from: www.vernalis.com/ver/rdc2/neurology/v1512/
178. Stocchi F, Fabbri L, Vecsei L, et al. Clinical efficacy of a single afternoon dose of effervescent levodopa-carbidopa preparation (CHF 1512) in fluctuating Parkinson disease. Clin Neuropharmacol 2007;30:18-24
179. Information on targeted lipid transport technology for LD. Available from: www.amarincorp.com/products/amr103.480.html
180. Information on the AIR® pulmonary drug delivery technology. Available from: www.alkermes.com/products/inhaled.html.
181. Tasmar website. Available from: www.tasmar.com
182. Comtan website. Available from: www.comtan.com
183. Eldepryl information. Available from: www.somersetpharm.com/products/
184. Zelapar website. Available from: www.zelapar.com
185. Azilect website. Available from: www.azilect.com
186. Stocchi F, Vacca L, Grassini P, et al. Symptom relief in Parkinson's disease by safinamide. Biochemical and clinical evidence of efficacy beyond MAO-B inhibition. Neurology 2006;67:24-9
187. General information on Lisuride TDS and Lisuride sc. Available from: www.axxonis.com/projects_e.html
188. Mirapex website. Available from: www.mirapex.com/
189. Requip website. Available from: www.requip.com/
190. Aderis Pharmaceuticals website. Available from: www.aderis.com/products/rotigotine.htm
191. Information on apomorphine nasal powder. Available from: www.britannia-pharm.co.uk/partnerships .shtml#Apo-nasal%20PD
192. Information on sublingual apomorphine. Available from: www.amarincorp.com/products/sublingual_apomorphine.477.html
193. Information on amantadine. Available from: www.endo.com/PDF/symmetrel_pack_insert.pdf

Affiliation

Antonio Di Stefano†, Piera Sozio, Antonio Iannitelli & Laura Serafina Cerasa
†Author for correspondence
'G. d'Annunzio' University,
School of Pharmacy,
Department of Drug Sciences,
Via dei Vestini 31, 66100 Chieti, Italy
Tel: +39 871 355 4708; Fax: +39 871 355 4706;
E-mail: adistefano@unich.it