Emerging therapies for Parkinson's disease

Werner Poewe[a], *Philipp Mahlknecht*[a], *and Joseph Jankovic*[b]

Purpose of review
The experimental therapeutics of Parkinson's disease are reviewed, highlighting the current pipeline of emerging therapeutic approaches.

Recent findings
This review includes novel approaches to dopaminergic drug delivery such as intraintestinal infusions or new extended-release formulations of levodopa and also intrapulmonary delivery of apomorphine as well as novel dopaminergic agents like the monoamine oxidase-B inhibitor safinamide or novel catechol-O-methyl transferase inhibitors. An even greater number of ongoing clinical trials assess the efficacy and safety of nondopaminergic approaches to enhance motor control or reduce motor complications like fluctuations and dyskinesias. These include adenosine A_{2A} antagonists, α-adrenergic and serotonergic agonists as well as drugs acting on the glutamatergic system. Gene-based or cell-based intrastriatal delivery of therapeutic principles that enhance striatal dopaminergic transmission directly or via the stimulation of trophic activity has also reached phase II clinical development with encouraging results in some studies. Finally, a wide spectrum of agents with a potential for slowing disease progression is currently tested.

Summary
A variety of medical and nonmedical interventions in different phases of clinical development provide an interesting and promising portfolio of emerging therapies for Parkinson's disease.

Keywords
drug delivery, experimental therapies, gene therapy, neuroprotection, nondopaminergic drug

INTRODUCTION

Until now, Parkinson's disease stands out as the only neurodegenerative disorder for which there are highly efficacious symptomatic therapies. Dopamine replacement strategies can virtually abolish motor symptoms and in this respect, after almost 50 years of clinical use, levodopa is still the gold standard of symptomatic efficacy. Its long-term use, however, is associated with the development of motor complications, in particular response oscillations and dyskinesias in a majority of patients [1]. There is evidence to suggest that these may be induced by unphysiological, pulsatile dopamine-receptor stimulation following discontinuous drug delivery through multiple daily dosing [2]. Furthermore, current dopaminergic therapies do not seem to alter the underlying progression of Parkinson's disease [3] such that disease modifying therapies are still a major medical unmet need [4]. This is also true for effective therapies to treat the many nonmotor symptoms of Parkinson's disease for which there are currently only few interventions with established efficacy through randomized controlled trials.

This review will highlight novel therapies for Parkinson's disease that are currently in clinical development and testing. These include novel approaches to dopaminergic drug delivery, novel dopaminergic and nondopaminergic agents, gene and cell-based therapies (Table 1 [5▪,6–24,25▪▪,26–39,40▪,41–53,54▪▪,55–57]) and neuroprotective or disease-modifying strategies (Table 2 [58–63]).

[a]University–Klinik für Neurologie, University of Innsbruck, Innsbruck, Austria and [b]Department of Neurology, Parkinson's Disease Center and Movement Disorders Clinic, Baylor College of Medicine, Houston, Texas, USA

Correspondence to Professor Werner Poewe, Department of Neurology, Innsbruck Medical University, Anichstrasse 35, A-6020 Innsbruck, Austria. Tel: +43 512 504 23850; fax: +43 512 504 23852; e-mail: werner.poewe@i-med.ac.at

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KEY POINTS

- Novel approaches to dopaminergic drug delivery including novel extended-release oral formulations as well as delivery via nonoral routes are a promising approach to treat and potentially prevent motor complications associated with chronic levodopa therapy.
- Antiglutamatergic drugs targeting the metabotropic glutamate receptor type 5 may develop into clinically useful antidyskinetic agents.
- Drugs targeting adenosine A_{2A}, α-adrenergic and serotonergic receptors may complement the spectrum of available drugs to treat motor complications in advanced Parkinson's disease.
- Delivery of therapeutic genes has included trophic factors and critical enzymes for neurotransmitter synthesis with promising results in phase II trials.
- Current attempts to develop disease-modifying (neuroprotective) agents to treat Parkinson's disease are targeting cellular calcium homeostasis, oxidative stress, mitochondrial energy production as well as apoptotic mechanisms.

NOVEL APPROACHES TO DOPAMINERGIC DRUG DELIVERY IN PARKINSON'S DISEASE

Converging evidence from experimental and clinical studies suggests that discontinuous drug delivery is a major factor for the development of levodopa-related response oscillations and dyskinesias [2]. Several new approaches to improve dopaminergic drug delivery have reached an advanced stage of clinical development.

Levodopa/carbidopa intestinal gel

Initial studies on the efficacy of continuous levodopa delivery as a strategy to smooth out motor fluctuations date back to the 1980s when several groups were able to show dramatic effects of constant rate intravenous infusions of levodopa solutions in patients with advanced Parkinson's disease [64,65].

Recently, a novel formulation of infusible levodopa has been developed in which the drug is embedded in a carboxymethylcellulose gel providing a concentration of levodopa/carbidopa of 2/0.5 g in only 100 ml (Duodopa, Abbott Healthcare, North Chicago, IL, USA). A 100 ml cassette thus contains 2 g of levodopa allowing for a full-day coverage. This novel delivery system uses portable pumps that have programmable delivery rates for amounts between 10 and 2000 mg of levodopa/hour and delivery times of up to 24 h. Intrajejunal delivery is achieved through a percutaneous endoscopic gastrostomy tube in which the tip is positioned below the Treitz band in the proximal jejunum. Several short and longer duration open-label studies have consistently reported marked reductions in daily off time as well as reduced severity of preexisting levodopa-induced dyskinesia (LID) when such intrajejunal infusion systems were used in patients with fluctuating Parkinson's disease [5▪,6,7]. One randomized crossover trial comparing levodopa intestinal infusions with oral levodopa/carbidopa over 3 weeks showed marked reductions in plasma levodopa concentration variations and significant increases in 'on time' without troublesome dyskinesias as compared with traditional oral levodopa administration [66,67]. Currently, a parallel group, 12-week randomized double-dummy study comparing levodopa/carbidopa intestinal gel with oral levodopa/carbidopa is underway [66].

Extended release oral formulations of levodopa/carbidopa

Currently available extended-release formulations of levodopa use pharmacokinetic principles that are vulnerable to erratic gastric emptying and incomplete and variable intestinal absorption and have limited efficacy [67–71]. IPX066 is a novel levodopa/carbidopa extended-release oral formulation. A phase II trial in 27 patients with fluctuating Parkinson's disease showed significantly longer duration of action from a single dose of IPX066 as compared with standard levodopa/carbidopa. This trial had a crossover design of 1 week each of open-label treatment with IPX066 versus standard levodopa/carbidopa and there were 2 h less off-time per day during the IPX066 week and a reduced dosing frequency of 3.5 per day as compared with 5.5 for levodopa/carbidopa [8].

In a phase III randomized double-blind trial, 393 individuals with fluctuating Parkinson's disease initially underwent a 3-week dose optimization period of standard levodopa/carbidopa before being switched to IXP066 that was again optimized over a 6-week period [9,10]. For the final 13 weeks of the trial, individuals were randomized to their optimized doses of IPX066 or standard levodopa/carbidopa in a double-dummy design. Again, dose frequency was less for IPX066 (3.6 versus 5.1 per day) and there was an about 1-h gain in on time without troublesome dyskinesias in the IPX066 group compared with the conventional levodopa/carbidopa group. Another phase III active comparator study of IPX066 versus standard levodopa/carbidopa and the triple combination of levodopa/carbidopa/entacapone is

Table 1. Experimental therapeutics in Parkinson's disease

Intervention	Substance	Mechanism of action	References of completed clinical studies	Ongoing clinical trials and study type	(Primary) outcome measure
Novel deliveries					
	Duodopa	Levodopa/carbidopa intestinal gel infusion	[5▪,6,7]	NCT00360568; phase III RCT (13)	Long-term safety, off-time reduction
	ND0611	Transdermal levodopa ethyl ester		NCT01229332	Tolerability, pharmacokinetics
	IPX066	Carbidopa/levodopa extended-release formulation	[8–10]	Phase III NCT01130493 (RCT) NCT01096186 (OL) NCT01411137 (OL)	UPDRS I–IV, patient diary
	XP21279	Sustained-release prodrug of levodopa	[11]	NCT01171313, phase II RCT with active comparator (Sinemet, Merck, New Jersey, USA)	Off-time reduction
	CVT-301	Inhalable levodopa	–	–	
	VR040	Inhalable apomorphine	[12]	–	
Novel DA agonists					
	Pardoprunox (SLV308)	Partial dopamine agonist and full $5HT_{1A}$ agonist	[13–15]	Phase II/III RCT	Change of UPDRS III score, evaluation of safety, efficacy and tolerability
	Aplindore (DAB-452)	Dopamine agonist	[16]	NCT00623324; phase II RCT	Evaluation of safety and tolerability, change in UPDRS III
Strategies to treat MF/LID					
	IPX066	See above	See above		
	Sarizotan	$5\text{-}HT_{1A}$ antagonist	[17,18]	Phase II RCT, OL	Evaluation of safety, tolerability and efficacy, UPDRS, antidyskinetic effect (AIMS, UPDRS item 32 and 33)
	Piclozotan	$5\text{-}HT_{1A}$ antagonist	[19]	Phase II RCT	On time without dyskinesia (AIMS, UPDRS), safety and tolerability
	Perampanel	AMPA antagonist	[20–22]	Phase III RCT, OL	Off-time reduction (UPDRS), safety and tolerability
	Fipamezole (JP-1730)	Alpha-2 adrenergic antagonist	[23,24]	Phase II RCT	Antidyskinetic efficacy (LIDS, UPDRS III, mAIMS), safety
	AFQ056	mGluR5 antagonist	[25▪▪,26]	Phase II RCT, NCT01385592, NCT01491529	Antidyskinetic efficacy (mAIMS)
	Dipraglurant (ADX 48621)	mGluR5 antagonist	–	Phase II RCT NCT01336088	Safety and tolerability, antidyskinetic efficacy (mAIMS)
	Safinamide	MAO-B and glutamate inhibitor	[27–31]	Phase III RCT NCT01028586 NCT00605683 NCT00627640	Change in UPDRS III; change in daily on time

Table 1 (*Continued*)

Intervention	Substance	Mechanism of action	References of completed clinical studies	Ongoing clinical trials and study type	(Primary) outcome measure
	Istradefylline (KW-6002)	A_{2A} adenosine antagonist	[32–39]	Phase III RCT NCT00955526	Off-time reduction
	Preladenant	A_{2A} adenosine antagonist	[40▪]	Phase III RCT NCT01155479 NCT01227265 NCT01155466 NCT01215227	UPDRS II and III scores, off-time reduction, tolerability and safety
	SYN115	A_{2A} adenosine antagonist	[41,42]	Phase II/III RCT NCT01283594	Off-time reduction, tolerability and safety, UPDRS and dyskinesia scores (ongoing)
	Nebicapone (BIA 3-202)	COMT inhibitor	[43]	–	
	Opicapone (BIA 9-1067)	COMT inhibitor		Phase III RCT NCT01227655; NCT01520987	Off-time reduction
	Antibiotics against *Helicobacter pylori*	Improvement in drug absorption	[44]	Phase III RCT NCT00664209	Off-time reduction
Trophic agents					
	Neurturin (CERE-120)	Putaminal and/or nigral AAV-2 vector encoding for a neurotrophic factor (similar to GDNF)	[45,46]	Phase I/II RCT NCT00985517	UPDRS III in the off condition
	Cogane (PYM50028)	Oral neurotrophic factor modulator		Phase II RCT NCT01060878	Change from baseline in UPRDS II and III
	[a]Davunetide	Neuroprotective protein, nasal application		Phase II/III NCT01056965 NCT01110720	
Cell-based and gene delivery					
	Spheramine	Putaminal injection of cultured human retinal epithelial cells	[47,48]	Phase II RCT NCT00206687	UPDRS III in the off and on condition, levodopa reduction
	Autologous mesenchymal stem cells	Unilateral transplantation of autologous bone marrow-derived mesenchymal stem cells in the sublateral ventricular zone	[49]	NCT01446614	Adverse events, UPDRS III
	AAV–AADC	Intrastriatal infusion of AAV-mediated gene transfer of AADC	[50]	Phase I OL NCT00229736	Safety and efficacy
	Prosavin	Intrastriatal gene delivery of AADC, TH and CH 1	[51]	Phase I/II OL NCT00627588	Safety and efficacy measured by the UPDRS III
	Gene delivery of GAD	AAV–GAD gene transfer into the subthalamic nucleus (STN) $\geq$ reduction of STN hyperactivity	[52,53]	Phase II RCT[b] NCT00643890	Changes in UPDRS III
Other					
	rTMS	Repetitive noninvasive transcranial magnetic stimulation	[54▪▪,55] reviews	Phase II RCT NCT01080794 NCT01367782 NCT01275573	UPDRS III, depression, pain perception

Table 1 (*Continued*)

Intervention	Substance	Mechanism of action	References of completed clinical studies	Ongoing clinical trials and study type	(Primary) outcome measure
	Resonator device	Application of magnetic fields	–	Phase III RCT NCT00863226	Quality of life
	EMST	Expiratory muscle strength training for aspiration prevention	[56,57]	Phase II/III NCT00856518	Penetration-aspiration scale score

AADC, aromatic amino-acid-decarboxylase; AAV-2, adeno-associated virus serotype 2; AIMS, abnormal involuntary movement scale; AMPA, amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid; CH 1, cyclohydrolase-1; COMT, catechol-O-methyl transferase; DA, dopamine; EMST, expiratory muscle strength training; GAD, glutamic acid decarboxylase; GDNF, glial cell-derived neurotrophic factor; LID; levodopa-induced dyskinesia; LIDS, levodopa-induced dyskinesia rating scale; MAO-B, monoamine oxidase-B; MF, motor fluctuations; mGluR5, metabotropic glutamate receptor type 5; rTMS, repetitive transcranial magnetic stimulation; STN, subthalamic nucleus; TH, tyrosine hydrolase; UPDRS, unified Parkinson's disease rating scale.
[a]Currently tested in progressive supranuclear palsy.
[b]Trial terminated.

currently ongoing (ClinicalTrials NCT01130493 and NCT01096186).

Another formulation of levodopa currently undergoing clinical trials is XP21279, a sustained-release prodrug of levodopa that is actively absorbed by a high-capacity natural nutrient transport mechanisms located throughout the length of the gastrointestinal tract and then is rapidly converted to levodopa. In one study involving 10 Parkinson's disease patients with motor fluctuations, XP21279

Table 2. Neuroprotective/disease-modifying therapies

Substance	Mechanisms of action	Reference (first author)	Study type	(Primary) outcome measure	Acronym, Clinicaltrials.gov
Exendin-4	GLP-1 like peptide; promotes a cellular growth and reduces apoptosis	Harkavyi [58]	Phase II OL	Change from baseline in UPDRS III in off	NCT01174810
Isradipine	Calcium antagonist	Chan [59]	Phase II RCT	Tolerability; change in ADL and motor UPDRS	STEADY-PD, NCT00909545
Nicotine	Nicotinic acetylcholine receptor agonist	Quik [60]	Phase II RCT	Change from baseline in UPDRS III in off condition compared with PD controls	NICOPARK2, NCT00873392
Inosine	Urate precursor	Morelli [3]	Phase II RCT	Tolerability and safety of urate elevation	SURE-PD, NCT00833690
Caffeine	Nonspecific A_1/A_{2A} receptor antagonist	Morelli [3]	Phase II OL	Tolerability	NCT01190735
Green tea polyphenol	Catechin; antioxidant and iron chelator	Mandel [61], Li [62]	Phase II RCT	Delay of progression of motor dysfunction	NCT00461942
Deferiprone	Iron chelator	Li [62]	Phase II/III	Decrease of SN iron overload (assessed by T2[a] MRI sequence); UPDRS I–IV	FAIR-PARK-I, NCT00943748
Coenzyme Q10	Antioxidant, modulator of mitochondrial function	Chaturvedi [63]	Phase III RCT	Change in UPDRS I–III	QE3, NCT00740714[a]
Creatine	Energy supplier, modulator of mitochondrial function	Chaturvedi [63]	Phase III RCT	Disease progression over 5 years	NET-PD, NCT00449865
Cogane (PYM50028)	Oral neurotrophic factor modulator		Phase II RCT	Change from baseline in UPRDS II and III	CONFIDENT-PD, NCT01060878

ADL, activities of daily living; GLP-1, glucagon-like peptide 1; OL, open label; PD, Parkinson's disease; RCT, randomized controlled trial; SN, substantia nigra; UPDRS, unified Parkinson's disease rating scale.
[a]Trial has been terminated prematurely.

was associated with significantly less variability in levodopa concentration compared with standard levodopa ($P < 0.05$), indicative of improved pharmacokinetic profile [11].

Transdermal levodopa delivery

Transdermal patch delivery of levodopa has been attempted through the use of levodopa ethylester, but this approach was not further pursued due to application site reactions [9]. ND0611 is another formulation of levodopa that can be administered by patch application; phase I/II studies suggest promising bioavailability of levodopa over the day (ClinicalTrials NCT01229332) [9].

Intrapulmonary dopaminergic drug delivery

Apomorphine is the only dopamine agonist with similar effect size on the motor symptoms of Parkinson's disease as the gold standard drug levodopa. It is also the first of its class for which a dry powder formulation has been developed that can be delivered via oral inhalation. Drug inhalation provides ultrarapid access to the systemic circulation via the lung's large alveolar surface. Inhaled apomorphine has been shown to produce peak plasma levels with a T_{max} of 1–3 min. This would make this approach attractive for ultrafast off-period reversal in patients with fluctuating Parkinson's disease. A phase II proof-of-concept pilot study in 57 Parkinson's disease patients with multiple daily off periods has compared active versus placebo inhalations over a 4-week outpatient treatment period following in-hospital dose optimization. There was good short-term safety and 83% of off periods were successfully aborted with a mean time to switch on of around 5 min. Multiple daily inhalations were associated with a mean daily off-time reduction in the active treatment group of 2.3 h versus placebo. This novel drug delivery approach could thus prove a practically important therapeutic advance provided long-term pulmonary safety can be successfully demonstrated [12].

NOVEL DOPAMINERGIC DRUGS IN DEVELOPMENT

Several dopaminergic drugs in development are based on the principle of enzyme inhibition in order to enhance central dopaminergic transmission. These include novel inhibitors of monoamine oxidase-B (MAO-B) and catechol-O-methyl transferase (COMT) as well as an approach targeting inhibition of hydroxyphenylpyruvate dioxygenase (HPPD).

Novel monoamine oxidase-B inhibitors

Safinamide is a novel reversible MAO-B inhibitor with additional mechanisms of action including glutamate release inhibition and sodium channel blocking properties. A recent placebo-controlled trial of adjunct safinamide included 269 early Parkinson's disease patients receiving a stable dose of a single dopamine agonist.

A recent placebo-controlled, double-blind trial in 669 Parkinson's disease patients with levodopa-associated response oscillations showed significant increases in daily on time with both 50 and 100 mg of safinamide per day as compared with placebo. In addition, there was a significant gain in on function, as assessed by the motor section of the unified Parkinson's disease rating scale (UPDRS) [29].

Another trial assessed the efficacy of adjunct safinamide in 269 patients receiving dopamine agonist monotherapy. Whereas the lower dose (100 mg per day) was associated with significant improvements on UPDRS motor scores, the difference between the 200 mg per day dose and placebo failed to reach statistical significance.

Two additional randomized, phase III, placebo-controlled trials are currently underway assessing the efficacy of safinamide as adjunct therapy to dopamine agonists (MOTION – ClinicalTrials NCT01028586 and NCT00605683) as well as adjunct to levodopa in patients with response oscillations (SETTLE – ClinicalTrials NCT00627640).

Novel catechol-O-methyl transferase inhibitors

The nitrocatechol compound entacapone is currently the only COMT inhibitor available as first-line treatment for patients with levodopa-related motor response fluctuations. Two novel nitrocatechol compounds have recently entered clinical development.

Nebicapone (BIA 3-202) was assessed in a phase IIb placebo-controlled and active-controlled randomized study in 252 Parkinson's disease patients with levodopa-induced motor fluctuations and led to a significant reduction in off time of 1.8 h compared with placebo at the highest dose tested (150 mg administered concomitantly with each levodopa dose) comparable to the likewise significant reduction in off time of 1.4 h achieved with the active comparator entacapone [43]. Lower doses of 50 and 100 mg nebicapone did not meet this primary efficacy endpoint. However, clinically relevant liver enzyme elevation occurred in four out of 46 patients treated with 150 mg nebicapone, compromising further clinical development.

BIA 9-1067 is another highly potent COMT inhibitor [72]. The drug has an interesting pharmacokinetic profile with long half-life and a potential for once-daily dosing. Phase II studies have shown significant increases in on time. A phase III trial was initiated in 2011 and will test two doses of study drug regarding their efficacy to reduce daily off time as compared with placebo (BIPARKII – ClinicalTrials NCT01227655).

NONDOPAMINERGIC DRUGS IN DEVELOPMENT

A number of nondopamine receptors are expressed on different parts of the basal ganglia motor circuits and have become targets of Parkinson's disease drug development.

Adenosine A_{2A} antagonists

Of the four adenosine receptors, the A_{2A} subtype is highly expressed in the basal ganglia, especially the striatum. It colocalizes with dopamine D_2 receptors on medium spiny neurons projecting to the external segment of the globus pallidus (GPi) as part of the indirect pathway. Adenosine A_{2A} receptors act as modulators of the D_2 receptors and in Parkinson's disease their activation contributes to overactivity of the indirect pathway. Therefore, A_{2A} antagonists may reduce striatopallidal overactivity and ameliorate parkinsonism. Several candidates of this class of agents have reached the stage of clinical development.

Istradefylline

Istradefylline, the first A_{2A} antagonist evaluated in proof-of-concept studies and later in phase II trials, showed positive signal for reduced motor fluctuations when given to patients with fluctuating Parkinson's disease [32–35]. Two subsequent randomized controlled phase III trials showed off-time reduction of 0.7 h with 20 mg istradefylline in one trial [36] and 0.65 h with 20 mg and 0.92 h with 40 mg istradefylline per day in the other trial [37]. However, a third large randomized controlled phase III study in 610 Parkinson's disease patients on levodopa therapy with motor response complications failed to detect significant differences in daily off time with 10, 20 and 40 mg istradefylline per day. Istradefylline has also been studied as a monotherapy in 176 early Parkinson's disease patients, but at 40 mg per day had no beneficial effect in improving motor symptoms compared with placebo [38,39].

Preladenant

Preladenant is a potent and selective competitive antagonist of the A_{2A} receptors. This substance has recently been tested in a phase II trial in 253 advanced Parkinson's disease patients with motor fluctuations [40▪]. At 5 and 10 mg doses, preladenant exerted beneficial effects, including significantly reducing off time by 1.0 and 1.2 h, respectively. An increase in daily on time with nontroublesome dyskinesias was observed; troublesome dyskinesias, however, were not prolonged. Phase III trials of preladenant in early Parkinson's disease patients (ClinicalTrials NCT01155479) and advanced Parkinson's disease patients versus placebo (ClinicalTrials NCT01227265) and versus rasagiline (ClinicalTrials NCT01155466 and NCT01215227) are ongoing.

SYN115

SYN115 is a member of the novel nonxanthine–nonfuran A_{2A} antagonists that is currently in early phases of clinical development. SYN115 has 100-fold selectivity for A_{2A} versus other adenosine receptors and is currently in phase II of clinical development. A small phase IIa randomized, placebo-controlled, double-blind, crossover study assessed the effects of 1 week treatment (20 mg twice daily, $n = 12$, or 60 mg twice daily, $n = 14$) on the response to intravenous levodopa infusions as compared with results after 1 week of placebo treatment. At the higher dose, there was significantly enhanced tapping speed on active drug both before and during levodopa infusions [41]. A phase IIb trial is currently underway (ClinicalTrials NCT01283594). A proof-of-concept functional MRI study was able to demonstrate reduced activity of the indirect pathway following administration of SYN115, consistent with A_{2A} antagonism [42].

Glutamatergic antagonists

The development of levodopa-induced dyskinesias has been linked to excessive corticostriatal glutamatergic input, as shown in many animal experiments [73]. Glutamate receptors, especially *N*-methyl-D-aspartate (NMDA), metabotropic glutamate receptor type 5 (mGluR5) and amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid (AMPA) receptors abundantly expressed in striatal neurons are thought to increase dopamine D_1-mediated activity of the direct pathway of striatal neurons with chronic pulsatile administration of levodopa due to synaptic and molecular alterations [74]. This leads to increased inhibition of the internal segment of the GPi and other output regions of the basal ganglia, resulting in loss of normal thalamocortical inhibition and finally the development of dyskinesias. Indeed, amantadine, a weak NMDA receptor antagonist, remains the only drug to date used in clinical practice with proven antidyskinetic efficacy

[75▪▪,76]. Other antagonists of the NMDA receptor, however, failed to consistently prove antidyskinetic effects in animal models. Recent research focused on antagonism of the mGluR5 and AMPA receptors. Potential substances include perampanel, AFQ056 and ADX48621.

Perampanel

Perampanel is a selective and noncompetitive AMPA receptor antagonist that improves motor symptoms in Parkinson's disease animal models. A first randomized placebo-controlled phase II study failed to detect significant changes in daily off time compared with placebo with doses up to 2 mg perampanel once daily [20]. Two subsequent phase III randomized controlled trials assessed the efficacy of 2 and 4 mg perampanel compared with placebo in Parkinson's disease patients with response oscillations to levodopa [21]. In both studies, there was no significant difference in the primary endpoint of off-time reduction. In addition, there was no effect on the duration or disability of LID. A fourth randomized placebo-controlled and active-controlled study was prematurely terminated when the negative results of the other trials became available [22].

AFQ056

Metabotropic glutamate receptor type 5 is preferentially expressed in several brain areas including the striatum. Blocking mGluR5 receptors could therefore reduce direct pathway hyperactivity in LID in Parkinson's disease. This is further supported by animal data showing increased mGluR5 binding in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridin (MPTP)-treated monkeys following levodopa therapy. Preclinical studies with the mGluR5 negative allosteric modulator AFQ056 have indeed shown reductions of LID in the MPTP model [77▪]. Two small placebo-controlled phase II trials (34 patients each) have both shown significant reductions in dyskinesias as assessed by the abnormal involuntary movement scale (AIMS), the Lang–Fahn activities of daily living dyskinesia scales, or the UPDRS part IV items 32 and 33 [25▪▪].

A larger phase IIb dose-ranging study included 197 patients with LID treated with five dose levels of AFQ056 (10, 25, 50, 75 and 100 mg twice daily) or placebo for 3 months [26]. Significant improvements in the primary outcome, modified AIMS, were observed for the 100 mg twice daily dose compared with placebo, and the same dose also showed significant reductions in the UPDRS IV item 32 (dyskinesia severity), whereas other dyskinesias scales (Parkinson's Disease Dyskinesia Scale-26) or Clinician's Global Impression of Change did not show significant improvements.

Dipraglurant (ADX48621)

Dipraglurant, a negative allosteric modulator of the mGlu5 receptor, showed antidyskinetic effects in MPTP and haloperidol animal models of Parkinson's disease [78,79]. A phase II randomized controlled trial investigating the effects of dipraglurant on LID in advanced Parkinson's disease patients is ongoing (ClinicalTrials NCT01336088).

α-adrenergic antagonists

α-Adrenergic 2A and 2C receptors modulate gamma-aminobutyric acid (GABA)ergic transmission at the level of the striatopallidal projection, which is hyperactive in patients with LID dyskinesias [80]. α-Adrenergic antagonists are currently being tested as adjunct therapies for patients with levodopa-related motor complications.

Fipamezole

Fipamezole is an adrenergic α-2 receptor antagonist that has shown antidyskinetic activitiy in the MPTP Parkinson monkey model [81]. A proof-of-concept study in 21 Parkinson's disease patients with LID were studied using levodopa infusion paradigm to elicit dyskinesias [23]. The effects of fipamezole administered as a buccal spray in ascending doses of 30, 60 and 90 mg or placebo were assessed regarding both dyskinesia severity as well as duration of levodopa response following stop of infusion. Dyskinesia severity decreased by 23% at 60 mg of fipamezole and 31% at 90 mg ($P < 0.05$ vs. placebo). In addition, levodopa response duration was prolonged with the 90 mg dose by 41 min ($P < 0.05$).

A larger, double-blind, placebo-controlled, phase IIb study included 115 individuals in the USA and 64 patients in India [24]. Study duration was 4 weeks and doses were escalated to a maximum of 90 mg three times daily. Although there was no significant difference between placebo and active drug for this total study population on the primary endpoint of the levodopa-induced dyskinesia rating scale (LIDS), a prespecified subanalysis of US individuals demonstrated a significant dyskinesia reduction in the 90 mg dose.

Serotonergic agonists

Serotonin in the striatum is released by fibers derived from the dorsal raphe nucleus and serotonin receptors are expressed presynaptically and postsynaptically in striatal neurons, where they modulate

dopaminergic neurotransmission [74,82]. Recently, a histopathological study showed a significant increase of serotonin transporter levels as an index of serotonin innervation density in striatal brain tissue from dyskinetic animals (rat and monkey Parkinson's disease models) as well as human Parkinson's disease cases providing evidence that levodopa treatment induces sprouting of serotonin axon terminals in the dopamine-denervated striatum [83]. Different agonists of the serotonin $5HT_{1A}$ receptor have been tested for their ability to reduce off time and dyskinesias in Parkinson's disease animal models [84–86].

Sarizotan

Sarizotan is a full agonist for the 5-HT_{1A} receptor and an antagonist for the dopamine receptor with higher affinity for the D_4 and D_3 subtypes and lower affinity for the D_2 subtype [82,87]. An open-label study in 18 patients with advanced Parkinson's disease demonstrated reduction in dyskinesia [17]. However, it failed to demonstrate efficacy against dyskinesias compared with placebo in recent randomized controlled trials [18,88]. Reasons for the lack of efficacy may have included prominent placebo effects and partial antagonism at dopamine receptors further narrowing the therapeutic window of levodopa [82,87,88].

Piclozotan

Piclozotan is another 5-HT_{1A} receptor agonist that has been demonstrated to improve levodopa-induced motor complications in a Parkinson's disease animal model [86]. A phase II pilot study in 25 Parkinson's disease patients with LID reported a significant improvement in on time without dyskinesia and reduction of off time [19].

GENE AND CELL-BASED THERAPIES

Restoration of dopaminergic nigrostriatal innervation through embryonic dopaminergic cell transplants has already made Parkinson's disease a pioneer clinical arena for cell-based treatment approaches in neurodegeneration for more than two decades [89–91].

Unfortunately, sham-surgery controlled fetal cell transplant studies failed to provide clear evidence for the symptomatic efficacy of this approach on conventional endpoints like off-period motor function [92,93]. Furthermore, several recent studies have raised concerns about potential host-to-graft propagation of Lewy-body disease in Parkinson's disease patients who had received embryonic nigral transplants [94,95]. In addition, there are considerable ethical issues surrounding the use of embryonic cell transplants and, therefore, alternative sources for cell-based therapies in Parkinson's disease remain a key research priority. The Spheramine Safety And Efficacy Study used cultured human retinal epithelial cells supported by microcarriers (spheramine) as a cell-based approach of intrastriatal dopamine delivery [47]. A phase II randomized control trial in patients with advanced Parkinson's disease, however, failed to establish significant differences between patients receiving intraputaminal spheramine injections as compared with those undergoing sham surgery [48]. Trials of transplants studies using autologous mesenchymal stem cells derived from patients' bone marrow are currently under way (ClinicalTrials NCT01446614). In addition, a European and North American network of investigators is developing improved protocols for the use of fetal mesenchymal tissue for future transplant studies in Parkinson's disease patients (http://www.transeuro.org.uk/pages/disease.html).

An alternative approach to restorative treatments in neurodegeneration is represented by the viral vector-based targeted delivery of therapeutic genes. In Parkinson's disease, approaches include gene delivery of human aromatic amino-acid-decarboxylase (AADC) to the striatum in an attempt to enhance local dopamine production. An open-label 6-month study in six patients with Parkinson's disease using adeno-associated virus (AAV) for gene transfer into the striatum found improved off- medication motor function in the order of almost 50% reduction of UPDRS scores as compared with baseline [50]. In addition, there was evidence for increased AADC activity in the striatum as assessed by brain imaging using fluoro-tyrosine as a tracer. There is an ongoing open-label study using a tricistronic lentiviral vector encoding for three critical enzymes in dopamine synthesis, tyrosine hydrolase, AADC and cyclohydrolase-1 (CinicalTrials NCT00627588). Interim results suggesting decreases in UPDRS scores off medication have been presented [51].

Another gene therapeutic approach has targeted the subthalamic nucleus (STN), wherein glutamatergic overactivity contributes to increased firing in the GPi, which itself is a key factor in basal ganglia motor loop dysfunction underlying LID. Gene transfer of glutamic acid decarboxylase (GAD), the key enzyme for GABA synthesis, is therefore expected to reduce STN excitatory overactivity, and thereby produce antiparkinsonian benefit. Indeed, an open-label study in 12 patients with advanced Parkinson's disease followed over the period of 12 month after unilateral injections of AAV–GAD into the STN improved motor function on the site opposite to injections at 6 and 12 months follow-up [52]. A phase II sham-surgery controlled study of bilateral STN infusions of AAV–GAD bilaterally into

the STN included 45 patients (23 sham operated, 22 receiving STN infusions). Six-month evaluations in 37 (21 and 16, respectively) patients showed significant reductions in off-medication UPDRS motor scores in the AAV–GAD group (−8.1 points) as compared with the sham group (−4.7 points, $P = 0.04$ for difference between groups) without serious safety concerns reported so far [53].

Another approach for therapeutic gene delivery in Parkinson's disease has focused on the targeted delivery of the neurotrophic factor neurturin, which has been shown to restore and protect dysfunctional dopaminergic neurons in animal models of Parkinson's disease [96]. An initial open-label phase I study in six advanced Parkinson's disease patients demonstrated a mean off-medication motor UPDRS improvement of 14 points 1 year after bilateral stereotactic intraputaminal injection of AAV2–neurturin compared with baseline [46]. Moreover, there was a mean increase in on time without troublesome dyskinesia of 2.3 h. A subsequent phase II randomized sham-surgery controlled trial in 58 patients with advanced Parkinson's disease failed to detect significant differences in off-state motor UPDRS scores after 1 year [45]. A subgroup analysis of 30 patients followed up for longer than 12 months, however, showed significant improvements in the off-state motor UPDRS of 8 points and a significant gain in on time without troublesome dyskinesia of 2.5 h in the AAV2–neurturin-injected group compared with the control group after 18 months. Serious adverse event occurred in 34% of the patients treated with AAV2–neurturin and in 20% of the sham-surgery group.

Another trial, currently in progress, is targeting not only the putamen but also the substantia nigra (ClinicalTrials NCT00985517). The latter strategy is based on the hypothesis that neurturin will be transported from degenerating terminals to their cell bodies in the substantia nigra to the striatum. This is supported by the postmortem findings in two brains of patients who participated in the above-described phase II trial with neurturin immunostaining in the targeted striatum (15% of the putamen), but there was no evidence of expression in the substantia nigra [96].

PYM50028 (Cogane; Phytopharm, Huntingdon, United Kingdom) is an orally active, nonpeptide, neurotrophic factor inducer that readily crosses the blood–brain barrier. It has been shown to induce neurotrophic factors and exert neuroprotective effects in dopaminergic neurons *in vitro*. Oral administration of PYM50028 reverses MPTP-induced dopaminergic neuronal damage in several Parkinson's disease animal models. Preclinical studies suggest that this small molecule may have utility in treating not only the motor symptoms but also some cognitive, behavioral and other nonmotor symptoms of Parkinson's disease. The drug is currently undergoing phase II clinical trials in patients with early Parkinson's disease (www.clinicaltrials.gov, NCT01060878).

Davunetide (Allon Therapeutics, Vancouver, Canada) is another drug with potential neurotrophic effects. An analogue of vasoactive intestinal peptide that enhances the synthesis of the activity-dependent neuroprotective protein is administered as a nasal spray. This molecule has been shown to stimulate neurite elongation and synapse formation, prevent toxicity from amyloid beta peptides, and limit tau hyperphosphorylation [97]. The drug is currently undergoing phase II/III clinical trials in progressive supranuclear palsy and other tauopathies (www.clinicaltrials.gov, NCT 01110720), but may also have utility as a neurotrophic agent in Parkinson's disease.

Agents to slow disease progression in Parkinson's disease

Slowing the clinical progression of Parkinson's disease continues to be the central unmet therapeutic need in this illness. Past trials testing putative neuroprotective agents using different endpoints and clinical designs have, unfortunately, either failed or results have been inconclusive [98] [see also article by Jankovic and Poewe (pp. 433–447), this volume]. Current efforts focus on some of the pathogenic mechanisms of neuronal dysfunction and cell death identified in recent years. Targets include cellular calcium homeostasis, oxidative stress, mitochondrial energy production as well as antiapoptotic mechanisms (see Table 2; [3,58–63,99]), but results are not yet available.

CONCLUSION

Although the pipeline of truly innovative therapies for Parkinson's disease is not as robust as patients and physicians would wish, there are many novel approaches that are currently in development and will hopefully be soon incorporated into the anti-Parkinson's disease armamentarium.

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Conflicts of interest

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