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Parkinson's Disease Therapeutics: New Developments and Challenges Since the Introduction of Levodopa

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The demonstration that dopamine loss is the key pathological feature of Parkinson's disease (PD), and the subsequent introduction of levodopa have revolutionalized the field of PD therapeutics. This review will discuss the significant progress that has been made in the development of new pharmacological and surgical tools to treat PD motor symptoms since this major breakthrough in the 1960s. However, we will also highlight some of the challenges the field of PD therapeutics has been struggling with during the past decades. The lack of neuroprotective therapies and the limited treatment strategies for the nonmotor symptoms of the disease (ie, cognitive impairments, autonomic dysfunctions, psychiatric disorders, etc.) are among the most pressing issues to be addressed in the years to come. It appears that the combination of early PD nonmotor symptoms with imaging of the nigrostriatal dopaminergic system offers a promising path toward the identification of PD biomarkers, which, once characterized, will set the stage for efficient use of neuroprotective agents that could slow down and alter the course of the disease.

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INTRODUCTION

Since James Parkinson described the disease that is named after him in 1817 (Parkinson, 1817), there have been tremendous advances in our understanding of the etiology, pathophysiology, and genetics of this disorder, which have led to major breakthroughs in the development of novel and highly effective therapies for Parkinson's disease (PD) (Table 1). The goal of this review is to highlight the impact some of these developments have had during the past 50 years, and discuss the challenges emerging antiparkinsonian therapies may face in the years to come.

The pioneering works of Carlsson and colleagues identified striatal dopamine depletion as the main cause of parkinsonian motor symptoms (Carlsson *et al*, 1957; Carlsson and Waldeck, 1958; see also Bertler and Rosengren, 1959). Since then, PD treatments have largely focused on 'correcting' the dopaminergic deficit, thereby alleviating the cardinal motor symptoms of the disease (ie, bradykinesia, rigidity, rest tremor, and gait disturbances—Box 1). Treatment with the dopamine precursor levodopa, introduced soon after the discovery of nigral dopamine cell loss in PD (Birkmayer and Hornykiewicz, 1961; Barbeau *et al*, 1962), truly revolutionized the treatment of PD. For the past five decades, levodopa has been the gold-standard therapy for the motor symptoms of the disease. However, the introduction of levodopa also led to new and significant challenges in the clinical management of patients with PD, specifically the development of long-term motor complications, such as involuntary movements (dyskinesias; Cotzias *et al*, 1969; Godwin-Austen, 1973; Simuni and Hurtig, 2008) (Table 1).

Appreciation of the complications of levodopa therapy led to the use of dopamine receptor agonists early in the course of the disease because they offer antiparkinsonian effects with a lower risk of developing troublesome dyskinesias (Corrodi *et al*, 1973; Calne *et al*, 1974a, b). This was later confirmed in several large-scale randomized controlled trials of second-generation agents such as ropinirole and pramipexole (Parkinson Study Group, 2000; Rascol *et al*, 2000). However, it has become clear that the use of dopamine receptor agonists is not free of motor complications and, most importantly, they often result in more severe nonmotor side effects (psychiatric disorders including psychosis and impulse control disorders, nausea, vomiting, orthostatic hypotension, increased somnolence-sleep attacks, fatigue, and ankle edema) than levodopa (for a review, see Nisipeanu and Korczyn, 2008).

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TABLE 1 Historical Key Developments in Parkinson's Disease Therapeutics Since the First Description of the Disease

Year	Milestone discoveries	References
1817	Publication of James Parkinson's treatise 'An Essay on the Shaking Palsy'	Parkinson (1817)
1861	Publication of a seminal article by Jean-Marie Charcot entitled 'La Paralysie Agitante' that separates Parkinson's disease from other tremorous conditions	Charcot and Vulpian (1861)
1865	First suggestion to rename 'Shaking Palsy' as 'Parkinson's Disease'	Sanders (1865)
1879	Charcot describes evidence that 'atropine' induces symptomatic relief of parkinsonism	Charcot (1879)
1911	First synthesis of D/L Dopa	Funk (1911)
1912	First description of Lewy bodies in the brain of Parkinson's disease patients	Lewy (1912)
1940	First series of neurosurgeries of the basal ganglia to treat movement disorders	Meyers (1940)
1950s	First use of synthetic anticholinergic drugs for the treatment of Parkinson's disease	Fahn (1989)
1951	First evidence for high concentrations of 'encephalin' (now referred to as dopamine) in the human striatum	Raab and Gigee (1951)
1957	First evidence that L-DOPA reverses parkinsonian symptoms in animals treated with reserpine	Carlsson *et al* (1957)
1958	First use of chemical assay to demonstrate high concentrations of dopamine in the brain	Carlsson *et al* (1958)
1960	First evidence for striatal dopamine deficiency in Parkinson's disease	Ehringer and Hornykiewicz (1960)
1961	First evidence that low doses of L-DOPA administered 'intravenously' have antiparkinsonian effects	Birkmayer and Hornykiewicz (1961)
1962	First evidence that 'oral' low doses of L-DOPA have antiparkinsonian effects	Barbeau *et al* (1962)
1967	First evidence that large oral doses of D,L-Dopa induce marked improvements of parkinsonian symptoms	Cotzias *et al* (1967)
1969	First evidence that amantadine is an effective treatment of PD symptoms	Schwab *et al* (1969)
1974	First evidence that oral D2 dopamine receptor agonist (bromocriptine) has antiparkinsonian effects	Calne *et al* (1974a, b)
1975	First evidence that the MAO-B inhibitor, L-deprenyl, has clinical efficacy in PD	Kapp (1992)
1983	First detailed description of MPTP-induced parkinsonism in humans	Langston and Ballard Jr (1983)
1988/1989	First open-label clinical trials testing the antiparkinsonian efficacy of fetal ventral mesencephalic tissue transplants in the striatum of PD patients	Madrazo *et al* (1988); Lindvall *et al* (1989)
1989	First evidence that thalamic deep brain stimulation reduces tremor in PD patients	Benabid *et al* (1989)
1989/1990	Introduction of the 'direct and indirect' pathway model of the basal ganglia circuitry	Albin *et al* (1989); Crossman (1989); DeLong (1990)
1990	First evidence that unilateral subthalamotomy alleviates parkinsonian symptoms in MPTP-treated monkeys	Bergman *et al* (1990)
1992	Reintroduction of pallidotomy as a treatment for PD	Laitinen *et al* (1992)
1995	First evidence that subthalamic nucleus DBS is an effective treatment for Parkinson's disease	Limousin *et al* (1995a, b)
1997	First genetic form of PD identified mutation of the Park1 gene (encoding alpha-synuclein)	Polymeropoulos *et al* (1997)
2003	Introduction of the Braak and Braak model of ascending progression of Lewy body pathology in PD	Braak *et al* (2003)
2011	First publication of a double-blind gene therapy trial (viral vector of the GAD gene in the STN)	Lewitt *et al* (2011)

Thus, the development of these motor and nonmotor side effects in response to all types of dopamine replacement therapy clearly highlights the fact that symptomatic therapies that rely entirely on 'normalizing' dopaminergic transmission may have limited benefits along the course of the disease. The search for additional sites, which could be targeted alone or in combination with dopaminergic drugs, such as adenosine A2A receptors and metabotropic glutamate receptors, will be discussed in this review.

Another major breakthrough that has had a significant impact on the treatment of patients with advanced PD was the introduction of the functional model of the basal ganglia circuitry (Albin *et al*, 1989; Crossman, 1989; DeLong, 1990), which quickly led to renewed interest in surgical therapies for PD (Bergman *et al*, 1990; Laitinen *et al*, 1992; Limousin *et al*, 1995a, b) (Figure 1). Although surgeons originally opted for use of ablative techniques, targeting the internal pallidal segment (internal globus pallidus (GPi)) or the subthalamic nucleus (STN), the standard surgical treatment most commonly used in some patients with advanced PD is now deep brain stimulation (DBS) of the same targets (Benabid *et al*, 2009a, b). In spite of obvious therapeutic benefits toward PD motor symptoms, evidence for the significant nonmotor side effects of STN DBS published in recent years (including depression, psychosis, confusion, and impulse control disorders) has raised concerns about the inappropriate choice of patients and misplacement of DBS electrodes within nonmotor regions of the STN. In this review we will critically examine the rationale, significance, therapeutic benefits, and adverse effects of STN DBS over other potential targets.

Transplantation of dopaminergic tissue has long been considered as another potential therapy for PD (Brundin *et al*, 2010). However, the future of this approach is in doubt due to the lack of effectiveness and the appearance of unexpected side effects in large controlled clinical trials (Freed *et al*, 2001; Olanow *et al*, 2003). Similar to the general approach, there is significant interest in the use of stem cells

Box 1 Cardinal motor features of Parkinson's disease

Bradykinesia/akinesia
- Slowness of movement, fatiguing with decreased amplitude of movement, arrests in ongoing movement
- Decreased spontaneous movements such as eye blinking, swallowing, and arm swing
- Early feature

Tremor
- Rhythmic sinusoidal movement of a body part due to regular contractions of reciprocally innervated muscles (either synchronous or alternating)
- Occurs at rest
- Early feature

Muscle rigidity
- Increase in resistance to passive movement
- 'Cogwheel'
- Patients may complain of stiffness but not a major source of disability
- Early feature

Postural change
- Flexed posture
- Postural instability—retropulsion, propulsion, falls (*en bloc*)
- Late feature

Gait disorder
- Shuffling, lack of arm swing
- Festination: going from walking to running
- Freezing: Feet 'sticking to the floor like glue', occurs with turning, gait initiation, enclosures like doorways
- Late feature

as a treatment for PD. At the time of this writing, the use of these methods in humans remains limited by safety concerns and regulatory issues (Li *et al*, 2008a), which will be discussed below. Finally, this review will examine the current status of a variety of gene-therapy approaches, using viral vector-mediated enzyme replacement or growth factors delivery in specific brain regions of PD patients (Bjorklund and Kirik, 2009; Bjorklund *et al*, 2010a, b; Bjorklund and Kordower, 2010; Rangasamy *et al*, 2010).

All of the therapeutic approaches outlined above aim at treating the dopaminergic motor symptoms of PD, which remain the current focus of therapy development. However, it is clear that PD pathology extends far beyond the dopaminergic nigrostriatal system, and that nonmotor symptoms such as cognitive impairment, dementia, depression, psychosis, and autonomic dysfunction significantly contribute to the complex battery of deficits PD patients face, even at early stages of the disease (Chaudhuri *et al*, 2006, 2011; Chaudhuri and Schapira, 2009; Kasten *et al*, 2010; Lim and Lang, 2010; Poewe, 2010; Wood *et al*, 2010; Bassetti, 2011) (Table 3). Because most of these symptoms do not respond to, but are often exacerbated by, the traditional dopamine replacement therapy and STN DBS, the development of pharmacotherapy that could alleviate these nonmotor symptoms, while being effective in reducing parkinsonian motor signs, represents one of the most important challenges both basic and clinical PD scientists may face in the years to come. In this review, we will present and discuss the results of the double-blind randomized placebo-controlled trials for treatments of some of these nonmotor symptoms (psychosis, depression, dementia), but significant work remains to be done in this field (Table 4).

Another important feature to consider is the fact that current PD therapies discussed in this review do not reduce the rate or extent of dopaminergic cell loss, and thereby do not affect the course of the disease progression. Thus far, attempts to generate a neuroprotective therapy for PD have failed in humans, in spite of the results of promising preclinical animal studies (Siderowf and Stern, 2008; Schapira, 2009a, b). While this reflects in part the inadequacies of the available animal models, progress in this field is also significantly hindered by the lack of reliable biomarkers that would allow early (preclinical) diagnosis of the disease. Neuroprotective treatment trials are also complicated by the absence of endpoints that are biologically meaningful, and not confounded by the symptomatic effects of antiparkinsonian treatments (Schapira and Olanow, 2004; Siderowf and Stern, 2008). However, we will discuss recent evidence obtained in the Parkinson-Associated Risk Study (PARS) indicating that the combination of early nonmotor clinical markers of PD and dopaminergic imaging may provide a sensitive method to diagnose at-risk individuals before the development of motor symptoms and extensive brain degeneration.

This brief review will attempt at summarizing the recent clinical trials and preclinical studies that may impact the therapy of patients with PD in the future. Because of space limitations, we will not provide an extensive account of the previous literature in this field, but rather focus on a few promising research avenues that may have a significant impact in the improvement of PD therapeutics in the years to come. Reflecting the limited availability of specific treatments for the nonmotor features in PD (Chaudhuri *et al*, 2006; Chaudhuri and Schapira, 2009; Lim and Lang, 2010; Wood *et al*, 2010), this review will mainly focus on the treatment of the parkinsonian motor symptoms induced by degeneration of midbrain dopaminergic neurons. A summary of the main PD therapeutic approaches that will be discussed in this review is illustrated in Figure 2.

PD PHARMACOTHERAPEUTICS

Dopamine Replacement Therapy

Pros and cons of levodopa vs dopamine receptor agonists. Dopaminergic drugs have clearly been disease-modifying, bringing about improved daily function, quality of life, and survival (Box 2). Approval of the dopamine precursor LD in 1970 initiated the dopaminergic era (Table 1), followed by

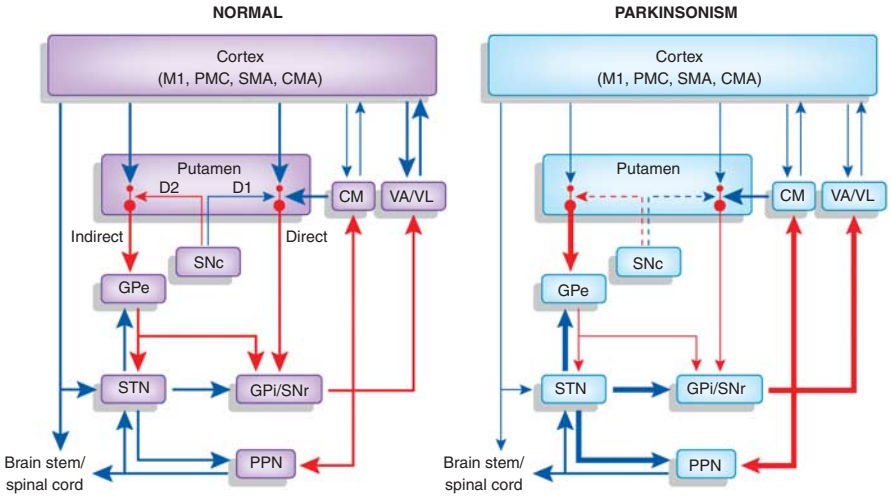

Figure 1. Schematic diagram of the direct (Dir.) and indirect (Indir.) pathways of the basal ganglia motor circuits in normal and parkinsonian states. Red arrows indicate inhibitory projections, and blue arrows indicate excitatory projections. The changes in the thickness of the arrows in the parkinsonian state indicate the proposed increase (larger arrow) or decrease (thinner arrow) in firing-rate activity of specific connections. The dashed arrows used to label the dopaminergic projection from the SNc to the putamen in parkinsonism indicate partial lesion of that system in this condition. Note that many connections have been purposefully omitted from this diagram. CM, centromedian nucleus; CMA, cingulate motor area; GPe, globus pallidus, external segment; GPi, globus pallidus, internal segment; M1, primary motor cortex; PMC, pre-motor cortex; PPN, pedunculopontine nucleus; SMA, supplementary motor area; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; VA/VL, ventral anterior/ventral lateral nucleus (modified from Galvan and Wichmann, 2008).

the development of numerous dopamine receptor agonists, as well as inhibitors of dopamine-metabolizing enzymes, including monoamine oxidase (MAO) B and (peripheral) catechol-*O*-methyltransferase (COMT). COMT inhibitors reduce the metabolism of LD to 3-*O*-methyldopa in the periphery, which extends the duration of the central effects of LD. In the brain, MAO B inhibitors can also enhance the effects of both endogenous and exogenous dopamine. Overall, the currently available agents include three forms of carbidopa/LD (immediate release, controlled release, and orally disintegrating), two orally active dopamine receptor agonists, pramipexole and ropinirole, one injectable dopamine receptor agonist (apomorphine), two MAO-B inhibitors, ie, selegiline (oral, and orally disintegrating) and rasagiline, and two peripheral COMT inhibitors, ie, tolcapone and entacapone. It is beyond the scope of this paper to review these agents in detail, but their characteristics, therapeutic benefits, and limitations have been discussed in previous reviews (Gottwald and Aminoff, 2008; Simuni and Hurtig, 2008; Rajput *et al*, 2008; Waters, 2008). A list of double-blind randomized placebo-controlled trials for dopamine replacement therapies achieved since 2000 is shown in Table 2.

There has not been a great deal of change regarding dopaminergic agents in the last 5–10 years, but there are a few points worth making about our current view of dopamine replacement therapy. LD remains the most potent symptomatic therapy available. Although the discovery of dopamine and LD is accepted as the most important breakthrough in the field of PD research and therapeutics (Hornykiewicz, 2002a, b), the use of this drug has been controversial for 25 years, because of concern that LD may be toxic to dopaminergic neurons, and that the chronic use of this drug may increase the rate of nigral degeneration (Fahn, 1996a, b, Agid, 1998; Simuni and Hurtig, 2008).

This notion was based on a body of evidence, indicating that decreased glutathione, increased Fe^{2+}, increased malondialdehyde, and decreased mitochondrial complex I activity occurred in the SN of parkinsonian patients, thereby suggesting an important role of free radicals in the pathogenesis and apoptotic death of midbrain dopaminergic neurons in PD (Fahn and Cohen, 1992; Blandini *et al*, 2003; Olanow *et al*, 2004). Dopamine, when metabolized by MAO or auto-oxidized, forms H_2O_2, a precursor to the toxic hydroxyl radical. In PD, after loss of a substantial number of nigral cells, surviving neurons increase their dopamine metabolism, thus, possibly increasing the risk of further free-radical formation and neurodegeneration, especially in an environment where protective mechanisms, such as glutathione activity, are diminished, and iron has accumulated (Ahlskog, 2005; Olanow, 1990). Thus, under such conditions, the rise in cytosolic LD was thought to lead to an increase in dopamine formation, and thereby to a further increase in dopamine metabolism with greater free-radical formation (Ahlskog, 2005; Olanow, 1990). These considerations, combined with the adverse side effects commonly associated with long-term LD treatment (see below), led many physicians to delay the use of this drug in PD patients, and relegate it to 'second line' after dopamine receptor agonists (for reviews, see Watts, 1997; Nisipeanu and Korczyn, 2008; Simuni and Hurtig, 2008). However, data from cell culture studies as well as *in vivo* animal and human studies led to conflicting results regarding the

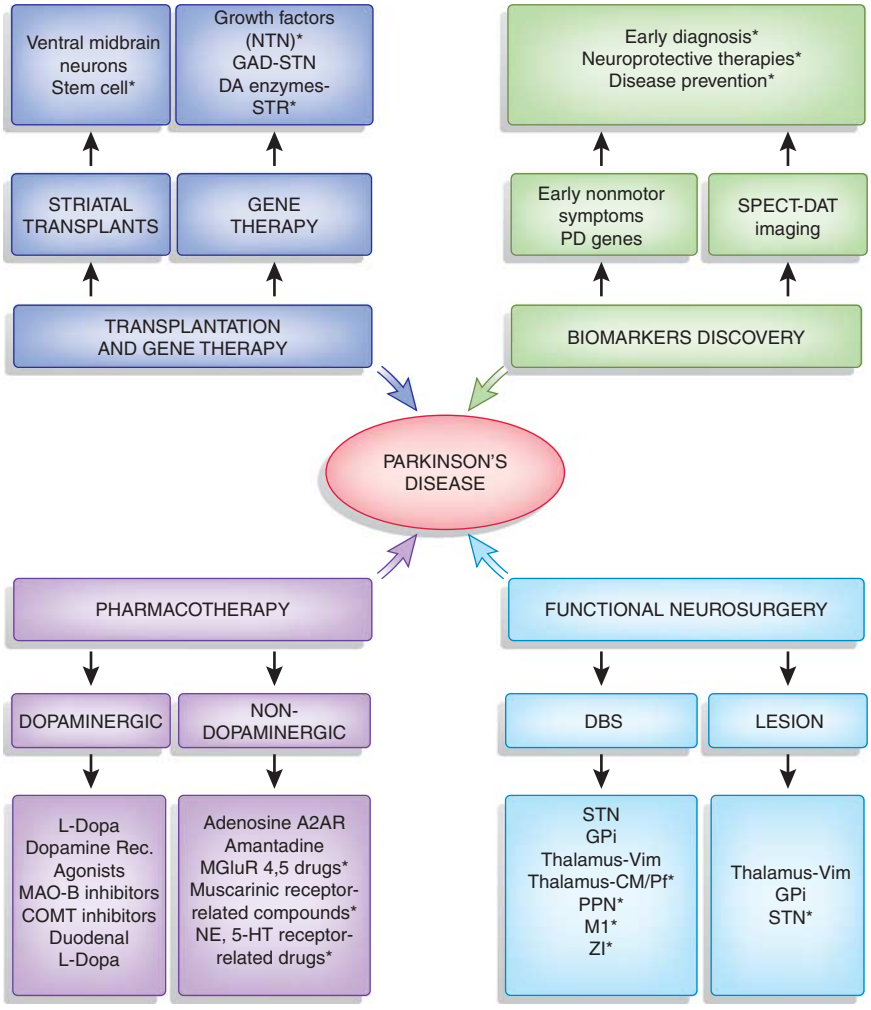

Figure 2. Summary of Parkinson's disease therapeutics discussed in this review. *Indicates agents that have not yet been tested through human double-blind trials.

Box 2 Dopamine replacement therapy

- There is no evidence that the long-term use of LD is toxic for dopaminergic neurons; thus LD remains the first drug of choice for most PD patients, even at early stages of the disease.
- Dyskinesias are the most common motor side effect associated with chronic LD treatment, but are not as prevalent following dopamine receptor agonist therapy.
- The use of dopamine receptor agonists is often complicated by the development of major autonomic and psychiatric side effects that outweigh the therapeutic benefits of these drugs on motor symptoms.
- The development of new delivery methods that attenuate fluctuations of circulating dopaminergic drugs may reduce the development of dyskinesias and other dopamine therapy-mediated side effects.

notion that LD is toxic (Agid, 1998; Agid *et al*, 1999; Simuni and Hurtig, 2008).

The most recent and prominent evidence for this lack of toxicity came from the ELLDOPA (Early *vs* Later Levodopa Therapy in Parkinson's Disease) trial (Fahn *et al*, 2004), a multicenter, placebo-controlled, randomized, double-blind clinical trial in which PD patients with a disease duration of <2 years and a Hoehn & Yahr stage <3 were randomized to receive either placebo, or 50, 100, or 200 mg of LD three times daily. Of the 361 enrolled patients, 311 completed the study, which involved 40 weeks of therapy, including a 3-day taper and a 2-week withdrawal period. The primary outcome was the change in severity of PD symptoms between baseline and the end of the study, as measured by a standard clinical rating scale, the United Parkinson's Disease Rating Scale (UPDRS). The clinical results demonstrated that LD improves PD in a dose-dependent manner, beginning at week 9, and that this improvement lasts through the entire treatment period. Interestingly, after the 2-week withdrawal period, subjects receiving the higher dose of LD were less severely impaired than the other three groups. None of the active treatment groups deteriorated to the level of the placebo group after washout. The main conclusion of this trial was that there is no clinical evidence that LD accelerates PD progression, although imaging data showed an accelerated striatal dopaminergic denervation in LD-treated patients (Fahn *et al*, 2004).

TABLE 2 Key Clinical Trials in Dopamine Replacement Therapy Since 2000

References	Drugs	Study design	Patients	No. of subjects	Primary outcome measure	Results
Rascol *et al* (2000)	Ropinirole vs L-DOPA	DB, RA, PG	Early untreated	268	Occurrence of dyskinesia	Ropinirole caused less dyskinesia. L-DOPA resulted in greater improvement of UPDRS
Dewey *et al* (2001)	Apomorphine	DB, RA, PC, PG	Advanced fluctuating	29	In-patients: change in UPDRS; out-patients: decrease in OFF time	Apomorphone was significantly better than placebo
Parkinson Study Group—TEMPO (2002)	Rasagiline	DB, RA, PC, MD, PG	Early untreated	404	Change in UPDRS	Rasagiline was superior to placebo, no difference between 1 and 2 mg
Fahn and Parkinson Study Group (2005)	L-DOPA	DB, RA, PC, MD, PG	Early untreated	361	Change in UPDRS total between baseline and week 42 (after washout)	All active groups remained improved compared to placebo
Holloway *et al* (2004)	Pramipexole vs levodopa	DB, RA, PG	Early untreated	301	Time to first occurrence of motor complications	Pramipexole delayed motor complications. Levodopa resulted in greater improvement of UPDRS
Olanow *et al* (2004)	Entacapone	DB, RA, PC, PG	Non-fluctuators	750	Change in UPDRS and quality of life	Entacapone equal to placebo with UPDRS, but superior to placebo with quality of life
Waters *et al* (2004)	Orally disintegrating selegiline	DB, RA, PC, PG	Advanced fluctuating	140	Change in hours 'off'	Selegiline was superior to placebo
Rascol *et al* (2005)	Entacapone/ rasagiline	DB, RA, PC, PG	Advanced fluctuating	687	Change in hours 'off'	Rasagiline superior to placebo. Rasagiline and entacapone equivalent
Parkinson Study Group—PRESTO (2005)	Rasagiline	DB, RA, PC, MD, PG	Advanced fluctuating	472	Change in hours 'off'	Rasagiline was superior to placebo, 1 mg superior to 0.5 mg
Entacapone-Tolcapone Switch Study Investigators (2007)	Entacapone vs tolcapone	DB, CO	Advanced fluctuating	150	Change in hours 'on'	Tolcapone was superior to entacapone
Ondo *et al* (2007)	Orally disintegrating selegiline	DB, RA, PC, PG	Advanced fluctuating	148	Change in hours 'off'	Selegiline was not different from placebo
Stocchi *et al* (2010)	Entacapone+ levodopa vs levodopa	DB, RA, PG	Early untreated	747	Time to onset of dyskinesia	Entacapone+levodopa had a shorter time to dyskinesia than levodopa

Abbreviations: DB, double-blind; RA, randomized; PC, placebo-controlled; MD, multiple doses; PG, parallel group; CO, cross-over.

Since then, LD is once again recommended as a therapeutic intervention to be used early in the course of the disease (Obeso and Schapira, 2009; Schapira, 2009a, c; Schapira *et al*, 2009; Sethi, 2010), a recommendation that is supported by the American Academy of Neurology Practice Guidelines (Miyasaki *et al*, 2002). Currently, LD, oral dopamine receptor agonists, and MAO B inhibitors are approved by the Federal Drug Administration (FDA) for use in early and advanced PD, while COMT inhibitors and the broad-spectrum injectable dopamine agonist, apomorphine, are approved only for fluctuating PD symptoms. Clinical trials have demonstrated the usefulness of these drugs under their approved conditions (Factor, 2008).

Side effects of dopamine replacement therapies. Despite their obvious benefits for PD motor symptoms, both LD and dopamine receptor agonists produce important side effects, which, in the case of LD, generally appear after several years of chronic use. The development of motor fluctuations, drug-induced dyskinesia, and psychosis represent some of the key challenges faced by physicians treating PD patients with LD following the long-term use of the drug. Because it can affect as many as 50% of patients chronically treated with LD, the etiology and management of LD-induced dyskinesias have been the topic of a tremendous amount of literature since the early 1970s. However, in spite of these efforts, the underlying substrates of LD-induced dyskinesia remain poorly understood (Nutt, 2000; Gunzler and Nutt, 2008).

Although the use of dopamine receptor agonists represents a reasonable approach to reduce the prevalence of dyskinesias following chronic dopamine replacement therapy in PD, these drugs are not completely free of dyskinesias (5–10%) (Parkinson Study Group, 2000; Rascol *et al*, 2000) and, most importantly, induce disruptive nonmotor side effects to a greater degree than does LD (Antonini *et al*, 2009). Two main categories of dopamine receptor agonist drugs have been available as PD therapeutics, ie, D3/D2 non-ergot dopamine receptor agonists, such as ropinirole and pramipexole, and D2 ergot derivatives, such as bromocriptine, lisuride, cabergoline, and pergolide, which, in addition to their interactions with D2 family receptors, also affect D1 receptors, as well as specific serotonin and adrenergic receptors. Because of their

different chemical nature and pharmacological characteristics, D2 dopamine receptor agonists display distinctive adverse side-effect profiles.

The general pharmacological profiles of dopamine receptor agonists are sufficient to explain many of the differences in the clinical efficacy and side effects between these drugs and LD. In order to mediate their effects, dopamine receptor agonists bypass the degenerating dopaminergic neurons and directly stimulate the intact, although denervated, postsynaptic dopamine receptors in the striatum, and other cortical and subcortical brain regions. In addition, these drugs are not affected by the pharmacokinetic limitation of the short elimination half-life of LD; ie, 1.5 h for LD *vs* 8 and 6 h for pramipexole and ropinirole, respectively. These particular properties allow for a more prolonged stimulation of dopamine receptors when treated with agonists than with LD. Because dopamine receptor agonists target particular receptor subtypes, while LD impacts all dopamine receptors, agonists may mediate more specific therapeutic benefits, and eliminate certain side effects that could result from the broad-spectrum dopamine receptor activation induced by LD. Dopamine agonists may also provide a wider therapeutic window with a decrease in risk of dyskinesias, perhaps because of their longer half-life. Finally, these drugs may diminish the metabolism of dopamine and therefore decrease the formation of free radicals in the remaining dopaminergic neurons and striatum (Factor, 1999). Some of the most common problems that led to the dropout of dopamine receptor agonist therapy include marked peripheral effects such as nausea and orthostatic hypotension, most likely due to direct dopaminergic modulation of the chemoreceptor trigger zone in the vomiting center of the area postrema, and inhibition of the sympathetic nervous system combined with autonomic dysfunction frequently seen in PD. Other unwanted central side effects likely to be generated by dopamine receptor agonists include increased somnolence, sleep attacks, REM sleep disorder, and a variety of psychiatric symptoms (depression, euphoria, hypomania, hallucinations, delusions, paranoia, psychosis, pathologic gambling/shopping, hypersexuality) (for reviews, see Nisipeanu and Korczyn, 2008; Wood, 2010).

On the other hand, because retroperitoneal, pericardial, and pleuropulmonary fibrosis have been associated with the use of ergot derivatives (Rinne, 1987; Tintner *et al*, 2005), the use of this specific group of dopamine-related drugs as treatment for PD was ended, and pergolide in particular was removed from the market.

Sustained levels of circulating dopaminergic drugs: a key to reduce motor fluctuations and dyskinesias. Although the underlying substrate of motor fluctuations and dyskinesias remains unknown, there is good evidence that fluctuating levels (high peaks, low valleys) of circulating dopaminergic drugs favor the development of dyskinesias (Obeso *et al*, 2000; Olanow *et al*, 2006a, b; Antonini and Odin, 2009). The finding that LD, with its short (1.5 h) half-life and sharp peaks, is associated with a substantially higher frequency of dyskinesia than dopamine agonists, which have longer (6–8 h) half-lives and flatter pharmacokinetic curves, supports this notion. Furthermore, the finding that COMT inhibitors, which increase the half-life of LD, decrease motor fluctuations also suggests that longer-acting agents can treat or prevent these complications. Thus, the development of new delivery technology that provides more sustained levels of the therapeutic dopaminergic agents may be a useful approach to minimize the unwanted side effects (Nutt *et al*, 2000; Olanow *et al*, 2006a, b; Olanow, 2008; Odin *et al*, 2008). We will discuss two different approaches here.

One approach to accomplish this goal is through the continous infusion of a short-acting dopamine receptor agonist. Apomorphine hydrochloride has been used for this purpose. The drug is a non-ergot compound that has full dopamine receptor agonist properties, is one of the oldest of all dopamine receptor agonists, but also the most recently FDA-approved PD therapeutic agent in the United States. Its affinities to D1, D2, D3, and D4 dopamine receptors are similar to those of dopamine (Factor, 1999; Antonini and Tolosa, 2009). It is the only dopamine receptor agonist with antiparkinsonian efficacy similar to LD. Because the oral use of apomorphine is not effective due to extensive hepatic metabolism, other routes of administration must be used. The drug is rapidly absorbed after subcutaneous injection, and has a half-life of 30–60 min. Clinical improvements start within 20 min of administration when the drug appears in the cerebrospinal fluid. Double-blind clinical trials have shown the effectiveness of subcutaneously injected apomorphine in improving PD motor symptoms (Cotzias *et al*, 1970; Dewey *et al*, 2001). Despite these benefits, the long-term use of subcutaneous apomorphine infusions in the United Kingdom has been associated with significant technical difficulties and cutaneous adverse effects (Hughes *et al*, 1993). Because of these issues, infusions of apomorphine have not been very actively pursued in the United States. The development of other infusion methods (such as sublingual, intranasal, rectal, transdermal, or intravenous administration) may make apomorphine treatment a more attractive choice in the treatment of PD (Factor, 2004; LeWitt, 2004). The main autonomic side effects of apomorphine are the same as those described above for other dopamine receptor agonists (ie, nausea, hypotension, and drowsiness/sleep problems), although psychiatric problems appear to be less prevalent with intermittent apomorphine injections than with other agonists perhaps because of the short-term effect (Dewey *et al*, 2001, Factor, 2004).

Another approach to avoid the effects of pulsatile LD dosing is to deliver the drug in a continuous manner. A recently introduced method has been to deliver LD through direct duodenal infusion. This therapeutic approach requires surgical placement of a percutaneous enteroduodenal tube. Its use has been reserved for the most advanced patients, and particularly those who are not candidates for

surgical therapy. Early attempts to use LD in this way were found to be cumbersome and complicated by solubility issues (Nyholm and Aquilonius, 2004). After its approval in Europe, a recently introduced formulation and delivery device that relies on duodenal infusions of LD in a viscous gel (Duodopa) is being studied in a phase 3 trial in the United States (Annic *et al*, 2009; Westin *et al*, 2011). The gel medium prevents LD from coming out of the solution and avoids clogging of administration tubes. This form of treatment is safe as monotherapy and appears to provide significant improvement in motor fluctuations over various oral dopamine-related drug combinations (Nilsson *et al*, 2001). However, the common incidence of adverse effects such as movement of the cannula from the duodenum, irritation, and erosion of the skin around the port warrants further investigations before this approach can be safely used as routine PD treatment. A summary of the key developments about dopamine replacement therapy is shown in Box 2.

Non-Dopaminergic Therapies

Anticholinergic drugs: current cholinergic therapies. Anticholinergic drugs are the oldest therapeutic agents utilized in PD, dating back to the late 1800s and Charcot (Adler, 2008; Box 3). Initially, naturally occurring belladonna alkaloids were used, including atropine and scopolamine, but in the 1950s, synthetic formulations of muscarinic receptor blockers arrived on the scene, including benztropine, trihexyphenidyl, and ethopromazine. In the early 1960s, it was theorized that the dopaminergic deficit would lead to an increase in striatal cholinergic activity, contributing to tremor and other symptoms (Barbeau, 1962; Barbeau *et al*, 1962; Adler, 2008). There are surprisingly few trials of anticholinergic drugs in PD, and most of them have been carried out over 30 years ago (for a review, see Adler, 2008). In general, the clinical effects were found to be modest and much less robust than LD. The effect is believed to be most notable for rigidity and tremor (Doshay *et al*, 1956, Koller, 1986). In practice, the use of these drugs is fairly limited. They are associated with a range of adverse effects, including memory loss, confusion, hallucinations, constipation, urinary symptoms, dry mouth, dry eyes, and blurred vision. Because the anticholinergic drugs are poorly tolerated by the elderly, they are most often used in young patients with tremor-predominant disease and dystonia. The latter use is based on the effectiveness of these drugs in idiopathic dystonia (Chuang *et al*, 2002). In PD patients, these drugs can cause or increase dyskinesia as well. A summary of the key developments about dopamine replacement therapy is shown in Box 2.

Anticholinergic drugs: specific muscarinic cholinergic agents. Acetylcholine mediates its central effects through activation of two main groups of receptors, the ionotropic fast-acting nicotinic receptors and the metabotropic G protein-coupled muscarinic cholinergic receptors (mAChRs) that comprise five subtypes, namely M1–M5. M1, M3, and M5 couple to Gq and activate phospholipase C, whereas M2 and M4 couple to Gi/o and related ion channels and adenylyl cyclase. There is strong evidence that the main autonomic adverse effects of cholinergic drugs are mediated by the activation of peripheral M2 and M3 receptors, while cognitive effects may be related to M1 receptor activation (Anagnostaras *et al*, 2003; Bymaster *et al*, 2003a, b, c; Hasselmo, 2006; Fisher, 2008; Langmead *et al*, 2008; Conn *et al*, 2009a). Given this evidence, drugs acting specifically at M4 or M5 receptors may have fewer side effects than the current non-specific drugs. Unfortunately, previous efforts to develop selective ligands for individual mAChR subtypes have failed. However, recent studies have led to the discovery and characterization of ligands for individual mAChR subtypes, including M1, M4, and M5 (Conn *et al*, 2009a; Weaver *et al*, 2009a; Digby *et al*, 2010), that display a high specificity profile, at least when tested *in vitro*. The development of these compounds was achieved by targeting allosteric sites on the mAChRs that are not as highly conserved as the orthosteric acetylcholine binding site. These agents provide new opportunities to determine the physiological roles of individual mAChRs in the basal ganglia circuitry and to assess the antiparkinsonian efficacy of highly selective mAChR antagonists (Conn *et al*, 2009a, b), but to do so the full specificity profile of these compounds must be characterized *in vivo*. In this regard, recent *in vivo* studies indicate that the allosteric modulators display favorable pharmacokinetic properties and blood–brain barrier permeability, and have confirmed their potential therapeutic benefits in rodent models of Alzheimer's disease and schizophrenia (Caccamo *et al*, 2006; May *et al*, 2007; Brady *et al*, 2008; Chan *et al*, 2008; Shekhar *et al*, 2008; Conn *et al*, 2009a, b; Bridges *et al*, 2010; Digby *et al*, 2010).

Adenosine A_{2A} receptor antagonists: general overview. A potentially new symptomatic and/or neuroprotective approach in the treatment of PD is the use of adenosine

Box 3 Non-dopaminergic therapies

- Because of cognitive and autonomic side effects, anticholinergic drugs are not commonly used as PD therapeutics, but the recent development of specific muscarinic receptor-related allosteric modulators may open up new avenues for the targeting of the cholinergic system in PD.
- Despite promising preclinical evidence supporting the use of adenosine A_{2A} receptor antagonists as antiparkinsonian therapy, the results of recent human trials show only modest benefits, although studies assessing the efficacy of new compounds are still underway.
- Apart from amantadine, ionotropic glutamate receptor antagonists are not considered as suitable PD therapeutics because of debilitating side effects.
- mGluR5 and mGluR4 are the most promising metabotropic glutamate receptor targets for PD therapeutics. The recent development of new drugs with good pharmacokinetic profile and brain permeability that target these receptors offers promising avenues for the development of novel non-dopaminergic PD therapeutics.
- There is preclinical evidence that the combination therapy of A_{2A} receptor and mGluR5 receptor antagonists has synergistic antiparkinsonian efficacy.

A_{2A} receptor antagonists (Schwarzschild *et al*, 2006; Menon and Stacy, 2008; Morelli *et al*, 2010; Shah and Hodgson, 2010). Adenosine is a ubiquitous purine with signaling properties that mediate its effects through four subtypes of G-protein-coupled adenosine receptors: A_1, A_{2A}, A_{2B}, and A_3 (Schwarzschild *et al*, 2006; Menon and Stacy, 2008; Morelli *et al*, 2007, 2009, 2010; Shah and Hodgson, 2010).

A_1 and A_{2A} receptors are expressed in the brain, with A_{2A} being primarily localized to the dorsal striatum, nucleus accumbens, olfactory tubercle, and external globus pallidus (GPe) (Schwarzschild *et al*, 2006). In the striatum, A_{2A} receptors are co-localized with dopamine D_2 receptors, the peptide enkephalin, and the metabotropic glutamate receptor 5 (mGluR5), with which they functionally interact in dendrites and spines of medium spiny striatopallidal neurons within the indirect pathway of the basal ganglia (Fuxe *et al*, 2003, 2007a, b, 2010a, b; Tanganelli *et al*, 2004; Kachroo *et al*, 2005; Simola *et al*, 2008; Agnati *et al*, 2010; Tozzi *et al*, 2011) (Figure 1). D_2 and A_{2A} receptors have opposite effects on the activity of striatal neurons (Ferré *et al*, 1997). Because of their preferential localization on the D2 receptor containing striatofugal neurons of the basal ganglia, combined with basic electrophysiological data showing that A_{2A} receptor activation regulates GABAergic transmission at striatopallidal synapses and modulates both glutamatergic and GABAergic transmission in the striatum, these receptors have generated significant interest as potential non-dopaminergic targets for PD therapy (Schwarzschild *et al*, 2006; Morelli *et al*, 2007; Simola *et al*, 2008; Shah and Hodgson, 2010). This interest stems from the idea that blockade of A_{2A} receptors at the striatopallidal GABAergic synapse or at corticostriatal glutamatergic synapses, both known to be overactive in PD, may help to restore the balance between the striatofugal pathways and may thereby alleviate the motor symptoms of PD (DeLong, 1990; Wichmann and DeLong, 2003; Hauser and Schwarzschild, 2005; Schwarzschild *et al*, 2006) (Figure 1).

While the symptomatic anti-parkinsonian and anti-dyskinetic benefits of the drugs (see below) have generated most interest, the targeting of adenosine transmission as PD therapy is reinforced by epidemiological data suggesting that caffeine (a non-selective adenosine receptor antagonist) may protect nigral dopaminergic neurons against degeneration in PD (Jiménez-Jiménez *et al*, 1992; Ross *et al*, 2000; Ascherio *et al*, 2001; Hernan *et al*, 2002; Powers *et al*, 2008; McCulloch *et al*, 2008).

Adenosine A_{2A} receptor antagonists: clinical trials in PD. So far, three A_{2A} receptor antagonists have been developed for use as antiparkinsonian or anti-dyskinetic agents in PD. The first generation of these compounds was the xanthine istradefylline (previously known as KW-6002). Preclinical data from rat and nonhuman primate models of PD were very promising, showing that this drug can alleviate parkinsonian symptoms and reduce the incidence of LD-induced dyskinesias (Kanda *et al*, 1998; Grondin *et al*, 1999; Bibbiani *et al*, 2003; Lundblad *et al*, 2003; Jenner *et al*, 2009). However, four phase III double-blind, randomized, placebo-controlled trials in humans have not met these expectations. In these studies, istradefylline was utilized as add-on therapy to 1500 PD patients with motor fluctuations and dyskinesia. These studies demonstrated a statistically significant, but modest decrease of 0.7–1.2 h 'off' time, associated with a similar increase in 'on' time (LeWitt *et al*, 2008; Stacy *et al*, 2008). The frequency of dyskinesia in the treated group was actually greater than that observed in the group treated with placebo. The improvement in 'off' time and 'on' time lasted up to 52 weeks (Factor *et al*, 2010). A negative outcome was recently reported when istradefylline was used as first-line therapy (Fernandez *et al*, 2010). Together, these outcomes resulted in a 'nonapprovable' letter from the FDA.

However, it is important to notice that none of these studies examined the potential of istradefylline to prevent dyskinesia as done in the preclinical primate studies (Grondin *et al*, 1999), most likely because this would have required a forced decrease of LD, risking the development of severe parkinsonism in advanced patients.

A second-generation drug under examination in humans is the non-xanthine preladenant (previously known as SCH420814). The potency, affinity, and selectivity of this A_{2A} receptor antagonist are higher than those of the other available A_{2A} receptor antagonists (Hodgson *et al*, 2009). Like istradefylline, this agent has antiparkinsonian and antidyskinetic effects in rat and monkey models of PD (Hodgson *et al*, 2009, 2010). So far, the results of one double-blind, placebo-controlled phase II trial in PD subjects have been reported with preladenant, but, as with istradefylline, the antiparkinsonian effects were modest (Hauser *et al*, 2011). However, in contrast to istradefylline, preledenant does not increase dyskinesia, as demonstrated in the preclinical MPTP-treated monkey study (Hodgson *et al*, 2010). Phase III trials are currently underway for early untreated, as well as advanced PD patients.

Finally, human investigations of the two additional A_{2A} antagonists, SYN 115 and BII014, have just begun. In a small blinded, crossover trial, perfusion magnetic resonance imaging (MRI) demonstrated that SYN 115 reduces cerebral blood flow in the thalamus of PD subjects, consistent with a potential reduction of overinhibition from the indirect pathway (Black *et al*, 2010). Phase II trials are underway.

Glutamate receptor-related compounds: ionotropic glutamate receptor antagonists. In the CNS, glutamate mediates its effects through two broad categories of receptors, namely the fast-acting ionotropic receptors, or slow modulatory G-protein-coupled metabotropic glutamate receptors (mGluRs). The family of ionotropic receptors comprises three main subtypes: the alpha-amino-3-hydroxy-5-methyl-4-isoxzazole-propionic acid (AMPA), the *N*-methyl-D-aspartate (NMDA), and the kainate (KA) receptors. These receptors, made up of combinations of different subunits, are coupled with sodium or calcium ion channels, and participate in fast excitatory neurotransmission, while the

mGluRs, pooled into three main groups (called groups I, II, and III) based on their sequence homology and pharmacological properties, are coupled with different G proteins and mediate slow modulatory effects on postsynaptic neurons via either pre- or post-synaptic mechanisms (Pin and Duvoisin, 1995; Conn and Pin, 1997; Nakanishi *et al*, 1998; Anwyl, 1999).

PD is thought to be associated with increased glutamatergic transmission at corticostriatal as well as subthalamofugal synapses in the basal ganglia circuitry, resulting in substantial interest in the use of glutamate receptor blockers as treatment in patients with PD (DeLong, 1990; Blandini and Greenamyre, 1998; Chase *et al*, 1998; Oh and Chase, 2002; Greene, 2008) (Figure 1). Although various antagonists of ionotropic glutamate receptors have proven to be good antiparkinsonian agents to reduce motor symptoms in preclinical studies, most of these compounds were found to induce debilitating nonmotor side effects in humans that were not assessed in animal studies, most likely due to the fact that AMPA and NMDA receptors are widely distributed and essential for normal brain functioning (Starr, 1995; Blandini and Greenamyre, 1998). Apart from amantadine, a serendipitously discovered NMDA receptor antagonist with good anti-dyskinetic properties (Factor and Molho, 1999), no other glutamate receptor antagonists are clinically used to treat PD. In contrast to amantadine, the non-selective glutamate receptor antagonists memantine, riluzole, and remacemide failed to reduce dyskinesias (Merello *et al*, 1999; Braz *et al*, 2004). Infenprodil and related compounds, which belong to a family of polyamine channel blockers with high affinity for specific NMDA receptors that comprise the NR2B subunit, have anti-parkinsonian and anti-dyskinetic effects in rodent and monkey models of PD (Papa and Chase, 1996; Blanchet *et al*, 1999; Nash *et al*, 1999, 2000). However, preliminary human studies of these compounds led to negative outcomes (Montastruc *et al*, 1992). To date, there are no clinical trials of ionotropic glutamate receptor-active agents.

Metabotropic glutamate receptor ligands: MGluR5 antagonists. In general, the group I mGluRs (mGluR1 and mGluR5) are expressed postsynaptically and mediate excitatory effects on their postsynaptic targets, whereas group II (mGluR2/3) and group III (mGluR4,6,7,8) are mainly expressed presynaptically, where they act as inhibitory regulators of glutamatergic or GABAergic transmission (Schoepp and Conn, 1993; Pin and Duvoisin, 1995; Conn and Pin, 1997; Cartmell and Schoepp, 2000; DeBlasi *et al*, 2001; Galvan *et al*, 2006; Ferraguti *et al*, 2008; Niswender and Conn, 2010). Apart from mGluR6, which is confined to the retina, mGluRs are expressed to varying degrees in different brain regions, including the basal ganglia (Conn and Pin, 1997; Conn *et al*, 2005; Galvan *et al*, 2006). Most mGluRs are predominantly found in neurons, but mGluR2 and a significant contingent of mGluR5 are also expressed in glial cells. The mGluRs regulate neuronal activity via modulation of ion channels, release of intracellular calcium, and functional interactions with ionotropic glutamate receptors and other G-protein-coupled receptors (including D2 dopamine receptors and A_{2A} adenosine receptors). Because of their modulatory nature, different pharmacological properties, enrichment in specific brain regions, and drug specificity, the mGluRs are considered as highly relevant potential drug targets for the treatment of various brain diseases, including PD (Ossowska *et al*, 2002; Conn *et al*, 2005; Swanson *et al*, 2005; Marino and Conn, 2006; Johnson *et al*, 2009; Lindsley *et al*, 2009; Dolen *et al*, 2010; Duty, 2010; Niswender and Conn, 2010; Spooren *et al*, 2010; Nicoletti *et al*, 2011).

All three groups of mGluRs are significantly enriched in the basal ganglia. Based on their distribution, physiological effects on synaptic transmission, and availability of specific drugs, mGluR5 and mGluR4 are currently being investigated as potentially relevant targets for PD therapy. Although group II mGluRs are also widely distributed throughout the basal ganglia circuitry, the modulation of these receptors does not offer significant benefit in animal models of PD (Smith *et al*, 2000, 2001; Conn *et al*, 2005; Niswender and Conn, 2010). The mGluR5 is heavily distributed postsynaptically in key basal ganglia nuclei, including the striatum, the globus pallidus, and the STN (Hanson and Smith, 1999; Smith *et al*, 2000, 2001; Hubert *et al*, 2001; Paquet and Smith, 2003; Kuwajima *et al*, 2004; Conn *et al*, 2005; Kuwajima *et al*, 2007; Poisik *et al*, 2007; Niswender and Conn, 2010). In each of these structures, the localization and physiological properties of this receptor have been carefully studied in rodents and nonhuman primates (Smith *et al*, 2000, 2001; Awad *et al*, 2000; Marino *et al*, 2001; Poisik *et al*, 2003; Conn *et al*, 2005; Galvan *et al*, 2006).

mGluR5 activation mediates slow excitatory effects upon basal ganglia nuclei. There is also evidence that the expression and function of mGluR5 vary in acute and chronic models of dopamine denervation (Samadi *et al*, 2008; Ouattara *et al*, 2010, 2011). The mGluR5 antagonists, MPEP (2-methyl-6-(phenlethenyl)-pyridine) and MTEP (3-(2-methyl-1,3-thiazol-4-yl(ethynyl)pyridine)), are among the potential antiparkinsonian therapeutic agents that have been tested in rodent and nonhuman primate models of PD. Although the antiparkinsonian effects of acute administration of these drugs are modest, behavioral data suggest that chronic exposure to MPEP may be more effective than acute administration in alleviating parkinsonian motor signs in partially dopamine-depleted rats (Breysse *et al*, 2002, 2003; Coccurello *et al*, 2004; Ossowska *et al*, 2005). In addition, antidyskinetic effects of the mGluR5 antagonist have been seen in both rat and monkey models of PD (Mela *et al*, 2007; Rylander *et al*, 2009; DeKundy *et al*, 2010; Johnston *et al*, 2010; Gregoire *et al*, 2011; Marin *et al*, 2011). Interestingly, mGluR5 and A_{2A} receptor antagonists exert synergistic antiparkinsonian effects in rat models of PD (Coccurello *et al*, 2004). It is noteworthy that MPEP and MTEP are also neuroprotective toward degeneration of midbrain dopaminergic neurons in mice and monkey models of PD (Flor

et al, 2002; Battaglia *et al*, 2004; Masilamoni *et al*, 2011). In MPTP-treated nonhuman primates, MTEP also protects locus coeruleus noradrenergic neurons from degeneration (Masilamoni *et al*, 2011). The translation of these preclinical studies in animal models to patients with PD must be interpreted with caution.

Although MTEP and MPEP are mGluR5 antagonists with high specificity and affinity, their pharmacological profile is not suitable for chronic therapeutic use in humans because of their short half-life and rapid clearance from the brain (Gasparini *et al*, 2008; Rodriguez *et al*, 2010). However, the recent development of new negative allosteric modulators of mGluR5 that offer better pharmacokinetic properties for this purpose may provide the necessary tools to further assess the clinical relevance of these drugs in humans (Gasparini *et al*, 2008; Zhou *et al*, 2009; Rodriguez *et al*, 2010; Nicoletti *et al*, 2011).

Metabotropic glutamate receptor ligands: MGluR4 agonists. Another mGluR that has generated significant interest as a potential antiparkinsonian target is mGluR4. Its strong expression at striatal GABAergic synapses in the GP and cortical glutamatergic synapses in the striatum, combined with electrophysiological *in vitro* data showing that its activation significantly reduces synaptic transmission at these key synapses of the basal ganglia circuitry (Valenti *et al*, 2003; Conn *et al*, 2005; Marino and Conn, 2006; Beurrier *et al*, 2009), has provided the rationale to examine the antiparkinsonian effects of mGluR4 agonists in rodent models of PD. Because of the lack of group III mGluR-related compounds that could cross the blood–brain barrier, the original evidence that mGluR4 activation would alleviate PD symptoms came from studies using intracerebroventricular or intrapallidal administration of either the broad-spectrum group III mGluR agonist L-AP4 (L-2-amino-4-phosphono-butanoate) or the mGluR4 allosteric potentiator PHCCC (*N*-phenyl-7-(hydroxylimino)cyclopropa[b]chromen-1a-carboxamide) (Marino *et al*, 2003; Valenti *et al*, 2003; Marino and Conn, 2006; Lopez *et al*, 2007, 2008; Johnson *et al*, 2009; Nicoletti *et al*, 2011).

The recent development of a series of allosteric mGluR4 potentiators that display good pharmacokinetic properties, cross the blood–brain barrier, and have significant antiparkinsonian effects in various rodent models of PD provides a promising avenue toward the development of mGluR4-related therapeutic agents in PD (Niswender *et al*, 2008; Hopkins *et al*, 2009; Johnson *et al*, 2009; Williams *et al*, 2009; Niswender and Conn, 2010; Engers *et al*, 2011).

Other potential non-dopaminergic PD pharmacotherapeutics. Other agents that are being considered as non-dopaminergic PD therapeutics include modulators of the noradrenergic system. In small open-label studies, the epinephrine precursor L-threo-DOPS was found to have beneficial effects on freezing and gait disturbances in PD patients (Tohgi *et al*, 1993; Giladi, 2008; Devos *et al*, 2010). Furthermore, methylphenidate, a mixed dopamine and noradrenaline reuptake inhibitor, was found to show benefit on gait and freezing scores in a randomized controlled trial of 17 advanced PD patients (Devos *et al*, 2007), but results of a more recent trial in 27 PD patients revealed that methylphenidate did not improve gait and tended to worsen measures of motor functions, sleepiness, and quality of life (Espay *et al*, 2011). Other trials using lower doses of this compound in PD patients with gait impairment are currently underway. Another category of noradrenaline-related agents being considered as a potential anti-dyskinetic therapy in PD are alpha 2c adrenoreceptor antagonists, such as idazoxan and fipamezole. A recent phase IIa study in 21 PD patients showed a significant beneficial effect of fipamezole on dyskinesia (Bara-Jimenez *et al*, 2004). A more extensive trial of this compound is underway.

Serotonin and serotonin receptors (5HT1a, 5HT 1b, d, 5HT 2a, c) are widely distributed throughout the basal ganglia, where they modulate GABAergic, glutamatergic, and dopaminergic transmission (Di Matteo *et al*, 2008). Changes in serotonergic transmission are usually not considered in models of the pathophysiology of PD, but the 5HT1a agonist, sarizotan, was recently found to reduce dyskinesias and extend the duration of action of LD in a recent phase II study in 18 patients with advanced PD (Bara-Jimenez *et al*, 2005). However, further studies failed to confirm these beneficial effects, most likely due to the additional dopamine D2 receptor antagonist properties of sarizotan (Goetz *et al*, 2007, 2008). Another, more selective, 5HT1A agonist, piclozotan, has also been developed, and is currently being tested in a multi-center, phase II trial in dyskinetic PD patients. There is also preliminary evidence that non-selective 5HT-2a, c receptor antagonists may have anti-dyskinetic effects (Oh *et al*, 2002; Durif *et al*, 2004), although additional randomized trials are needed to confirm these observations (Katzenschlager *et al*, 2004). A summary of the key recent findings related to non-dopaminergic pharmacotherapies for Parkinson's disease is discussed in Box 3.

THERAPEUTICS FOR NONMOTOR SYMPTOMS OF PD

Nonmotor symptoms are very common in PD and often result in significant disability and decrease in quality of life of these patients, often more so than the motor features (Box 4). The key nonmotor symptoms of PD are listed in Table 3. Unfortunately, most of these symptoms, which in some cases can occur at early stages of the disease, years prior to the appearance of motor deficits, are often poorly recognized by the clinicians and remain inadequately managed. Nonmotor symptoms are classified under four main categories: neuropsychiatric, sleep, autonomic, and sensory. Many of these symptoms, which are unresponsive, exacerbated, or even induced by conventional PD therapy, are very prevalent, affecting the vast majority of patients, most particularly those who survive for many years with the disease (Hely *et al*, 2005). For these reasons, nonmotor symptoms have become one of the greatest challenges to the

Box 4 Therapeutics for nonmotor symptoms of PD

- Nonmotor symptoms in PD are pooled in neuropsychiatric, sleep, autonomic, and sensory disorders. Many of these deficits are highly prevalent and significantly reduce PD patients' quality of life.
- Clozapine is the most efficient antipsychotic agent in PD patients, but due to the possible development of agranulocytosis, quetiapine is the first-line antipsychotic drug being used.
- Because of their limited power, randomized controlled trials comparing the efficacy of tricyclic agents over SSRIs in depressed PD patients led to conflicting results. Larger trials are needed.
- Early cognitive decline and dementia are common in PD. Monoaminergic cell loss, cortical Lewy bodies, and basal forebrain cholinergic neuron degeneration contribute to these deficits. Acetylcholinesterase inhibitors are the first-line treatment for dementia in PD, but these drugs suffer from significant adverse effects.
- There is no randomized clinical trial of therapeutics for autonomic dysfunctions and sleep disorders. Their management is solely based on symptom control.
- The development of better diagnostic and therapeutic tools to recognize and manage nonmotor symptoms of PD is one of the greatest challenges for PD therapeutics.

TABLE 3 Nonmotor Symptoms of Parkinson's Disease

Neuropsychiatric
• Psychosis (hallucinations, delusions, illusions)
• Depression
• Apathy
• Anxiety
• Anhedonia
• Attention deficit
• Impulsive and compulsive behaviors
• Panic attacks
• Cognitive impairments[a]
• Dementia
Sleep disorders
• Rapid eye movement (REM) sleep behavior disorder (loss of atonia)[a]
• Vivid dreaming
• Restless legs syndrome
• Excessive daytime somnolence
• Insomnia
Autonomic symptoms
• Orthostatic hypotension (related falls)
• Gastrointestinal dysfunctions (constipation, fecal incontinence)[a]
• Bladder disturbances (urgency, frequency)
• Nausea
• Vomiting
• Drooling
• Increased sweating
• Sexual dysfunctions (hypersexuality, erectile dysfunction)
• Dysphagia/choking
Sensory deficits
• Amosmia (olfactory deficits)[a]
• Ageusia (taste deficits)[a]
• Pain
• Paresthesia

[a]Nonmotor symptoms that often precede PD motor dysfunctions.

current clinical management of PD. There have been a small number of placebo-controlled trials of treatment for specific PD nonmotor symptoms (Table 4), but this field remains largely unexplored and will deserve significant attention in the years to come. Treatments of hallucinations psychosis, depression, and dementia have received the greatest attention in recent years because they occur in such a large proportion of PD patients.

The efficacy and safety of clozapine for psychosis in PD has been confirmed in two randomized, placebo-controlled, double-blind trials, but owing to the small (<1%) but serious risk of developing agranulocytosis and the requirement for white blood cell monitoring, clinicians are hesitant in using this drug as a first-line antipsychotic agent. Quetiapine, which is not associated with this side effect and does not require long-term blood monitoring, is generally utilized first line because of its ease of use. Unfortunately, two recent small randomized controlled trials of quetiapine were negative, but owing to the small number of patients enrolled, additional larger-scale studies would be required to clearly assess the antipsychotic efficacy of quetiapine in PD (Table 4). Despite these trials, quetiapine continues to be used because it does not worsen motor features (this is also true of clozapine) as seen with other atypical antipsychotics such as olanzapine, risperidone, aripirazole, and others. If quetiapine fails, then clozapine is generally prescribed.

Although variable degrees of depression afflict as many as 40–70% of PD patients, only a small proportion suffers from major depressive disorder (Wood *et al*, 2010). There is no clear correlation between the severity of motor symptoms and depression, nor is there any obvious relationship with the PD age of onset and family history of depression in these patients (Wood *et al*, 2010). Large randomized control trials in depressed PD patients are rare. The small and short trials completed thus far, which compared the relative efficacies of tricyclic antidepressants (TCAs) *vs* selective serotonin reuptake inhibitors (SSRIs), led to conflicting results that are hard to interpret because of the limited power of these studies. The largest published trial to date, which involved 52 patients with PD and depression, showed that that the TCA nortriptyline, known as a non-specific norepinephrine reuptake blocker (SNRI), was more efficacious than the SSRI paroxetine CR in reducing depression in PD (Menza *et al*, 2009) (Table 4). However, another small trial ($N=55$ subjects) assessing the antidepressant efficacy of a more selective SNRI, atomoxetine, led to negative results, but showed that this drug was associated with improvement in global cognitive performance and daytime sleepiness (Weintraub *et al*, 2010). Finally, the most recent and largest trial ($N=115$ subjects) that compared the

TABLE 4 Double-Blind Placebo-Controlled Trials for PD Nonmotor Symptoms

References	Drugs	Study design	Type of patients	No. of subjects	Length	Primary outcome	Results
PSYCHOSIS							
The Parkinson Study Group (1999)	Clozapine vs placebo	Randomized, double-blind, placebo-controlled	PD with drug-induced psychosis	60	4W	CGIS, BPRS, SAPS	Clozapine significantly improves drug-induced psychosis without worsening PD.
The French Clozapine Parkinson Study Group (1999)	Clozapine vs placebo	Randomized, double-blind, placebo-controlled	PD with psychosis	60	4W	CGIS, PANSS	Clozapine significantly improves drug-induced psychosis without worsening PD.
Pollak *et al* (2004)	Clozapine vs placebo	Randomized, double-blind, placebo-controlled	PD with psychosis	46	4W (+12W open-label extension)	CGIS, PANSS	Clozapine significantly improves psychosis without worsening motor symptoms and cognitive functions.
Ondo *et al* (2005)	Quetiapine vs placebo	Randomized, double-blind, placebo-controlled	PD with visual hallucinations	31	12W	BPRS	No significant effect of quetiapine on psychosis rating scale. No change in UPDRS score.
Rabey *et al* (2007)	Quetiapine vs placebo	Randomized, double-blind, placebo-controlled	PD with psychosis	58	12W	BPRS	No significant effect of quetiapine on psychosis rating scale. No change in UPDRS score.
DEPRESSION							
Devos *et al* (2008)	Desipramine (TCA) vs citalopram (SSRI)	Randomized, double-blind, placebo-controlled	PD with major depression	48	14, 30 days	MADRS	Short-term significant effect of desipramine; both drugs have similar effects on depression after 1-month treatment.
Menza *et al* (2009)	Nortriptyline (TCA) vs paroxetine CR (SSRI) vs placebo	Randomized, double-blind, placebo-controlled	PD with major depression	52	8W	HAM-D	Nortriptyline is more efficacious than paroxetine CR for the treatment of depression in PD.
Weintraub *et al* (2010)	Atomoxetine (TCA) vs placebo	Randomized, double-blind, placebo-controlled	PD with depression	55	8W	IDS-C score	Atomoxetine is not an efficacious anti-depressant drug in PD. Improves global cognitive performance and reduces daytime sleepiness.
Dobkin *et al* (2011)	Nortriptyline (TCA) vs paroxetine CR (SSRI) vs placebo	Randomized, double-blind, placebo-controlled	PD with major depression	52	8W	HAM-D	Nortriptyline is an efficacious antidepressant in PD.
Ondo *et al* (2011)	Memantine vs placebo	Randomized, double-blind, placebo-controlled	PD with depression	40	8W	HAM-D	Memantine is well tolerated, but does not improve depression, fatigue and sleepiness in PD.
Richard *et al* (2010)	Venlafaxine (TCA) vs paroxetine (SSRI) vs placebo	Randomized, double-blind, placebo-controlled	PD with depression	115	12W	HAM-D	Both drugs significantly improve depression in PD. None of the drugs worsen motor function.
IMPULSE CONTROL DISORDER (ICD)							
Thomas *et al* (2010)	Amantadine vs lacebo	Randomized, double-blind, placebo-controlled	PD with pathological gambling	17	4W baseline, 4W trial	G-SAS and Y-BOCS for pathological gambling	Amantadine abolished pathological gambling in all patients.
PARKINSON'S DISEASE WITH DEMENTIA (PDD)							
Aarsland *et al* (2002)	Donepezil vs placebo	Randomized, double-blind, placebo-controlled	PD and cognitive impairment	14	20W	MMSE score	Donepezil improves MMSE score and does not worsen motor function. Well tolerated.
Leroi *et al* (2004)	Donepezil vs placebo	Randomized, double-blind, placebo-controlled	PD and cognitive impairment or dementia	16	15W	DRS	Donepezil improves DRS score. Does not worsen motor function. Well tolerated.
Emre *et al* (2004)	Rivastigmine vs placebo	Randomized, double-blind, placebo-controlled	PD with mild to moderate dementia, >2 years post PD diagnosis	410	24W	ADAS-Cog; ADCS-CGIC	Rivastigmine significantly improves PDD, but is also associated with higher rates of nausea, vomiting and tremor.
Ravina *et al* (2005)	Donepezil vs placebo	Randomized, double-blind, placebo-controlled	PD with dementia	22	10W	ADAS-Cog	No significant effect of donepezil toward improvement of the primary endpoint (ADAS-Cog), but significant improvement of MMSE and CGI (secondary endpoints). No worsening of motor function.

TABLE 4 Continued

References	Drugs	Study design	Type of patients	No. of subjects	Length	Primary outcome	Results
Burn *et al* (2006)	Rivastigmine vs placebo	Randomized, double-blind, placebo-controlled	PD with dementia +/ visual hallucinations	536	24W	ADAS-Cog	Rivastigmine significantly improves ADAS-Cog in PDD patients with or without visual hallucinations.
Poewe *et al* (2006)	Rivastigmine vs placebo	Randomized, double-blind, placebo-controlled	PD with dementia	334	48W	ADAS-Cog	Rivastigmine significantly improves ADAS-Cog in PDD patients.
Aarsland *et al* (2009)	Memantine vs placebo	Randomized, double-blind, placebo-controlled	PD with dementia	72	24W	CGIC score	Memantine improves CGIC score in PDD. No difference in other measures.
Leroi *et al* (2009)	Memantine vs placebo	Randomized, double-blind, placebo-controlled	PD with dementia	25	22W	DRS	Memantine does not significantly improve DRS. Well tolerated

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; ADCS-CGIC, Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; BPRS, Brief Psychiatric Rating Scale; CGIC, Clinical Global Impression of Change; CGIS, Clinical Global Impression Scale; DRS, Dementia Rating Scale; G-SAS, Gambling-Symptom Assessment Scale; HAM-D, Hamilton Depression Rating Scale; IDS-C, Inventory of Depressive Symptomatology-Clinician; MADRS, Montgomery Asberg Depression Rating Scale; MMSE, Mini-Mental State Examination; PANSS, Positive and Negative Syndrome Scale; SAPS, Survey Assessment of Positive Symptoms; SSRI, Selective Serotonin Reuptake Inhibitor; TCA, tricyclic antidepressant; W, weeks; Y-BOCS, Yale–Brown–Obsessive Compulsive Scale.

antidepressant effects of SSRI (paroxetine) and SNRI (venlafaxine XR) concluded that both drugs significantly improve depression in PD patients (personal communication, Stewart A Factor). Additional larger multi-center trials, using depression-rating scales validated in PD, are needed to fully address this issue, and come up with clear recommendations about the best treatment strategies to treat depression in PD.

Cognitive impairment and dementia are often associated with PD. In contrast to dementia, which usually occurs at late stages of the disease, and causes significant impairment in social and occupational functioning, cognitive decline is often noted much earlier, and usually does not significantly hamper social and occupational activities. This early form is referred to as mild cognitive impairment, a terminology utilized in the Alzheimer literature as well. The reported prevalence of cognitive decline in PD is highly variable, ranging from 10 to 90%, while dementia affects about 30–40% of PD patients, although some studies indicate that dementia is as frequent as nearly 80% (Aarsland *et al*, 2002; Wood *et al*, 2010). The risk of dementia significantly increases with age. Cholinergic deficits and cortical Lewy bodies have been associated with the occurrence of PD dementia (PDD), while cognitive impairments are most likely due to the early and progressive degeneration of monoaminergic systems to associative cortical and subcortical regions (Rinne *et al*, 2000; Emre, 2003). Acetylcholinesterase inhibitors are first-line therapy in patients with PDD. Rivastigmine is the only FDA-approved acetylcholinesterase inhibitor for PDD, but donepezil and galantamine are two other commonly used agents. Although each of these drugs has significant benefits on global functioning (Table 4), they suffer from adverse effects (gastrointestinal distress, worsening of motor symptoms, nausea, vomiting). They have also been shown to improve psychotic symptoms associated with dementia. The outcomes of double-blind randomized trials that assess the efficacy of various acetylcholinesterase inhibitors in PDD are presented in Table 4.

To our knowledge, there are no randomized double-blind controlled trials that have assessed the efficacy of drug treatments for other nonmotor symptoms of PD, except for the recent assessment of the efficacy of amantadine toward pathological gambling (Thomas *et al*, 2010). There is little literature on the possible role of dopamine pathophysiology in anxiety and apathy, but no significant trials have yet been achieved to assess treatment for these disorders (Chaudhuri and Schapira, 2009). The management of autonomic and sleep disorders is merely symptomatic (Wood *et al*, 2010). Because of the morbidity and significant impact of nonmotor manifestations on PD patients' quality of life, it is imperative that better diagnostic and therapeutic tools are developed to recognize and alter the course of these symptoms. A summary of the recent findings related to the therapeutic of nonmotor symptoms of PD is presented in Box 4.

SURGICAL THERAPIES FOR PD

Current Surgical Targets

In the 1950s and 60s, stereotactic ablative approaches targeting the GPi and the ventrolateral thalamus (VL) were commonly used to treat PD patients (Box 5). These procedures were abandoned in the late 1960s with the introduction of LD as an effective pharmacological treatment of PD. Over the past two decades, however, based on a better understanding of the pathophysiological basis of PD (Albin *et al*, 1989; Crossman, 1989; Bergman *et al*, 1990; DeLong, 1990; Galvan and Wichmann, 2008) (Figure 1), studies of the effects of ablation in animal models of PD, and the introduction of DBS, there has been a virtual renaissance of neurosurgical treatments of intractable and advanced PD.

In these procedures, nodes of the basal ganglia–thalamocortical motor circuit are targeted, specifically the STN and GPi (Figure 1). Based on a long historical record, ablative

Box 5 Surgical therapies for Parkinson's disease

- STN DBS is the most commonly used surgical therapy in PD, although clinical trials did not reveal any significant difference in the efficacy of STN *vs* GPi DBS in reducing major PD symptoms and the development of side effects.
- Both STN and GPi DBS are accompanied by cognitive and psychiatric adverse effects in a significant subset of patients.
- The discovery of new targets or stimulation parameters that could alleviate some of the nonmotor PD deficits could have a significant impact in the field of PD therapeutics.
- The clinical effectiveness of refined subthalamotomy compared with STN DBS should be thoroughly assessed in light of recent data showing the efficacious antiparkinsonian effects of ablative subthalamotomies in large cohorts of PD patients.
- The CM/Pf and PPN represent two other brain regions currently being investigated as potential DBS targets in PD.

procedures at these locations became very popular in the 1990s, but have now been largely abandoned in developed countries in favor of DBS. DBS involves implantation of electrodes into STN or GPi, guided by imaging and electrophysiological techniques. The patients are also implanted with an externally programmable stimulator that is connected to the electrodes. The system can then be used to deliver continuous high-frequency electrical stimulation (most commonly in the 100–150-Hz range) to the implanted brain areas. Implantation of DBS electrodes is associated with a small surgical risk, which includes complications such as intracerebral hemorrhages, infection, or stroke. A list of the main DBS trials that have been performed since 2000 appears in Table 5.

The most common indications for surgery in PD are the presence of intractable tremor and drug-induced motor fluctuations or dyskinesias. Candidates for DBS treatment in PD should have documented LD responsiveness and should be free of significant dementia, psychiatric co-morbidities (Chang and Chou, 2006; Bronstein *et al*, 2011), and signs of atypical parkinsonism. DBS of the STN is most often performed bilaterally, although unilateral DBS of STN or GPi can be highly effective in some cases of asymmetric parkinsonism. In most patients, DBS alleviates parkinsonian motor signs, shortens 'off' periods, and reduces drug-induced dyskinesias, dystonia, and motor fluctuations (Rodriguez-Oroz *et al*, 2004; Anderson *et al*, 2005; Weaver *et al*, 2005; Portman *et al*, 2006; Bronstein *et al*, 2011). In general, both GPi- and STN-DBS are more effective than medical management alone to alleviate motor deficits in patients with advanced PD (Just and Ostergaard, 2002; Martinez-Martin *et al*, 2002; Troster *et al*, 2003; Lezcano *et al*, 2004; Diamond and Jankovic, 2005; Erola *et al*, 2005; Halbig *et al*, 2005; Lyons and Pahwa, 2005; Deuschl *et al*, 2006; Rodrigues *et al*, 2007a, b; Montel and Bungener, 2009; Weaver *et al*, 2009b; Zahodne *et al*, 2009). In contrast to patients with GPi-DBS, those with STN-DBS are often able to substantially reduce the medication doses (Breit *et al*, 2004; Rodriguez-Oroz *et al*, 2004; Anderson *et al*, 2005; Erola *et al*, 2005; Follett *et al*, 2010; Moro *et al*, 2010).

Non-Motor Side Effects of STN and GPi-DBS

Both STN- and GPi-DBS can have non-motor side effects, especially affecting verbal fluency, cognition and mood (Kumar *et al*, 1999a, b; Dujardin *et al*, 2001; Schupbach *et al*, 2005; Smeding *et al*, 2005, 2006, 2011; Castelli *et al*, 2006; De Gaspari *et al*, 2006, Merello *et al*, 2008). Verbal fluency and cognition problems are more often seen in old patients (Hariz *et al*, 2000; Saint-Cyr *et al*, 2000; Funkiewiez *et al*, 2004; Smeding *et al*, 2011), or in those with poor cognition or depression at baseline (De Gaspari *et al*, 2006). Specific cognition deficits include impairments of working memory (Saint-Cyr *et al*, 2000; Higginson *et al*, 2009; Okun *et al*, 2009), cognitive processing, visuo-spatial skills and set-shifting (Saint-Cyr *et al*, 2000; Alegret *et al*, 2001), response inhibition (Witt *et al*, 2004), or the decoding of facial expressions (Dujardin *et al*, 2004; Schroeder *et al*, 2004; Biseul *et al*, 2005; Drapier *et al*, 2008). Even when present, the impact of changes in verbal fluency on the quality of life appears to be relatively small (Alegret *et al*, 2004; Morrison *et al*, 2004; Montel and Bungener, 2009; Zahodne *et al*, 2009). Although almost half patients with DBS experience variable degrees of cognitive changes (Higginson *et al*, 2009), these deficits become 'relevant' in less than 10% treated patients (Castelli *et al*, 2006; Tir *et al*, 2007). However, because DBS is now widely used, even for patients with early PD in some centers, these adverse effects remain a major concern.

There is evidence that DBS may also worsen depression and mania, increase apathy, affect emotional lability, and increase the risk of suicide (Berney *et al*, 2002; Doshi *et al*, 2002; Okun *et al*, 2003, 2009; Funkiewiez *et al*, 2004; Smeding *et al*, 2005, 2006; Drapier *et al*, 2008; Voon *et al*, 2008). Mood problems are more common in patients treated with STN-DBS than those treated with GPi-DBS (Rodriguez-Oroz *et al*, 2005; Follett *et al*, 2010; Moro *et al*, 2010; Bronstein *et al*, 2011). Although the underlying substrate of these side effects remains to be characterized, it has been suggested that they may be induced by stimulation in non-motor areas of STN or GPi, inadvertent involvement of limbic structures outside of the target regions (Bejjani *et al*, 1999; Krack and Vercueil, 2001; Kulisevsky *et al*, 2002; Romito *et al*, 2002; Herzog *et al*, 2003a; Okun *et al*, 2003; Stefurak *et al*, 2003), and pre-existing psychiatric conditions (Lilleeng and Dietrichs, 2008). Although significant unpleasant mood side effects following STN or GPi DBS are relatively rare (Funkiewiez *et al*, 2004; Castelli *et al*, 2006; Tir *et al*, 2007), their occurrence significantly disrupts patients' quality of life.

STN *vs* GPi as Targets for DBS in PD?

Most neurosurgeons currently prefer the STN over the GPi as a target for DBS in PD, because of the perceived greater antiparkinsonian benefit of STN-DBS (Anderson *et al*, 2005; Moro *et al*, 2010). However, there is no clear evidence that the STN is, in fact, a better target than GPi. Small clinical

TABLE 5 Key Trials on DBS Effects for PD Since 2000

References	Year	Study objective	Study design	Type of patients	No. of subjects	Primary outcome measure	Main results	Duration of follow-up
Simuni *et al* (*J Neurosurg* **96**: 666)	2002	STN-DBS	Single-center, unblinded	Advanced PD	12	Change in UPDRS	Stable benefit at 12 months postop, benefits no greater than medication. DBS reduces medication side effects	12 months
Durif *et al* (*Movement Disord* **17**: 803)	2002	GPi-DBS	Single-center, unblinded	Advanced PD	6	UPDRS, ADL scores, dyskinesia severity	ADL and dyskinesia remain improved throughout study, off-score improvement lost after 3 years	3 years
Lyons *et al* (*Stereotact Funct Neurosurg* **79**: 214)	2002	GPi-DBS	Single-center, unblinded	Advanced PD	9	UPDRS, 2-day diaries	Long-term effectiveness in all measures (ADL, motor scores, dyskinesias)	48.5 months
Herzog *et al* (*Movement Disord* **18**: 1332)	2003b	STN-DBS	Single-center, unblinded	Advanced PD	48	UPDRS	Stable, strong benefit; multiple relatively transient side effects	12–24 months
Germano *et al* (*J Neurosurg* **101**: 36)	2004	STN-DBS	Single-center, unblinded	Advanced PD	12	Change in UPDRS, home diaries	Large contralateral improvement, lesser ipsilateral and axial improvements, reduced dyskinesias	12 months
Volkman *et al* (*Ann Neurol* **55**: 871)	2004	Bilateral GPi DBS	Single-center, unblinded	Advanced PD	11	UPDRS, dyskinesia scores, ADL assessment	Gradual loss of effect of antiparkinsonian effects, retained antidyskinetic effects	5 years
Rodriguez-Oroz *et al* (*J Neurol Neurosurg Psychiatr* **75**: 1382)	2004	STN-DBS	Single-center, double-blind crossover evaluation	Advanced PD	10	Change in UPDRS, timed tests, daily living scale, dyskinesias	Significant improvement, 50% reduction in levodopa	4 years
Rodriguez-Oroz *et al* (*Brain* **128**: 2240)	2005	STN or GPi stimulation	Multi-center, unblinded	Advanced PD	69	UPDRS, ADL	Off scores, ADLs, gait, and dyskinesias improved (more in STN than in GPi), side effects more common in STN	3–4 years
Anderson *et al* (*Arch Neurol* **62**: 554)	2005	STN vs GPi DBS	Results from previously published, randomized, blinded, parallel-group study, plus patients in a single-center extension study	Advanced PD	23	UPDRS scores	Bradykinesia improved more in STN than in the GPi group, on scores not improved in either group. Levodopa dose reduction in STN group, antidyskinetic effects greater in the GPi DBS group. Cognitive complications only in the STN group	12 months
Merello *et al* (*Br J Neurosurg* **22**: 415)	2008	Bilateral STN-DBS vs bilateral STN lesion vs combined ipsilateral STN lesion/DBS contralateral	Randomized study, unblinded	Advanced PD	15	UPDRS scores	All procedures improved UPDRS, dyskinesias similarly	1 year

TABLE 5 Continued

References	Year	Study objective	Study design	Type of patients	No. of subjects	Primary outcome measure	Main results	Duration of follow-up
Zahodne *et al* (*J Neurol* **256**: 1321) and Taba *et al* (*J Neurosurg* **113**: 1224)	2009/2010	STN vs GPi DBS	Randomized, unblinded	Advanced PD	42 (Zahodne), 44 (Taba)	UPDRS scores, QoL measures	UPDRS scores similar, GPi DBS superior to STN DBS on QoL measures (specifically mood/apathy changes)	6 months
Weaver *et al* (*JAMA* **301**: 63) and Follet *et al* (*N Engl J Med* **362**: 2077)	2009b/2010	DBS (STN or GPi) vs best medical therapy (Weaver); STN vs GPi (Follett)	Randomized, controlled multi-center trial	Advanced PD	255 (Weaver), 299 (Follett)	UPDRS, Motor diaries, hours 'on', QoL measurements	Significant gain in 'on' without dyskinesias, strong QoL benefits, subtle cognition side effects; high number of serious adverse events; no difference between benefits of STN or GPi DBS; depression better in GPi-DBS group, worse in STN-DBS group	6 months (Weaver), 24 months (Follett)
Moro *et al* (*Movement Disord* **25**: 578)	2010	STN vs GPi DBS	Prospective, crossover, double-blind assessment+unblinded assessments	Advanced PD	41	UPDRS scores, ADL, drug doses, dyskinesias	Both procedures effective, STN-DBS superior to GPi-DBS. Drugs only reduced in STN group. Adverse events more frequent in STN-DBS group	5–6 years

studies and a recent large randomized controlled trial have compared GPi- and STN-DBS, and found no significant differences in terms of the motor outcome of the procedures (Table 5). In fact, these studies have documented that patients with GPi-DBS decline less in terms of visuomotor processing speed, and have better depression scores than patients with STN-DBS (Follett *et al*, 2010). Another recent report concluded that, although patients experience improvement in health-related quality of life measures following STN-DBS, scale items concerning general life issues (eg, occupational function, interpersonal relationships or leisure activities) do not improve (Ferrara *et al*, 2010). Given these findings, the pendulum may swing towards the pallidal target in a greater proportion of patients in the future, based on the slightly lesser incidence of side effects rather than differences in efficacy.

New Targets for DBS in PD

The effects of DBS in brain areas other than STN or GPi are much less studied in PD patients. For the treatment of patients with severe tremor-predominant PD, thalamic DBS of the ventral intermediate nucleus (Vim) can be considered (Obeso *et al*, 1997; Ondo *et al*, 1998), but is not routinely used because it does not have much effect on the other cardinal symptoms of PD, such as bradykinesia and rigidity, which may subsequently develop. Recently, DBS of the centre median/parafascicular (CM/Pf) complex has been used in a small number of PD patients (Benabid, 2009). Although preliminary, some reports have suggested that CM/Pf stimulation may have therapeutic benefits in some PD patients towards dyskinesia (Caparros-Lefebvre *et al*, 1999), freezing of gait (Stefani *et al*, 2009), and rest tremor (Krauss *et al*, 2002; Peppe *et al*, 2008; Stefani *et al*, 2009). However, the mechanism of action, specific target sites and stimulation parameters of this surgical approach must be further characterized. Recent studies indicate widespread basal ganglia cellular responses associated with efficient anti-parkinsonian effects of Pf DBS in rat models of PD (Goff *et al*, 2009; Jouve *et al*, 2010).

Another DBS target that has recently generated some interest is the pedunculopontine nucleus (PPN), a conglomerate of cholinergic, glutamatergic and GABAergic neurons in the upper brainstem, tightly linked with the basal ganglia, thalamus and lower tegmental regions (Mena-Segovia *et al*, 2004). Inactivation of the PPN induces akinesia, while electrical low-frequency stimulation has antiparkinsonian properties in animals (Kojima *et al*, 1997; Nandi *et al*, 2002a, b). In light of these data, small experimental trials of low frequency PPN stimulation in humans were carried out. These studies have lead to variable results (Plaha and Gill, 2005; Stefani *et al*, 2007, 2010; Mazzone *et al*, 2007, 2008; Pereira *et al*, 2008; Pierantozzi *et al*, 2008; Alessandro *et al*, 2010; Peppe *et al*, 2010; Rauch *et al*, 2010). In some patients, PPN DBS reduces gait and freezing problems unresponsive to drug and conventional stimulation approaches directed at subthalamic

and pallidal targets, reduces falls and occasionally improves patients' state of vigilance and quality of sleep (Pereira *et al*, 2008; Ferraye *et al*, 2010). The magnitude of the effects, the exact location of the stimulation electrode and best technique of implantation of DBS leads into this nucleus are still being debated (Aravamuthan *et al*, 2007, 2008, 2009; Weinberger *et al*, 2008; Zrinzo and Zrinzo, 2008; Zrinzo *et al*, 2008; Fu *et al*, 2009; Shimamoto *et al*, 2010).

There have also been several small experimental trials of extradural motor cortex stimulation in human patients (Benvenuti *et al*, 2006; Strafella *et al*, 2007; Cilia *et al*, 2007, 2008; Arle *et al*, 2008; Lefaucheur, 2009; Pagni *et al*, 2008). This procedure results in small improvements of motor performance, and reductions in dyskinesias and psychiatric symptoms, perhaps mostly because of reductions in medication requirements. In contrast to DBS, extradural cortical stimulation is easy to perform and could be an alternative surgical therapy for PD. However, the development of new subdural leads and further efficacy tests of this approach in larger cohorts of PD patients are needed before one could consider cortical stimulation as a potential PD therapy (Lefaucheur, 2009). The notion that cortical stimulation may be an effective strategy to treat PD has recently been further strengthened by animal experiments that suggested that some of the antiparkinsonian effects of STN-DBS may, in fact, be mediated by antidromic stimulation of the motor cortex (Li *et al*, 2007; Dejean *et al*, 2009; Gradinaru *et al*, 2009).

Stimulation of the caudal ZI may provide beneficial effects on parkinsonian tremor, and lesser benefits for rigidity and akinesia (Kitagawa *et al*, 2005; Plaha *et al*, 2006), most likely through its effects on ZI itself, but also through stimulation of ascending cerebellar projections and pallidofugal fibers to the thalamus that pass through the stimulated areas.

Opportunities for Further Development of Neurosurgical Therapies for PD

The impact of the development of DBS for PD has been likened to that of the introduction of LD in the 1960s. However, while it is true that DBS can be highly effective for the cardinal motor features of PD, tremor, rigidity, and bradykinesia, it does not affect the non-motor features of the disorder or the non-dopaminergic motor features, such as speech, swallowing, gait, and balance difficulties. The search for new surgical targets that may allow treatment of other symptoms is therefore a high priority. Other areas of development involve the use of smaller, rechargeable stimulators, feedback-controlled on-demand stimulation, and the development of stimulation electrodes that allow 'sculpting' of the electrical field, which may then help to reduce stimulation side effects further. Long-over-due changes in stimulator design should also allow the use of more flexible stimulation regimes. An example for this would be the use of short episodes of 'desynchronizing' stimulation, which may result in therapeutic effects that outlast the stimulation for long period of time, thus saving battery energy, and potentially also reducing the incidence of side effects of DBS (Hauptmann and Tass, 2010). Another technical development in DBS would be a better integration of imaging techniques, such as intraoperative MRI, which offers the potential of solely image-guided placement of DBS electrodes and lesioning without the use of intraoperative microelectrode recordings (Martin *et al*, 2005; Shahlaie *et al*, 2011).

DBS *vs* Ablative Surgeries for PD

A specific challenge for neurosurgical treatments is that, as for any treatment for lifelong progressive diseases, they must be affordable in order to be practical for large numbers of patients. In the United States and other developed countries, DBS procedures have been embraced by both physicians and the public despite their high up-front costs, the substantial costs arising from the need to test and adjust stimulation parameters in the postoperative period, replacement of batteries, and the need for a high level of medical expertise throughout the pre-, peri-, and postoperative phases of the treatment. Similar conditions do not exist in developing countries, amounting to a continued need to optimize and develop less-costly alternatives, including ablative procedures. An important advancement in this field has been the demonstration that STN lesions are effective in the treatment of PD (Alvarez *et al*, 2001, 2005, 2009; Parkin *et al*, 2001; Su *et al*, 2002; Patel *et al*, 2003). A significant complication is, however, the development of persistent hemi-chorea in a small percentage of patients, requiring subsequent pallidotomy. The need for future long-term studies that explore the clinical effectiveness of refined and more selective methods of subthalamotomy, and the development of surgical techniques to reduce the occurrence of dyskinesias, is warranted. A summary of the main findings related surgical therapies for PD is presented in Box 5.

NEURAL TRANSPLANTATION IN PD

Ventral Midbrain Neural Transplants in the Striatum

Neural transplantation has been considered as a potential therapy for PD for the past 30 years (Box 6). However, despite highly promising results from preclinical studies and open-label trials of the effects of grafted embryonic human dopaminergic neurons into the striatum in the 1990s (Brundin *et al*, 2010), the more recent results from double-blind placebo-controlled trials of fetal ventral midbrain intrastriatal transplantation have failed to meet the primary endpoints and raised significant concerns about the use and safety of this approach (Freed *et al*, 2001; Olanow *et al*, 2003). The first of these trials involved 40 patients with advanced PD who were randomly assigned to receive either a transplant of fetal ventral midbrain tissue or sham surgery (Freed *et al*, 2001). Thirty-three patients received the transplant. The primary outcome, ie, global rating of clinical improvement 1 year post-transplant, did not reveal any significant difference

Box 6 Neural transplantation in Parkinson's disease

- The results of recent large-scale clinical trials have been inconclusive in demonstrating the efficacy of striatal ventral midbrain neural transplantation toward PD motor signs.
- A significant proportion of transplanted dopaminergic neurons display Lewy body inclusions similar to those seen in SNc dopaminergic neurons, but the functional relevance of this pathology remains unclear.
- Preclinical evidence indicates that graft-induced dyskinesias may be due to abnormal striatal serotonergic hyperinnervation and uncontrolled striatal release of dopamine.
- The potential use of stem cell therapy for PD remains uncertain due to major safety concerns and regulatory issues that must be overcome.

between the two groups. In addition to this disappointing result, these trials described for the first time the development of graft-induced, medication-independent dyskinesias. A second trial involving 34 patients with advanced PD showed similar results (Olanow *et al*, 2003).

Another important set of data that further complicated the use of ventral midbrain transplant in PD was the recent demonstration that some of the transplanted cells in PD patients who died 10–16 years after having received their transplants contained alpha-synuclein aggregates, suggesting that grafted neurons may be affected by the neurodegenerative process in the host's brain (Kordower *et al*, 2008a, b; Li *et al*, 2008b, 2010). However, controversy remains about the extent and functional relevance of Lewy body-like structures in surviving grafted dopaminergic neurons (Isacson and Kordower, 2008; Mendez *et al*, 2008; Cooper *et al*, 2009; Isacson and Mendez, 2010).

In recent years, Bjorklund and colleagues showed in rodent studies that graft-induced dyskinesias may result from the inclusion of serotonergic neurons into the transplants that lead to dysregulated release of dopamine as a 'false transmitter' from serotonergic terminals (Lane *et al*, 2006, 2010). These observations are further supported by the fact that systemic administration of buspirone, an agonist of the inhibitory 5HT1A autoreceptors that dampens serotonin neuron activity, alleviates graft-induced dyskinesias in PD patients and rat models of PD (Lane *et al*, 2006, 2010; Politis *et al*, 2010). The efficacy of such an approach to prevent the development of graft-induced dyskinesias in PD remains to be determined.

Stem Cell-derived Neurons for PD Therapy?

In the past decade, PD has often been mentioned as one of the neurodegenerative disorders that could benefit from stem cell-derived transplant therapy. Various stem cell types are currently being considered as sources of dopamine neurons, including lineage-specific stem cells, pluripotent stem cells, and re-programmed somatic cells (Astradsson *et al*, 2008; Isacson and Kordower, 2008; Sanchez-Pernaute *et al*, 2008; Pruszak and Isacson, 2009; Hargus *et al*, 2010). However, the transplantation of proliferative populations of neurons into the brain suffers from major safety concerns, most importantly the possibility that stem cell transplants may give rise to unchecked proliferation of tissue, eventually resulting in the formation of brain tumors (Li *et al*, 2008a; Amariglio *et al*, 2009; Brundin *et al*, 2010). Despite the severe safety and regulatory issues that will have to be overcome before PD patients can be treated with stem cell therapy, the increased knowledge gained in human embryonic stem cell biology is likely to result in the development of new stem cell-based therapies for PD (Isacson, 2009; Allan *et al*, 2010; Arenas, 2010; Fricker-Gates and Gates, 2010; Xu *et al*, 2010; Kim, 2011). A summary of the key findings about neural transplantation in PD presented in Box 6.

NEURORESTORATIVE GROWTH FACTOR THERAPIES FOR PARKINSON'S DISEASE

Trophic factors are members of a class of proteins that promote development, growth, survival, and restoration of neurons in the CNS (Box 7). Because of these properties, they are often seen as key therapeutic tools for neurorestorative therapies in the CNS. The first of these trophic factors was nerve growth factor (NGF), with many others following in recent decades (Levi-Montalcini and Hamburger, 1951; Rangasamy *et al*, 2010; Aron and Klein, 2011). It is now well known that these factors display a wide range of structural, biochemical, pharmacological and biological properties in the CNS.

Growth factors are grouped into two main families: the neurotrophin family, which includes NGF, brain-derived neurotrophic factor (BDNF), neurotrophin-3, and neurotrophin-4/5, and the glial cell-derived neurotrophic factor (GDNF) family, which comprises four main trophic factors, GDNF, neurturin (NTN), artemin, and persephin (Rangasamy *et al*, 2010; Aron and Klein, 2011).

Neurotrophic factor therapy is an approach that has generated significant interest in the field of PD therapeutics for almost 20 years. GDNF has been most particularly scrutinized because of its powerful effects toward growth, survival, and protection of midbrain dopaminergic neurons against toxic insults (Lin *et al*, 1993; Tomac *et al*, 1995a, b; Bjorklund *et al*, 2000; Kordower *et al*, 2000). In light of promising preclinical data, the first human double-blinded trial with GDNF protein administration into the lateral ventricles was launched in 1996 (Nutt *et al*, 2003). Fifty patients suffering from advanced idiopathic PD were enrolled. The results were disappointing. In addition to a lack of significant improvement of parkinsonian motor signs, many patients suffered from side effects, including nausea, anorexia, vomiting, and in some cases, depression, for several days after GDNF administration. The mechanisms underlying these negative effects remained unclear, but it is possible that the poor penetration of GDNF from the lateral ventricles into the striatum may have contributed. To examine this possibility, another double-blind placebo-

Box 7 Neurorestorative growth factor therapies for Parkinson's disease

- Preclinical studies show that GDNF and neurturin are the two most promising growth factors considered for neurorestoration of the nigrostriatal dopaminergic system in animal models of PD.
- Neither of these compounds was successful in alleviating parkinsonian motor signs when delivered in the striatum of PD patients.
- The antiparkinsonian efficacy of both striatal and nigral delivery of neurturin is currently being tested in another clinical trial.

controlled trial using intraputamenal convection-enhanced infusion of GDNF or placebo was undertaken in 34 subjects, half of whom received GDNF (Lang *et al*, 2006). Unfortunately, the outcome of this trial corroborated the disappointing findings of the first trial (Lang *et al*, 2006; Penn *et al*, 2006).

Most recently, interest has shifted towards NTN, which displays pharmacological features closely similar to GDNF, and has powerful effects on midbrain dopaminergic cell growth (Kotzbauer *et al*, 1996). Following the development of a recombinant adeno-associated viral vector (AAV)2-based vector encoding the human NTN (known as CERE-120), and its successful application in rodent and nonhuman primate models of PD (Kordower *et al*, 2006; Gasmi *et al*, 2007a, b; Herzog *et al*, 2007, 2008) combined with the promising results of human open trial studies (Marks *et al*, 2008), a phase II double-blinded trial was initiated in 59 parkinsonian patients, two-thirds of whom received CERE-120 injections into their putamen (Marks *et al*, 2010). As in the GDNF trials, the primary endpoint was not met. Positron emission tomography (PET) ^{18}F-DOPA scans, examining the dopamine metabolism in the striatum, also showed no difference. However, an 18-month analysis in 30 of the subjects demonstrated a significant difference between groups in the UPDRS scores. Postmortem pathology of two patients who died during or after the study, unrelated to the treatment, indicated that NTN expression was present in the striatum (15% of total putamen), but was minimal in the SNc, as opposed to that seen in preclinical non-human primate studies (Kordower *et al*, 2006; Herzog *et al*, 2007; Marks *et al*, 2010).

It is unclear why such disparity exists between the results of these studies, but some authors have suggested that it may be related to the lack of efficient retrograde transport of the gene and protein from the striatum to the cell bodies in the SNc (Bartus *et al*, 2011). This could relate to species-specific differences in protein transport, but most likely to the nature and severity of dopaminergic cell loss between the MPTP-treated non-human primate models used in preclinical studies and the advanced PD patients who were enrolled in the trial (Kordower *et al*, 2006; Marks *et al*, 2010; Bartus *et al*, 2011). In light of these disappointing data, it was suggested that direct nigral injections may more effectively deliver NTN to its primary location of action in PD (Bartus *et al*, 2011). A second phase II trial is currently underway, in which a larger dose of NTN is directly injected into the SNc, and in which patients are observed for longer periods of time (up to 15 months). A six-patient open-label safety trial was completed, which did not identify significant adverse effects. The double-blind, sham-controlled study has now been initiated with a target of 52 subjects.

BDNF and mesencephalic astrocyte-derived neurotrophic factor (MANF) are two other targets of interest for the possible development of growth factor-based therapies for PD patients (Rangasamy *et al*, 2010; Aron and Klein, 2011). A summary of the key findings related to neurorestorative therapies in PD is shown in Box 7.

GENE THERAPY FOR PD

Gene therapy using viral vector-mediated enzyme replacement is another area of interest for future promising developments in the field of PD therapeutics (Baekelandt *et al*, 2000; Bjorklund *et al*, 2000; Feng and Maguire-Zeiss, 2010; Box 8). The basic principle behind this approach is to render neurons capable of producing another neurotransmitter and displaying a different chemical phenotype. Studies have aimed at two main anatomical targets, the STN, in which an AAV vector has been used to deliver the enzyme glutamic acid decarboxylase (GAD) with the hope of transforming some glutamatergic STN neurons into GABA-releasing cells (Kaplitt *et al*, 2007; Lewitt *et al*, 2011), and the striatum, in which AAV or lentiviral vectors are used to generate striatal neurons that produce dopamine either by themselves or from dietary tyrosine or LD administered as a drug (Eberling *et al*, 2008; Christine *et al*, 2009; Jarraya *et al*, 2009). Ongoing trials are in progress to assess the efficacy of these approaches in advanced PD patients.

Viral Vector-Mediated GAD in STN Neurons

The development of the AAV2-GAD vector and its implantation into the STN cells was meant to be a non-dopaminergic alternative to STN DBS. The rationale behind this approach is the possibility of converting the chemical phenotype of STN neurons into GABAergic cells that would release GABA, instead of, or in addition to, glutamate, into the GPi, thereby reducing the presumed pathological over-excitation of basal ganglia output neurons (During *et al*, 2001; Luo *et al*, 2002). Based on pre-clinical rodent data (During *et al*, 2001), and the results of a positive open phase I trial in 12 patients with moderately advanced PD who were unilaterally infused (Kaplitt *et al*, 2007), a phase II double-blind, randomized, sham-controlled trial was recently completed at seven US centers (Lewitt *et al*, 2011), enrolling 45 patients diagnosed with PD for at least 5 years. The subjects were randomized 1:1 for bilateral STN AAV2-GAD infusion or sham surgery (a partial thickness burr hole). Assessments were carried out at baseline, and at 1, 3, and 6 months post surgery. The primary endpoint was a change in UPDRS motor scores from baseline to 6 months. Of the 45 patients, 8 were excluded on the basis of infusion catheter placement outside of the predetermined target zone or

Box 8 Gene therapy for Parkinson's disease

- The use of the AAV2 viral vector to transfect STN neurons with GAD genes resulted in small therapeutic benefits in PD patients.
- The antiparkinsonian efficacy of both AAV2 and lentiviral vectors to transfect dopamine-related genes into striatal neurons is being investigated in human trials.
- The safe and efficient use of gene therapy approaches as PD therapeutics remains limited by the lack of reliable regulatory methods to control the amount of gene delivery products being delivered in patients' brains.

infusion pump failure (5 in the active group and 3 in the sham group). This study resulted in a significant, though modest, change in the primary endpoint, consisting of a 23.1% change in UPDRS motor scores in the AAV2-GAD group compared with 12.7% in the sham group, at all postoperative time points (ie, 1, 3, 6 months). The main adverse events, more commonly found in the active group, were nausea, headache, and depression. While the benefits demonstrated by this study are relatively small compared with those of conventional drug or surgical therapies, this is, nevertheless, the first phase II controlled, blinded gene therapy trial to be positive. A larger phase III study is currently being planned.

Viral Vector-Mediated Striatal Dopamine Replacement

Approaches using transfection of dopamine-synthesizing enzymes and related factors into striatal neurons in order to convert them into dopamine-producing cells have also generated significant interest. In light of findings from various *in vitro* preparations and rat models of PD (Azzouz *et al*, 2002; Bankiewicz *et al*, 2006a, b; Forsayeth *et al*, 2006; Jarraya *et al*, 2009), two gene therapy approaches to render striatal neurons as sources of dopamine or DOPA are currently being explored in clinical trials. In the first trial, the utility of a triple enzyme transfer is examined. Striatal neurons are transfected with a lentiviral vector of non-human origin, the equine infectious anemia virus, that delivers three genes essential in dopamine biosynthesis, namely tyrosine hydroxylase (TH), aromatic acid decarboxylase (AADC), and guanosine 5′-triphosphate (GTP) cyclohydrolase 1 (GCH1). After encouraging results were obtained in rat and monkey models of PD with intrastriatal administration of this vector (Azzouz *et al*, 2002; Jarraya *et al*, 2009), a phase I/II clinical trial was launched in 2007.

A second trial currently in progress uses striatal AAV-based delivery of AADC, thereby making striatal neurons capable of producing dopamine from peripherally administered LD. This approach is based on the fact that there is a significant reduction in striatal AADC in patients with advanced PD (Lloyd and Hornykiewicz, 1970; Nagatsu *et al*, 1979), and that the intrastriatal conversion of LD into dopamine should, therefore, be enhanced if additional AADC is expressed, which may then eventually result in reduced need for LD. In this case, active neurotransmitter production is expected only after the patients take LD, so that the magnitude of the functional effects could be adjusted by regulating the oral LD dose (Bjorklund *et al*, 2010b). Testing in MPTP-treated monkeys (Bankiewicz *et al*, 2006a, b; Forsayeth *et al*, 2006) showed stable long-term expression of the vector for up to 6 years, which was accompanied by improvement in clinical rating scores and a reduction of LD-associated side effects (Bankiewicz *et al*, 2006a, b; Forsayeth *et al*, 2006). A phase I clinical trial, started in 2005 in five patients who received bilateral intrastriatal vector administration, showed only modest efficacy in 'off' state 6 months post transfection. In a second cohort of patients, who received a higher concentration of vector, there was also no significant improvement in the UPDRS rating scale despite increased ^{18}F-fluoro-l-m-tyrosine binding in PET studies (Christine *et al*, 2009).

Both these viral vector approaches rely on the assumption that striatal neurons can be converted into dopamine-releasing cells, despite the fact that these neurons do not express mechanisms of vesicular storage and release of dopamine. The lack of these basic features may potentially prove harmful to striatal neurons because of an over-production of cytosolic dopamine, which may lead to oxidative stress in transfected cells (Chen *et al*, 2008), and the possibility that non-regulated release of dopamine by striatal neurons aggravates dyskinesias, as seen in MPTP-treated monkeys (Bankiewicz *et al*, 2006a, b) and some patients enrolled in the safety trial (Christine *et al*, 2009). Thus, a third approach being considered that could overcome these problems is a continuous LD delivery strategy, achieved by delivery of TH and GTP cyclohydrolase 1 (a key co-factor needed for TH function), resulting in LD production without interference with endogenous AADC, and without the production of the potentially toxic dopamine. If dyskinesias partly develop because of fluctuations of synaptic dopamine levels due to intermittent administration of LD (see above), it is possible that striatal serotonergic terminals partly contribute to the swings in the release of LD-derived dopamine because they express AADC, which make them capable of converting exogenous LD to dopamine and release it in an uncontrolled fashion as a false transmitter (Lane *et al*, 2010; see above). Such problem could be overcome if LD was continuously produced as expected with the AAV-mediated TH/GCH1 delivery. In fact, preclinical testing of this method in rat models of LD-induced dyskinesias has resulted in promising results (Bjorklund *et al*, 2009).

There are still many unanswered critical questions regarding the use of gene therapy in PD. For instance, it is not clear how the proper regulation of the viral vector to induce the production of a physiologically relevant amount of transmitter can be ensured. The combination of genes that will produce the best results and fewest side effects remains to be determined. Finally, the possibility of reversing the approach in order to adjust the amount of gene product delivery to the patient's needs is another

Box 9 Biomarkers and neuroprotective strategies in PD

- Current antiparkinsonian therapies do not have any significant effect on the progressive loss of midbrain dopaminergic neurons and thus do not influence the course of this disease.
- Despite promising preclinical results, neuroprotective trials have failed in PD patients.
- The combination of early nonmotor symptoms, most particularly anosmia, with imaging techniques (SPECT, PET) to assess changes in striatal dopamine transporter may be a suitable approach to identify at-risk PD patients prior to the appearance of motor symptoms, thus allowing early start of neuroprotective therapy.
- Proteomics and related 'omics' methods represent other interesting avenues to identify PD biomarkers.

key criterion to consider in the successful development of this therapeutic approach for PD and other brain diseases. A summary of the key findings related to gene therapy for PD is shown in Box 8.

THE SEARCH FOR BIOMARKERS AND NEUROPROTECTIVE THERAPIES: FUTURE CHALLENGES IN PD

The therapeutic approaches discussed so far highlight the progress that has been made toward the development of symptomatic PD therapies. However, one of the most important challenges PD researchers and physicians have faced has not been successfully overcome, ie, the discovery of biomarkers that could predict disease onset, and, thus, guide the use of neuroprotective treatments. Knowing that PD motor symptoms develop only when the dopaminergic denervation of the striatum has reached 70–80%, and that as much as 50% of SNc dopaminergic neurons are lost, the identification of such biomarkers is absolutely essential for the effective use of neuroprotective therapies that could alter the progression and course of the disease. The current lack of such markers most likely explains the numerous disappointing failures of neuroprotective clinical trials that have been completed during the past 10 years (Schapira, 2004; Lang, 2009; Olanow, 2009; Rascol, 2009).

There are many potential biomarkers and early nonmotor clinical signs of PD that are currently being considered in combination to identify at-risk PD patients (Box 9). In the final section of this review, we will discuss the current status of knowledge of each of these approaches, and critically examine their limitations in their application toward early PD diagnosis.

Early Anosmia

The first evidence for an association between olfactory dysfunction and PD was published more than 30 years ago (Ansari and Johnson, 1975). Since then, there have been numerous reports confirming this association, and most importantly, suggesting that the loss of smell may precede the onset of motor disorders (Haehner *et al*, 2007, 2009; Morley and Duda, 2010). Although the reported prevalence of olfactory loss in PD varies across studies, it appears that as much as 50–90% of PD patients experience varying degrees of olfactory dysfunction, and that there is no correlation between the degree of olfactory dysfunction and the duration or clinical severity of the disease (Doty *et al*, 1988; Stern *et al*, 1994; Hawkes *et al*, 1997; Hawkes, 2003). The pathological substrate for this olfactory loss is not clear, some studies reporting conflicting information about damage to the olfactory epithelium or changes in olfactory bulb volumes as potential sources of these deficits (Muller *et al*, 2005; Witt *et al*, 2009; Wang *et al*, 2011). However, various studies have now reported an increase in the total number of periglomerular dopaminergic cells in the olfactory bulb of parkinsonian patients (Huisman *et al*, 2004; Haehner *et al*, 2009; Morley and Duda, 2010).

A number of studies have provided evidence that PD patients commonly report a loss of their sense of smell prior to the development of motor PD symptoms (Doty *et al*, 1988; Tissingh *et al*, 2001; Muller *et al*, 2002a, b; Ponsen *et al*, 2004; Sommer *et al*, 2004). The results of a recent longitudinal study in 2267 elderly men in the Honolulu Heart Study demonstrate that loss of olfaction can precede PD motor symptoms by at least 4 years, thereby suggesting that it could serve as a screening tool to predict the future development of PD (Ross *et al*, 2008). There is also evidence that olfactory disturbances could be used to differentiate PD from other movement disorders such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), but not from multiple system atrophy (MSA) (Wenning *et al*, 1995; Hummel *et al*, 1997; Muller *et al*, 2002b). In light of these observations, the American Academy of Neurology recommends the use of olfactory testing to differentiate PD from PSP and CBD, but not from MSA (McKinnon *et al*, 2007). It is noteworthy that olfactory impairment is not restricted to PD and MSA, but also occurs in Lewy body disease and Alzheimer's disease, old age, and as a side effect of the use of numerous medications (Liberini *et al*, 2000; Hawkes, 2003; Williams *et al*, 2009; Goldstein and Sewell, 2009). The possible role of Lewy body pathology in PD olfactory loss has been suggested (Braak *et al*, 2003; Morley and Duda, 2010).

Thus, although olfactory dysfunction alone cannot be used as a reliable early diagnostic tool to predict the development of PD, it can be added to a battery of other premotor deficits and imaging techniques, which, together, can serve as biomarkers for early PD diagnosis, thereby allowing neuroprotective therapies to be initiated prior to the development of motor disorders and extensive dopaminergic cell loss (Haehner *et al*, 2009; Marek and Jennings, 2009; Morley and Duda, 2010).

Neuroimaging

Three main imaging methods are being considered as tools for early (preclinical) diagnosis of PD. These include PET, single-photon emission computed tomography (SPECT)

and MRI. PET and SPECT, which can be used to map changes in the abundance and function of dopamine terminals in the striatum, are considered as the two most sensitive approaches to identify patients with PD (Piccini and Whone, 2004; Lang and Mikulis, 2009). However, the high cost of PET scans limits considerably the use of this imaging method to identify PD biomarkers. SPECT dopamine transporter (DAT) imaging has received most attention because it is less costly and sensitive enough to detect early striatal dopaminergic deficit (Kagi *et al*, 2010). Various DAT ligands (^{123}IFB-CIT, ^{123}I-β-CIT, ^{99m}Tc-TRO-DAT-1, ^{18}F-FECNT) have been developed and successfully applied to human PD studies. The use of these methods can facilitate accurate PD diagnosis in certain patients with non-conventional PD symptomatology. It can also help rule out PD diagnosis in drug-induced, psychogenic, and other forms of parkinsonism that do not rely on nigrostriatal dopaminergic dysfunction. ^{123}Ioflupane, an analog of ^{123}I-β-CIT, has recently been approved by the FDA to be used to image DAT distribution in the diagnosis of PD.

Another critical benefit of DAT imaging is its potential use as a biomarker that could help identify future PD subjects at an early stage of dopaminergic degeneration before the appearance of any motor symptoms. However, although attractive, this approach must be combined with other early signs of PD, such as olfactory loss, autonomic dysfunctions (constipation, hypotension), cognitive decline, cardiac sympathetic dysfunction, or sleep disturbances (REM behavior disorder; RBD) to identify at-risk subjects who have not yet been diagnosed (Langston, 2006; Tolosa, 2007; Tolosa *et al*, 2007). The combination of smell loss or RBD with DAT imaging has already been successfully used to identify groups of individuals with increased risk of developing PD (Ponsen *et al*, 2004; Stiasny-Kolster *et al*, 2005). These observations have led to the development of an extensive clinical effort called the PARS to generate a strategy that could help detect parkinsonism in a cohort of 30 000 first-degree relatives of PD patients using combined changes in olfaction and DAT imaging as biomarkers (Stern, 2004; Siderowf and Stern, 2006; Blekher *et al*, 2009; Marek and Jennings, 2009). Longitudinal clinical and imaging evaluations will help assess the progression of deficits and the state of DAT imaging in these individuals, and determine if these changes predict the eventual development of PD signs in a subset of patients. Should this be the case, neuroprotective studies could then be initiated in a presymptomatic PD cohort, in order to assess the efficacy of therapies that could slow down neuronal degeneration and delay the onset of symptomatic PD (Marek and Jennings, 2009). It is noteworthy that chronic LD treatment may modify DAT expression, leading some imaging centers to use tetrabenazine (vesicular monoamine transporter ligand) as a ligand for striatal dopamine innervation.

The recent identification of multiple genes associated with PD provides another 'biomarker' approach to identify at-risk PD individuals (Farrer, 2006; Hardy *et al*, 2006; Klein and Schlossmacher, 2007; Pankratz and Foroud, 2007; Cookson, 2010; Dachsel and Farrer, 2010). Although most monogenic mutations account for only a very small proportion of the PD population, the mutation of specific genes like LRRK2 may be associated with as much as 30% of PD patients in some populations like Ashkenazi Jews (Ozelius *et al*, 2006; Saunders-Pullman *et al*, 2006; Cookson, 2010; Dachsel and Farrer, 2010). Some imaging studies have demonstrated abnormal dopaminergic function in the striatum in small groups of patients with LRRK2 or other Park gene mutations (Khan *et al*, 2002; Adams *et al*, 2005). Various large-scale consortium efforts are currently underway to characterize the status of striatal dopamine imaging in larger cohorts of LRRK2 family relatives (Healy *et al*, 2008; Cookson, 2010; Dachsel and Farrer, 2010).

The use of brain imaging as a PD biomarker can extend beyond the dopaminergic system to include other markers indicative of PD pathology, such as inflammation, mitochondrial dysfunction, alpha-synuclein deposition, protein misfolding, and others. Inflammatory changes have received significant attention as an early marker of PD risk (Chen *et al*, 2005; 2008; Hirsch and Hunot, 2009). Imaging tracers that target activated microglia are significantly increased in the brain of PD patients (Ouchi *et al*, 2005; Gerhard *et al*, 2006; Hirsch and Hunot, 2009). The usefulness of these additional imaging targets in combination with early signs of PD as useful biomarkers relies on the development of specific ligands that offer high sensitivity and suitable longitudinal time-course assessment.

Proteomics and Related 'Omics' Approaches

The recent emergence of highly sensitive 'omics' methods to identify possible pathways associated with the progressive development of PD is another promising avenue for the identification of PD biomarkers (Antoniades and Barker, 2008; Caudle *et al*, 2010). The identification of changes in gene expression (transcriptomics), protein levels (proteomics), or metabolites (metabolomics) in various biological specimens (brain tissue, cerebrospinal fluid, blood) may allow us to characterize dysfunctional pathways specifically involved in the progressive degenerative process in PD, such as mitochondrial dysfunction, oxidative stress, axon guidance, and synaptogenesis. Together, the findings gathered through these different methods will provide a comprehensive analysis of the molecular mechanisms and functional pathways affected in PD. A summary of the main findings related to biomarkers for PD is discussed in Box 9.

CONCLUSION

In this review we have discussed some of the major breakthroughs that have characterized the field of PD therapeutics since the discovery of LD in the 1960s. Although much remains to be known about the etiology of PD, the refinement of symptomatic therapies and the recent start of large-scale studies of PD biomarkers are

highly exciting initiatives that may lead to the introduction of novel neuroprotective therapies that will eventually alter the course of the disease, and provide PD patients with a better quality of life. The main challenge PD researchers and physicians have to overcome in the coming decades is to further characterize the underpinnings of the complex nonmotor symptoms in PD in order to develop appropriate treatment strategies for the complex array of autonomic, psychiatric, and cognitive disturbances that affect these patients.

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