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

Yoland Smith^{*1,2}, Thomas Wichmann^{1,2}, Stewart A Factor² and Mahlon R DeLong²

¹Yerkes National Primate Research Center, Emory University, Atlanta, GA, USA and ²Department of Neurology, Emory University, Atlanta, GA, USA

The demonstration that dopamine loss is the key pathological feature of Parkinson's disease (PD), and the subsequent introduction of levodopa have revolutionized 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.

Neuropsychopharmacology Reviews (2012) **37**, 213–246; doi:10.1038/npp.2011.212; published online 28 September 2011

Keywords: dopamine; nonmotor symptoms; striatum; substantia nigra; deep brain stimulation; transplantation

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).

*Correspondence: Dr Y Smith, Yerkes National Primate Research Center, Emory University, 954, Gatewood Road NE, Atlanta, GA 30322, USA, Tel: +1 404 727 7519, Fax: +1 404 727 3278, E-mail: ysmit01@emory.edu

Received 17 May 2011; revised 28 July 2011; accepted 29 July 2011

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 Paralyse 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 Giguee (1951)
1957	First evidence that L-DOPA reverses parkinsonian symptoms in animals treated with reserpine	Carlsson <i>et al</i> (1957)
1958	First use of chemical assay to demonstrate high concentrations of dopamine in the brain	Carlsson <i>et al</i> (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 <i>et al</i> (1962)
1967	First evidence that large oral doses of D,L-Dopa induce marked improvements of parkinsonian symptoms	Cotzias <i>et al</i> (1967)
1969	First evidence that amantadine is an effective treatment of PD symptoms	Schwab <i>et al</i> (1969)
1974	First evidence that oral D2 dopamine receptor agonist (bromocriptine) has antiparkinsonian effects	Calne <i>et al</i> (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 <i>et al</i> (1988); Lindvall <i>et al</i> (1989)
1989	First evidence that thalamic deep brain stimulation reduces tremor in PD patients	Benabid <i>et al</i> (1989)
1989/1990	Introduction of the 'direct and indirect' pathway model of the basal ganglia circuitry	Albin <i>et al</i> (1989); Crossman (1989); DeLong (1990)
1990	First evidence that unilateral subthalamotomy alleviates parkinsonian symptoms in MPTP-treated monkeys	Bergman <i>et al</i> (1990)
1992	Reintroduction of pallidotomy as a treatment for PD	Laitinen <i>et al</i> (1992)
1995	First evidence that subthalamic nucleus DBS is an effective treatment for Parkinson's disease	Limousin <i>et al</i> (1995a,b)
1997	First genetic form of PD identified mutation of the Park1 gene (encoding alpha-synuclein)	Polymeropoulos <i>et al</i> (1997)
2003	Introduction of the Braak and Braak model of ascending progression of Lewy body pathology in PD	Braak <i>et al</i> (2003)
2011	First publication of a double-blind gene therapy trial (viral vector of the GAD gene in the STN)	Lewitt <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (2001)	Apomorphine	DB, RA, PC, PG	Advanced fluctuating	29	In-patients: change in UPDRS; out-patients: decrease in OFF time	Apomorphine 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 <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (2004)	Orally disintegrating selegiline	DB, RA, PC, PG	Advanced fluctuating	140	Change in hours 'off'	Selegiline was superior to placebo
Rascol <i>et al</i> (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 <i>et al</i> (2007)	Orally disintegrating selegiline	DB, RA, PC, PG	Advanced fluctuating	148	Change in hours 'off'	Selegiline was not different from placebo
Stocchi <i>et al</i> (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 continuous 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,

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.

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

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: A₁, A_{2A}, A_{2B}, and A₃ (Schwarzschild *et al*, 2006; Menon and Stacy, 2008; Morelli *et al*, 2007, 2009, 2010; Shah and Hodgson, 2010).

A₁ 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 D₂ 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). D₂ 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 antidyskinetic 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, preladenant 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-isoxazole-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). Ifenprodil 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-(phenylethynyl)-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 (Breyse *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 adrenoceptor 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, 5HT1b, d, 5HT2a, 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.

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, aripiprazole, 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

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

^aNonmotor symptoms that often precede PD motor dysfunctions.

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 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 <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (2010)	Amantadine vs placebo	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 <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (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-thalamo-cortical 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 comorbidities (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 (<i>J Neurosurg</i> 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 (<i>Movement Disord</i> 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 (<i>Stereotact Funct Neurosurg</i> 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 (<i>Movement Disord</i> 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 (<i>J Neurosurg</i> 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 (<i>Ann Neurol</i> 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 (<i>J Neurol Neurosurg Psychiatr</i> 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 (<i>Brain</i> 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 (<i>Arch Neurol</i> 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 (<i>Br J Neurosurg</i> 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 <i>et al</i> (<i>J Neurol</i> 256 : 1321) and Taba <i>et al</i> (<i>J Neurosurg</i> 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 <i>et al</i> (<i>JAMA</i> 301 : 63) and Follet <i>et al</i> (<i>N Engl J Med</i> 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 <i>et al</i> (<i>Movement Disord</i> 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 5HT_{1A} 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; Pruszek 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 intrastratial 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 intrastratial 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 intrastratial 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 ¹⁸F-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 overproduction 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 ($^{123}\text{IFB-CIT}$, $^{123}\text{I-}\beta\text{-CIT}$, $^{99\text{m}}\text{Tc-TRO-DAT-1}$, $^{18}\text{F-FECNT}$) 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}I oflupane, an analog of $^{123}\text{I-}\beta\text{-CIT}$, 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 tetraabenazine (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.

DISCLOSURE

Dr Smith declares that he has received a research grant from Oxford Biomedica in the past 3 years. Dr Factor declares that he has received research grant support from the following companies: Ceregene, TEVA Neurosciences, Ipsen and EMD Serono. He has also received educational grants from Allergan and Lundbeck, and personal compensation for consulting from Merz, Allergan. Dr DeLong declares over the past three years he has received compensation for consulting from Merck and for professional services from The Dystonia Medical Research Foundation. The other authors declare that this review was prepared in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

REFERENCES

- Aarsland D, Laake K, Larsen JP, Janvin C (2002). Donepezil for cognitive impairment in Parkinson's disease: a randomised controlled study. *J Neurol Neurosurg Psychiatry* **72**: 708–712.
- Aarsland D, Ballard C, Walker Z, Bostrom F, Alves G, Kossakowski K et al (2009). Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial. *Lancet Neurol* **8**: 613–618.
- Adams JR, van Netten H, Schulzer M, Mak E, McKenzie J, Strongosky A et al (2005). PET in LRRK2 mutations: comparison to sporadic Parkinson's disease and evidence for presymptomatic compensation. *Brain* **128**: 2777–2785.
- Adler CH (2008). Amantadine and anticholinergics. In: Factor SA, Weiner WJ (eds). *Parkinson's Disease-Diagnostic and Clinical Management*. Demos: New York. pp 491–497.
- Agid Y (1998). Levodopa: is toxicity a myth? *Neurology* **50**: 858–863.
- Agid Y, Ahlskog E, Albanese A, Calne D, Chase T, De Yebenes J et al (1999). Levodopa in the treatment of Parkinson's disease: a consensus meeting. *Mov Disord* **14**: 911–913.
- Agnati LF, Guidolin D, Leo G, Carone C, Genedani S, Fuxe K (2010). Receptor-receptor interactions: a novel concept in brain integration. *Prog Neurobiol* **90**: 157–175.
- Ahlskog JE (2005). Challenging conventional wisdom: the etiologic role of dopamine oxidative stress in Parkinson's disease. *Mov Disord* **20**: 271–282.
- Albin RL, Young AB, Penney JB (1989). The functional anatomy of basal ganglia disorders. *Trends Neurosci* **12**: 366–375. **One of the first descriptions of the direct and indirect pathway models of the basal ganglia circuitry in normal and diseased states.**
- Alegret M, Junque C, Valldeoriola F, Vendrell P, Pilleri M, Rumia J et al (2001). Effects of bilateral subthalamic stimulation on cognitive function in Parkinson disease. *Arch Neurol* **58**: 1223–1227.
- Alegret M, Valldeoriola F, Marti M, Pilleri M, Junque C, Rumia J et al (2004). Comparative cognitive effects of bilateral subthalamic stimulation and subcutaneous continuous infusion of apomorphine in Parkinson's disease. *Mov Disord* **19**: 1463–1469.
- Alessandro S, Ceravolo R, Brusa L, Pierantozzi M, Costa A, Galati S et al (2010). Non-motor functions in parkinsonian patients implanted in the pedunculopontine nucleus: focus on sleep and cognitive domains. *J Neurol Sci* **289**: 44–48.
- Allan LE, Petit GH, Brundin P (2010). Cell transplantation in Parkinson's disease: problems and perspectives. *Curr Opin Neurol* **23**: 426–432. **Concise overview of the limitations and future developments in the use of cell transplantation for Parkinson's disease.**
- Alvarez L, Macias R, Guridi J, Lopez G, Alvarez E, Maragoto C et al (2001). Dorsal subthalamotomy for Parkinson's disease. *Mov Disord* **16**: 72–78.
- Alvarez L, Macias R, Lopez G, Alvarez E, Pavon N, Rodriguez-Oroz MC et al (2005). Bilateral subthalamotomy in Parkinson's disease: initial and long-term response. *Brain* **128**: 570–583.
- Alvarez L, Macias R, Pavon N, Lopez G, Rodriguez-Oroz MC, Rodriguez R et al (2009). Therapeutic efficacy of unilateral subthalamotomy in Parkinson's disease: results in 89 patients followed for up to 36 months. *J Neurol Neurosurg Psychiatry* **80**: 979–985.
- Amariglio N, Hirshberg A, Scheithauer BW, Cohen Y, Loewenthal R, Traktenbrot L et al (2009). Donor-derived brain tumor following neural stem cell transplantation in an ataxia telangiectasia patient. *PLoS Med* **6**: e1000029.
- Anagnostaras SG, Murphy GG, Hamilton SE, Mitchell SL, Rahnama NP, Nathanson NM et al (2003). Selective cognitive dysfunction in acetylcholine M1 muscarinic receptor mutant mice. *Nat Neurosci* **6**: 51–58.
- Anderson VC, Burchiel KJ, Hogarth P, Favre J, Hammerstad JP (2005). Pallidal vs subthalamic nucleus deep brain stimulation in Parkinson disease. *Arch Neurol* **62**: 554–601.
- Annic A, Devos D, Seguy D, Dujardin K, Destee A, Defebvre L (2009). Continuous dopaminergic stimulation by Duodopa in advanced Parkinson's disease: Efficacy and safety. *Rev Neurol (Paris)* **165**: 718–727.
- Ansari KA, Johnson A (1975). Olfactory function in patients with Parkinson's disease. *J Chronic Dis* **28**: 493–497. **First direct association between olfactory dysfunctions and Parkinson's disease.**
- Antoniades CA, Barker RA (2008). The search for biomarkers in Parkinson's disease: a critical review. *Expert Rev Neurother* **8**: 1841–1852.
- Antonini A, Odin P (2009). Pros and cons of apomorphine and L-dopa continuous infusion in advanced Parkinson's disease. *Parkinsonism Relat Disord* **15**(Suppl 4): S97–S100.
- Antonini A, Tolosa E (2009). Apomorphine and levodopa infusion therapies for advanced Parkinson's disease: selection criteria and patient management. *Expert Rev Neurother* **9**: 859–867.
- Antonini A, Tolosa E, Mizuno Y, Yamamoto M, Poewe WH (2009). A reassessment of risks and benefits of dopamine agonists in Parkinson's disease. *Lancet Neurol* **8**: 929–937. **A comprehensive review of the therapeutic benefits and adverse effects of dopamine receptor agonists as antiparkinsonian therapy.**
- Anwyl R (1999). Metabotropic glutamate receptors: electrophysiological properties and role in plasticity. *Brain Res Rev* **29**: 83–120.
- Aravamuthan BR, McNab JA, Miller KL, Rushworth M, Jenkinson N, Stein JF et al (2009). Cortical and subcortical connections within the pedunculopontine nucleus of the primate *Macaca mulatta* determined using probabilistic diffusion tractography. *J Clin Neurosci* **16**: 413–420.
- Aravamuthan BR, Muthusamy KA, Stein JF, Aziz TZ, Johansen-Berg H (2007). Topography of cortical and subcortical connections of the human pedunculopontine and subthalamic nuclei. *Neuroimage* **37**: 694–705.
- Aravamuthan BR, Stein JF, Aziz TZ (2008). The anatomy and localization of the pedunculopontine nucleus determined using probabilistic diffusion tractography [corrected]. *Br J Neurosurg* **22**(Suppl 1): S25–S32.
- Arenas E (2010). Towards stem cell replacement therapies for Parkinson's disease. *Biochem Biophys Res Commun* **396**: 152–156.
- Arle JE, Apetauerova D, Zani J, Deletis DV, Penney DL, Hoit D et al (2008). Motor cortex stimulation in patients with Parkinson disease: 12-month follow-up in 4 patients. *J Neurosurg* **109**: 133–139.
- Aron L, Klein R (2011). Repairing the parkinsonian brain with neurotrophic factors. *Trends Neurosci* **34**: 88–100.
- Ascherio A, Zhang SM, Hernan MA, Kawachi I, Colditz GA, Speizer FE et al (2001). Prospective study of caffeine consumption and risk of Parkinson's disease in men and women. *Ann Neurol* **50**: 56–63.
- Astradsson A, Cooper O, Vinuela A, Isacson O (2008). Recent advances in cell-based therapy for Parkinson's disease. *Neurosurg Focus* **24**: E6.
- Awad H, Hubert GW, Smith Y, Levey AI, Conn PJ (2000). Activation of metabotropic glutamate receptor 5 has direct excitatory effects and potentiates NMDA receptor currents in neurons of the subthalamic nucleus. *J Neurosci* **20**: 7871–7879.
- Azzouz M, Martin-Rendon E, Barber RD, Mitrophanous KA, Carter EE, Rohll JB et al (2002). Multicistronic lentiviral vector-mediated striatal gene transfer of aromatic L-amino acid decarboxylase, tyrosine hydroxylase, and GTP cyclohydrolase I induces sustained transgene expression, dopamine production, and functional improvement in a rat model of Parkinson's disease. *J Neurosci* **22**: 10302–10312.

- Baekelandt V, De Strooper B, Nuttin B, Debyser Z (2000). Gene therapeutic strategies for neurodegenerative diseases. *Curr Opin Mol Ther* 2: 540–554.
- Bankiewicz KS, Daadi M, Pivrotto P, Bringas J, Sanftner L, Cunningham J et al (2006a). Focal striatal dopamine may potentiate dyskinesias in parkinsonian monkeys. *Exp Neurol* 197: 363–372.
- Bankiewicz KS, Forsayeth J, Eberling JL, Sanchez-Pernaute R, Pivrotto P, Bringas J et al (2006b). Long-term clinical improvement in MPTP-lesioned primates after gene therapy with AAV-hAADC. *Mol Ther* 14: 564–570.
- Pre-clinical evidence for the successful use of gene therapy to restore striatal dopamine and alleviate parkinsonian motor symptoms in MPTP-treated monkeys.**
- Bara-Jimenez W, Bibbiani F, Morris MJ, Dimitrova T, Sherzai A, Mouradian MM et al (2005). Effects of serotonin 5-HT1A agonist in advanced Parkinson's disease. *Mov Disord* 20: 932–936.
- Bara-Jimenez W, Dimitrova T, Sherzai A, Favit A, Mouradian MM, Chase TN (2004). Effect of monoamine reuptake inhibitor NS 2330 in advanced Parkinson's disease. *Mov Disord* 19: 1183–1186.
- Barbeau A (1962). The pathogenesis of Parkinson's disease: a new hypothesis. *Can Med Assoc J* 87: 802–807.
- Barbeau A, Sourkes TL, Murphy CF (1962). Les catecholamines de la maladie de Parkinson. In: de Ajuriaguerra J (ed). *Monoamines et systeme Nerveux Central*. Goerg & Cie SA: Geneva. pp 247–262. **First evidence that oral L-DOPA is an effective treatment for Parkinson's disease.**
- Bartus RT, Herzog CD, Chu Y, Wilson A, Brown L, Siffert J et al (2011). Bioactivity of AAV2-neurturin gene therapy (CERE-120): differences between Parkinson's disease and nonhuman primate brains. *Mov Disord* 26: 27–36.
- Bassetti CL (2011). Nonmotor disturbances in Parkinson's disease. *Neurodegener Dis* 8: 95–108.
- Battaglia G, Busceti CL, Molinaro G, Biagioni F, Storto M, Fornai F et al (2004). Endogenous activation of mGlu5 metabotropic glutamate receptors contributes to the development of nigro-striatal damage induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in mice. *J Neurosci* 24: 828–835.
- Bejjani BP, Damier P, Arnulf I, Thivard L, Bonnet AM, Dormont D et al (1999). Transient acute depression induced by high-frequency deep-brain stimulation. *N Engl J Med* 340: 1476–1480.
- Benabid AL (2009). Targeting the caudal intralaminar nuclei for functional neurosurgery of movement disorders. *Brain Res Bull* 78: 109–112.
- Benabid AL, Chabardes S, Mitrofanis J, Pollak P (2009a). Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. *Lancet Neurol* 8: 67–81. **A comprehensive review of the beneficial and adverse effects of deep brain stimulation of the STN in patients with Parkinson's disease.**
- Benabid AL, Chabardes S, Torres N, Pialat B, Krack P, Fraix V et al (2009b). Functional neurosurgery for movement disorders: a historical perspective. *Prog Brain Res* 175: 379–391.
- Benabid AL, Pollak P, Hommel M, Gaio JM, de Rougemont J, Perret J (1989). Treatment of Parkinson tremor by chronic stimulation of the ventral intermediate nucleus of the thalamus. *Rev Neurol (Paris)* 145: 320–323.
- Benvenuti E, Cecchi F, Colombini A, Gori G (2006). Extradural motor cortex stimulation as a method to treat advanced Parkinson's disease: new perspectives in geriatric medicine. *Aging Clin Exp Res* 18: 347–348.
- Bergman H, Wichmann T, DeLong MR (1990). Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. *Science* 249: 1436–1438. **The first direct evidence that lesion of the subthalamic nucleus in the MPTP-treated monkey model of Parkinson's disease alleviates parkinsonian motor symptoms.**
- Berney A, Vingerhoets F, Perrin A, Guex P, Villemure JG, Burkhard PR et al (2002). Effect on mood of subthalamic DBS for Parkinson's disease: a consecutive series of 24 patients. *Neurology* 59: 1427–1429.
- Bertler A, Rosengren E (1959). Occurrence and distribution of catecholamines in brain. *Acta Physiol Scand* 47: 350–361.
- Beurrier C, Lopez S, Revy D, Selvam C, Goudet C, Lherondel M et al (2009). Electrophysiological and behavioral evidence that modulation of metabotropic glutamate receptor 4 with a new agonist reverses experimental parkinsonism. *FASEB J* 23: 3619–3628.
- Bibbiani F, Oh JD, Petzer JP, Castagnoli Jr N, Chen JF, Schwarzschild MA et al (2003). A2A antagonist prevents dopamine agonist-induced motor complications in animal models of Parkinson's disease. *Exp Neurol* 184: 285–294.
- Birkmayer W, Hornykiewicz O (1961). (The L-3,4-dioxyphenylalanine (DOPA)-effect in Parkinson-akinesia). *Wien Klin Wochenschr* 73: 787–788. **First evidence that L-DOPA may be a therapeutic agent for Parkinson's disease.**
- Biseul I, Sauleau P, Haegelen C, Trebon P, Drapier D, Raoul S et al (2005). Fear recognition is impaired by subthalamic nucleus stimulation in Parkinson's disease. *Neuropsychologia* 43: 1054–1059.
- Bjorklund A, Kirik D, Rosenblad C, Georgievska B, Lundberg C, Mandel RJ (2000). Towards a neuroprotective gene therapy for Parkinson's disease: use of adenovirus, AAV and lentivirus vectors for gene transfer of GDNF to the nigrostriatal system in the rat Parkinson model. *Brain Res* 886: 82–98.
- Bjorklund T, Carlsson T, Cederfjall EA, Carta M, Kirik D (2010a). Optimized adeno-associated viral vector-mediated striatal DOPA delivery restores sensorimotor function and prevents dyskinesias in a model of advanced Parkinson's disease. *Brain* 133: 496–511.
- Bjorklund T, Kirik D (2010b). Gene therapy for dopamine replacement. *Prog Brain Res* 184: 221–235. **A detailed review of the use of gene therapy for striatal dopamine replacement in Parkinson's disease.**
- Bjorklund T, Hall H, Breyse N, Sonesson C, Carlsson T, Mandel RJ et al (2009). Optimization of continuous *in vivo* DOPA production and studies on ectopic DA synthesis using rAAV5 vectors in Parkinsonian rats. *J Neurochem* 111: 355–367.
- Bjorklund T, Kirik D (2009). Scientific rationale for the development of gene therapy strategies for Parkinson's disease. *Biochim Biophys Acta* 1792: 703–713.
- Bjorklund T, Kordower JH (2010). Gene therapy for Parkinson's disease. *Mov Disord* 25(Suppl 1): S161–S173.
- Black KJ, Koller JM, Campbell MC, Gusnard DA, Bandak SI (2010). Quantification of indirect pathway inhibition by the adenosine A2a antagonist SYN115 in Parkinson disease. *J Neurosci* 30: 16284–16292.
- Blanchet PJ, Konitsiotis S, Whittemore ER, Zhou ZL, Woodward RM, Chase TN (1999). Differing effects of N-methyl-D-aspartate receptor subtype selective antagonists on dyskinesias in levodopa-treated 1-methyl-4-phenyl-tetrahydropyridine monkeys. *J Pharmacol Exp Ther* 290: 1034–1040.
- Blandini F, Greenamyre JT (1998). Prospects of glutamate antagonists in the therapy of Parkinson's disease. *Fundam Clin Pharmacol* 12: 4–12.
- Blandini F, Mangiagalli A, Consentino M, Marino F, Samuele A, Rasini E et al (2003). Peripheral markers of apoptosis in Parkinson's disease: the effects of dopaminergic drugs. *Ann NY Acad Sci* 1010: 675–678.
- Bleker T, Weaver M, Rupp J, Nichols WC, Hui SL, Gray J et al (2009). Multiple step pattern as a biomarker in Parkinson disease. *Parkinsonism Relat Disord* 15: 506–510.
- Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 24: 197–211. **Introduction of the Braak and Braak stages of Parkinson's disease from the brainstem to the cerebral cortex based on the presence of Lewy body pathology. This paper had a significant impact on the recognition of nonmotor symptoms in PD.**
- Brady AE, Jones CK, Bridges TM, Kennedy JP, Thompson AD, Heiman JU et al (2008). Centrally active allosteric potentiators of the M4 muscarinic acetylcholine receptor reverse amphetamine-induced hyperlocomotor activity in rats. *J Pharmacol Exp Ther* 327: 941–953.
- Braz CA, Borges V, Ferraz HB (2004). Effect of riluzole on dyskinesia and duration of the on state in Parkinson disease patients: a double-blind, placebo-controlled pilot study. *Clin Neuropharmacol* 27: 25–29.
- Breit S, Schulz JB, Benabid AL (2004). Deep brain stimulation. *Cell Tissue Res* 318: 275–288.
- Breyse N, Amalric M, Salin P (2003). Metabotropic glutamate 5 receptor blockade alleviates akinesia by normalizing activity of selective basal-ganglia structures in parkinsonian rats. *J Neurosci* 23: 8302–8309.
- Breyse N, Baunez C, Spooren W, Gasparini F, Amalric M (2002). Chronic but not acute treatment with a metabotropic glutamate 5 receptor antagonist reverses the akinetic deficits in a rat model of parkinsonism. *J Neurosci* 22: 5669–5678.
- Bridges TM, LeBois EP, Hopkins CR, Wood MR, Jones CK, Conn PJ et al (2010). The antipsychotic potential of muscarinic allosteric modulation. *Drug News Perspect* 23: 229–240.
- Bronstein JM, Tagliati M, Alterman RL, Lozano AM, Volkmann J, Stefani A et al (2011). Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. *Arch Neurol* 68: 165.
- Brundin P, Barker RA, Parmar M (2010). Neural grafting in Parkinson's disease problems and possibilities. *Prog Brain Res* 184: 265–294. **A comprehensive assessment of the current knowledge of the benefits and adverse effects of neural transplantation in Parkinson's disease.**
- Burn D, Emre M, McKeith I, De Deyn PP, Aarsland D, Hsu C et al (2006). Effects of rivastigmine in patients with and without visual hallucinations in dementia associated with Parkinson's disease. *Mov Disord* 21: 1899–1907.
- Bymaster FP, Carter PA, Yamada M, Gomez J, Wess J, Hamilton SE et al (2003a). Role of specific muscarinic receptor subtypes in cholinergic parasympathomimetic responses, *in vivo* phosphoinositide hydrolysis, and pilocarpine-induced seizure activity. *Eur J Neurosci* 17: 1403–1410.
- Bymaster FP, Felder CC, Tzavara E, Nomikos GG, Calligaro DO, McKinzie DL (2003b). Muscarinic mechanisms of antipsychotic atypicality. *Prog Neuropsychopharmacol Biol Psychiatry* 27: 1125–1143.

- Bymaster FP, McKinzie DL, Felder CC, Wess J (2003c). Use of M1-M5 muscarinic receptor knockout mice as novel tools to delineate the physiological roles of the muscarinic cholinergic system. *Neurochem Res* **28**: 437–442.
- Caccamo A, Oddo S, Billings LM, Green KN, Martinez-Coria H, Fisher A *et al* (2006). M1 receptors play a central role in modulating AD-like pathology in transgenic mice. *Neuron* **49**: 671–682.
- Calne DB, Teychenne PF, Claveria LE, Eastman R, Greenacre JK, Petrie A (1974a). Bromocriptine in Parkinsonism. *Br Med J* **4**: 442–444.
- Calne DB, Teychenne PF, Leigh PN, Bamji AN, Greenacre JK (1974b). Treatment of parkinsonism with bromocriptine. *Lancet* **2**: 1355–1356.
- Caparros-Lefebvre D, Blond S, Feltin MP, Pollak P, Benabid AL (1999). Improvement of levodopa induced dyskinesias by thalamic deep brain stimulation is related to slight variation in electrode placement: possible involvement of the centre median and parafascicularis complex. *J Neurol Neurosurg Psychiatry* **67**: 308–314.
- Carlsson A, Lindqvist M, Magnusson T (1957). 3,4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. *Nature* **180**: 1200. **First evidence that Parkinson's disease may be due to loss of striatal dopamine.**
- Carlsson A, Lindqvist M, Magnusson T, Waldeck B (1958). On the presence of 3-hydroxytyramine in brain. *Science* **127**: 471–472.
- Cartmell J, Schoepp DD (2000). Regulation of neurotransmitter release by metabotropic glutamate receptors. *J Neurochem* **75**: 889–907.
- Castelli L, Perozzo P, Zibetti M, Crivelli B, Morabito U, Lanotte M *et al* (2006). Chronic deep brain stimulation of the subthalamic nucleus for Parkinson's disease: effects on cognition, mood, anxiety and personality traits. *Eur Neurol* **55**: 136–144.
- Caudle WM, Bammler TK, Lin Y, Pan S, Zhang J (2010). Using 'omics' to define pathogenesis and biomarkers of Parkinson's disease. *Expert Rev Neurother* **10**: 925–942.
- Chan WY, McKinzie DL, Bose S, Mitchell SN, Witkin JM, Thompson RC *et al* (2008). Allosteric modulation of the muscarinic M4 receptor as an approach to treating schizophrenia. *Proc Natl Acad Sci USA* **105**: 10978–10983.
- Chang VC, Chou KL (2006). Deep brain stimulation for Parkinson's disease: patient selection and motor outcomes. *Med Health R I* **89**: 142–144.
- Chase TN, Oh JD, Blanchet PJ (1998). Neostriatal mechanisms in Parkinson's disease. *Neurology* **51**: S30–S35.
- Chaudhuri KR, Healy DG, Schapira AHV (2006). Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol* **5**: 235–245.
- Chaudhuri KR, Odin P, Antonini A, Martinez-Martin P (2011). Parkinson's disease: the non-motor issues. *Parkinsonism Relat Disord*; e-pub ahead of print 7 July 2011 (in press).
- Chaudhuri KR, Schapira AHV (2009). Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurol* **8**: 464–474.
- Charcot J-M (1879). *Lectures on Diseases of the Nervous System*. HC Lea: Philadelphia.
- Charcot J-M, Vulpian A (1861). La paralysie agitante. *Gaz Hebdom Med Chir* **8**: 765–767, 816–820; **9**: 54–59.
- Chen L, Ding Y, Cagniard B, Van Laar AD, Mortimer A, Chi W *et al* (2008). Unregulated cytosolic dopamine causes neurodegeneration associated with oxidative stress in mice. *J Neurosci* **28**: 425–433.
- Chen LW, Yung KL, Chan YS (2005). Reactive astrocytes as potential manipulation targets in novel cell replacement therapy of Parkinson's disease. *Curr Drug Targets* **6**: 821–833.
- Christine CW, Starr PA, Larson PS, Eberling JL, Jagust WJ, Hawkins RA *et al* (2009). Safety and tolerability of putaminal AADC gene therapy for Parkinson disease. *Neurology* **73**: 1662–1669.
- Chuang C, Fahn S, Frucht SJ (2002). The natural history and treatment of acquired hemidystonia: report of 33 cases and review of the literature. *J Neurol Neurosurg Psychiatry* **72**: 59–67.
- Cilia R, Landi A, Vergani F, Sganzerla E, Pezzoli G, Antonini A (2007). Extradural motor cortex stimulation in Parkinson's disease. *Mov Disord* **22**: 111–114.
- Cilia R, Marotta G, Landi A, Isaias IU, Vergani F, Benti R *et al* (2008). Cerebral activity modulation by extradural motor cortex stimulation in Parkinson's disease: a perfusion SPECT study. *Eur J Neurol* **15**: 22–28.
- Coccurello R, Breyse N, Amalric M (2004). Simultaneous blockade of adenosine A2A and metabotropic glutamate mGlu5 receptors increase their efficacy in reversing Parkinsonian deficits in rats. *Neuropsychopharmacology* **29**: 1451–1461.
- Conn PJ, Battaglia G, Marino MJ, Nicoletti F (2005). Metabotropic glutamate receptors in the basal ganglia motor circuit. *Nat Rev Neurosci* **6**: 787–798.
- Conn PJ, Christopoulos A, Lindsley CW (2009b). Allosteric modulators of GPCRs: a novel approach for the treatment of CNS disorders. *Nat Rev Drug Discov* **8**: 41–54.
- Conn PJ, Jones CK, Lindsley CW (2009a). Subtype-selective allosteric modulators of muscarinic receptors for the treatment of CNS disorders. *Trends Pharmacol Sci* **30**: 148–155. **A concise review of the advantages of developing allosteric modulators of GPCRs for the treatment of brain disorders.**
- Conn PJ, Pin JP (1997). Pharmacology and functions of metabotropic glutamate receptors. *Annu Rev Pharmacol Toxicol* **37**: 205–237.
- Cookson MR (2010). Unravelling the role of defective genes. *Prog Brain Res* **183**: 43–57.
- Cooper O, Astradsson A, Hallett P, Robertson H, Mendez H, Isacson O (2009). Lack of functional relevance of isolated cell damage in transplants of Parkinson's disease patients. *J Neurol* **256**(Suppl 3): 310–316.
- Corrodi H, Fuxe K, Hokfelt T, Lidbrink P, Ungerstedt U (1973). Effect of ergot drugs on central catecholamine neurons: evidence for a stimulation of central dopamine neurons. *J Pharm Pharmacol* **25**: 409–412.
- Cotzias GC, Papavasiliou PS, Gellene R (1969). Modification of parkinsonism: chronic treatment with L-Dopa. *N Engl J Med* **280**: 337–345.
- Cotzias GC, Papavasiliou PS, Fehling C, Kaufman B, Mena I (1970). Similarities between neurologic effects of L-dopa and of apomorphine. *N Engl J Med* **282**: 31–33.
- Cotzias GC, Van Woert MH, Schiffer LM (1967). Aromatic amino acids and modification of parkinsonism. *N Engl J Med* **276**: 374–379.
- Crossman AR (1989). Neural mechanisms in disorders of movement. *Comp Biochem Physiol A Comp Physiol* **93**: 141–149.
- Dachsel JC, Farrer MJ (2010). LRRK2 and Parkinson disease. *Arch Neurol* **67**: 542–547.
- De Blasi A, Conn PJ, Pin J, Nicoletti F (2001). Molecular determinants of metabotropic glutamate receptor signaling. *Trends Pharmacol Sci* **22**: 114–120.
- De Gaspari D, Siri C, Landi A, Cilia R, Bonetti A, Natuzzi F *et al* (2006). Clinical and neuropsychological follow up at 12 months in patients with complicated Parkinson's disease treated with subcutaneous apomorphine infusion or deep brain stimulation of the subthalamic nucleus. *J Neurol Neurosurg Psychiatry* **77**: 450–453.
- Dejean C, Hyland B, Arbutnot G (2009). Cortical effects of subthalamic stimulation correlate with behavioral recovery from dopamine antagonist induced akinesia. *Cereb Cortex* **19**: 1055–1063.
- Dekundy A, Gravius A, Hechenberger M, Pietraszek M, Nagel J, Tober C *et al* (2010). Pharmacological characterization of MRZ-8676, a novel negative allosteric modulator of subtype 5 metabotropic glutamate receptor (mGluR5): focus on L-DOPA induced dyskinesia. *J Neural Transm* (e-pub ahead of print 16 December 2010).
- DeLong MR (1990). Primate models of movement disorders of basal ganglia origin. *Trends Neurosci* **13**: 281–285.
- Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schafer H, Botzel K *et al* (2006). A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* **355**: 896–908.
- Devos D, Defebvre L, Bordet R (2010). Dopaminergic and non-dopaminergic pharmacological hypotheses for gait disorders in Parkinson's disease. *Fundam Clin Pharmacol* **24**: 407–421.
- Devos D, Dujardin K, Poiriot I, Moreau C, Cottencin O, Thomas P *et al* (2008). Comparison of desipramine and citalopram treatments for depression in Parkinson's disease: a double-blind, randomized, placebo-controlled study. *Mov Disord* **23**: 850–857.
- Devos D, Krystkowiak P, Clement F, Dujardin K, Cottencin O, Wauquier N *et al* (2007). Improvement of gait by chronic, high doses of methylphenidate in patients with advanced Parkinson's disease. *J Neurol Neurosurg Psychiatry* **78**: 470–475.
- Dewey Jr RB, Hutton JT, LeWitt PA, Factor SA (2001). A randomized, double-blind, placebo-controlled trial of subcutaneously injected apomorphine for parkinsonian off-state events. *Arch Neurol* **58**: 1385–1392.
- Di Matteo V, Pierucci M, Esposito E, Crescimanno G, Benigno A, Di Giovanni G (2008). Serotonin modulation of the basal ganglia circuitry: therapeutic implication for Parkinson's disease and other motor disorders. *Prog Brain Res* **172**: 423–463.
- Diamond A, Jankovic J (2005). The effect of deep brain stimulation on quality of life in movement disorders. *J Neurol Neurosurg Psychiatry* **76**: 1188–1193.
- Digby GJ, Shirey JK, Conn PJ (2010). Allosteric activators of muscarinic receptors as novel approaches for treatment of CNS disorders. *Mol Biosyst* **6**: 1345–1354.
- Dobkin RD, Menza M, Bienfait KL, Gara M, Marin H, Mark MH *et al* (2011). Depression in Parkinson's disease: symptom improvement and residual symptoms after acute pharmacologic management. *Am J Geriatr Psychiatry* **19**: 222–229.
- Doshi PK, Chhaya N, Bhatt MH (2002). Depression leading to attempted suicide after bilateral subthalamic nucleus stimulation for Parkinson's disease. *Mov Disord* **17**: 1084–1085.
- Dolen G, Carpenter RL, Ocain TD, Bear MF (2010). Mechanism-based approaches to treating fragile X. *Pharmacol Ther* **127**: 78–93.
- Doshay LJ, Constable K, Agate Jr FJ (1956). Ethopropazine (parsidol) hydrochloride in treatment of paralysis agitans; posology, method of administration, and effects. *J Am Med Assoc* **160**: 348–351.

- Doty RL, Deems DA, Stellar S (1988). Olfactory dysfunction in parkinsonism: a general deficit unrelated to neurologic signs, disease stage, or disease duration. *Neurology* **38**: 1237–1244.
- Drapier D, Peron J, Leray E, Sauleau P, Biseul I, Drapier S et al (2008). Emotion recognition impairment and apathy after subthalamic nucleus stimulation in Parkinson's disease have separate neural substrates. *Neuropsychologia* **46**: 2796–2801.
- Dujardin K, Blairy S, Defebvre L, Krystkowiak P, Hess U, Blond S et al (2004). Subthalamic nucleus stimulation induces deficits in decoding emotional facial expressions in Parkinson's disease. *J Neurol Neurosurg Psychiatry* **75**: 202–208.
- Dujardin K, Defebvre L, Krystkowiak P, Blond S, Destee A (2001). Influence of chronic bilateral stimulation of the subthalamic nucleus on cognitive function in Parkinson's disease. *J Neurol* **248**: 603–611.
- Durif F, Debilly B, Galitzky M, Morand D, Viallet F, Borg M et al (2004). Clozapine improves dyskinesias in Parkinson disease: a double-blind, placebo-controlled study. *Neurology* **62**: 381–388.
- Durif F, Lemaire JJ, Debilly B, Dordain G (2002). Long-term follow-up of globus pallidus chronic stimulation in advanced Parkinson's disease. *Mov Disord* **17**: 803–807.
- During MJ, Kaplitt MG, Stern MB, Eidelberg D (2001). Subthalamic GAD gene transfer in Parkinson disease patients who are candidates for deep brain stimulation. *Hum Gene Ther* **12**: 1589–1591.
- Duty S (2010). Therapeutic potential of targeting group III metabotropic glutamate receptors in the treatment of Parkinson's disease. *Br J Pharmacol* **161**: 271–287.
- Eberling JL, Jagust WJ, Christine CW, Starr P, Larson P, Bankiewicz KS et al (2008). Results from a phase I safety trial of hAADC gene therapy for Parkinson disease. *Neurology* **70**: 1980–1983.
- Ehringer H, Hornykiewicz O (1960). Verteilung von Noradrenalin und Dopamin (3-hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Erkrankungen des extrapyramidalen Systems. *Klin Wochenschr* **38**: 1236–1239.
- Emre M (2003). What causes mental dysfunction in Parkinson's disease? *Mov Disord* **18**(Suppl 6): S63–S71.
- Emre M, Aarsland D, Albanese A, Byrne EJ, Deuschl G, De Deyn PP et al (2004). Rivastigmine for dementia associated with Parkinson's disease. *N Engl J Med* **351**: 2509–2518.
- Emre M, Tsolaki M, Bonuccelli U, Destee A, Tolosa E, Kutzelnigg A et al (2010). Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* **9**: 969–977.
- Engers DW, Field JR, Le U, Zhou Y, Bolinger JD, Zamorano R et al (2011). Discovery, synthesis, and structure-activity relationship development of a series of N-(4-acetamidophenyl)pyrrolidines as positive allosteric modulators of metabotropic glutamate receptor 4 (mGlu4) with CNS exposure in rats. *J Med Chem* **54**: 1106–1110.
- Entacapone-Tolcapone Switch Study Investigators (2007). Entacapone to tolcapone switch: multicenter double-blind, randomized, active-controlled trial in advanced Parkinson's disease. *Mov Disord* **22**: 14–19.
- Erola T, Karinen P, Heikkinen E, Tuominen J, Haapaniemi T, Koivukangas J et al (2005). Bilateral subthalamic nucleus stimulation improves health-related quality of life in Parkinsonian patients. *Parkinsonism Relat Disord* **11**: 89–94.
- Espay AJ, Dwivedi AK, Payne M, Gaines L, Vaughan JE, Maddux BN et al (2011). Methylphenidate for gait impairment in Parkinson disease: a randomized clinical trial. *Neurology* **76**: 1256–1262.
- Factor SA (1999). Dopamine agonists. *Med Clin North Am* **83**: 415–443, vi–vii.
- Factor SA (2004). Literature review: intermittent subcutaneous apomorphine therapy in Parkinson's disease. *Neurology* **62**: S12–S17.
- Factor SA (2008). Current status of symptomatic medical therapy in Parkinson's disease. *Neurotherapeutics* **5**: 164–180.
- Factor S, Mark MH, Watts R, Struck L, Mori A, Ballerini R, et al, Istradefylline 6002-US-007 Study Group (2010). A long-term study of istradefylline in subjects with Parkinson's disease. *Parkinsonism Relat Disorders* **16**: 423–426.
- Factor SA, Molho ES (1999). Transient benefit of amantadine in Parkinson's disease: the facts about the myth. *Mov Disord* **14**: 515–517.
- Fahn S (1989). The history of parkinsonism. *Mov Disord* **4**(Suppl 1): S2–S10.
- Fahn S (1996a). Controversies in the therapy of Parkinson's disease. *Adv Neurol* **69**: 477–486.
- Fahn S (1996b). Is levodopa toxic? *Neurology* **47**: S184–S195.
- Fahn S, Cohen G (1992). The oxidant stress hypothesis in Parkinson's disease: evidence supporting it. *Ann Neurol* **32**: 804–812.
- Fahn S, Oakes D, Shoulson I, Kieburtz K, Rudolph A, Lang A et al (2004). Levodopa and the progression of Parkinson's disease. *N Engl J Med* **351**: 2498–2508. **This paper presents the results of the ELLDOPA trial that assessed the efficacy of L-DOPA towards PD motor symptoms. This paper also demonstrates that L-DOPA therapy does not accelerate PD progression.**
- Fahn S, Parkinson Study Group (2005). Does levodopa slow or hasten the rate of progression of Parkinson's disease? *J Neurol* **252**(Suppl 4): IV37–IV42.
- Farrer MJ (2006). Genetics of Parkinson disease: paradigm shifts and future prospects. *Nat Rev Genet* **7**: 306–318.
- Feng LR, Maguire-Zeiss KA (2010). Gene therapy in Parkinson's disease: rationale and current status. *CNS Drugs* **24**: 177–192.
- Fernandez HH, Greeley DR, Zweig RM, Wojcieszek J, Mori A, Sussman NM (2010). Istradefylline as monotherapy for Parkinson disease: results of the 6002-US-051 trial. *Parkinsonism Relat Disord* **16**: 16–20.
- Ferraguti F, Crepaldi L, Nicoletti F (2008). Metabotropic glutamate receptor 1: current concepts and perspectives. *Pharmacol Rev* **60**: 536–581.
- Ferrara J, Diamond A, Hunter C, Davidson A, Almaguer M, Jankovic J (2010). Impact of STN-DBS on life and health satisfaction in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* **81**: 315–319.
- Ferraye MU, Debu V, Fraix V, Goetz L, Ardouin C, Yelnik J et al (2010). Effects of pedunculopontine nucleus area stimulation on gait disorders in Parkinson's disease. *Brain* **133**: 205–214.
- Ferré S, Fredholm BB, Morelli M, Popoli P, Fuxe K (1997). Adenosine-dopamine receptor-receptor interactions as an integrative mechanism in the basal ganglia. *Trends Neurosci* **20**: 482–487.
- Fisher A (2008). M1 muscarinic agonists target major hallmarks of Alzheimer's disease: The pivotal role of brain M1 receptors. *Neurodegener Dis* **5**: 237–240.
- Flor PJ, Battaglia G, Nicoletti F, Gasparini F, Bruno V (2002). Neuroprotective activity of metabotropic glutamate receptor ligands. *Adv Exp Med Biol* **513**: 197–223.
- Follett KA, Weaver FM, Stern M, Hur K, Harris CL, Luo P et al (2010). Pallidal vs subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med* **362**: 2077–2091. **A comprehensive comparative analysis of the benefits and adverse effects of GPI vs STN DBS in Parkinson's disease.**
- Forsayeth JR, Eberling JL, Sanftner LM, Zhen Z, Pivrotto P, Bringas J et al (2006). A dose-ranging study of AAV-hAADC therapy in Parkinsonian monkeys. *Mol Ther* **14**: 571–577.
- Freed CR, Greene PE, Breeze RE, Tsai WY, DuMouchel W, Kao R et al (2001). Transplantation of embryonic dopamine neurons for severe Parkinson's disease. *N Engl J Med* **344**: 710–719.
- French Clozapine Parkinson Study Group (1999). Clozapine in drug-induced psychosis in Parkinson's disease. *Lancet* **353**: 2041–2042.
- Fricker-Gates RA, Gates MA (2010). Stem cell-derived dopamine neurons for brain repair in Parkinson's disease. *Regen Med* **5**: 267–278.
- Fu Y, Gao W, Zhu M, Chen X, Lin Z, Wang S (2009). Computer-assisted automatic localization of the human pedunculopontine nucleus in T1-weighted MR images: a preliminary study. *Int J Med Robot* **5**: 309–318.
- Funk C (1911). *Synthese des d, 1-3-4, Dioxypheylanilins*. Chem Zentralbl.
- Funkiewicz A, Ardouin C, Caputo E, Krack P, Fraix V, Klinger H et al (2004). Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. *J Neurol Neurosurg Psychiatry* **75**: 834–839.
- Fuxe K, Agnati LF, Jacobsen K, Hillion J, Canals M, Torvinen M et al (2003). Receptor heteromerization in adenosine A2A receptor signalling: relevance for striatal function and Parkinson's disease. *Neurology* **61**: S19–S23.
- Fuxe K, Ferre S, Genedani S, Franco R, Agnati LF (2007a). Adenosine receptor-dopamine receptor interactions in the basal ganglia and their relevance for brain function. *Physiol Behav* **92**: 210–217.
- Fuxe K, Marcellino D, Borroto-Escuela DO, Guescini M, Fernandez-Duenas V, Tanganelli S et al (2010a). Adenosine-dopamine interactions in the pathophysiology and treatment of CNS disorders. *CNS Neurosci Ther* **16**: e18–e42.
- Fuxe K, Marcellino D, Genedani S, Agnati L (2007b). Adenosine A(2A) receptors, dopamine D(2) receptors and their interactions in Parkinson's disease. *Mov Disord* **22**: 1990–2017.
- Fuxe K, Marcellino D, Leo G, Agnati LF (2010b). Molecular integration via allosteric interactions in receptor heteromers. A working hypothesis. *Curr Opin Pharmacol* **10**: 14–22.
- Gallagher DA, Lees AJ, Schrag A (2010). What are the most important nonmotor symptoms in patients with Parkinson's disease and are we missing them? *Mov Disord* **25**: 2493–2500.
- Galvan A, Kuwajima M, Smith Y (2006). Glutamate and GABA receptors and transporters in the basal ganglia: what does their subsynaptic localization reveal about their function? *Neuroscience* **143**: 351–375.
- Galvan A, Wichmann T (2008). Pathophysiology of parkinsonism. *Clin Neurophysiol* **119**: 1459–1474.
- Gasmi M, Brandon EP, Herzog CD, Wilson A, Bishop KM, Hofer EK et al (2007a). AAV2-mediated delivery of human neurturin to the rat nigrostriatal system: long-term efficacy and tolerability of CERE-120 for Parkinson's disease. *Neurobiol Dis* **27**: 67–76.

- Gasmi M, Herzog CD, Brandon EP, Cunningham JJ, Ramirez GA, Ketchum ET *et al* (2007b). Striatal delivery of neurturin by CERE-120, an AAV2 vector for the treatment of dopaminergic neuron degeneration in Parkinson's disease. *Mol Ther* **15**: 62–68.
- Gasparini F, Bilbe G, Gomez-Mancilla B, Spooren W (2008). mGluR5 antagonists: discovery, characterization and drug development. *Curr Opin Drug Discov Devel* **11**: 655–665.
- Gerhard A, Pavese N, Hotton G, Turkheimer F, Es M, Hammers A *et al* (2006). *In vivo* imaging of microglial activation with [¹¹C](R)-PK11195 PET in idiopathic Parkinson's disease. *Neurobiol Dis* **21**: 404–412.
- Germano IM, Gracies JM, Weisz DJ, Tse W, Koller WC, Olanow CW (2004). Unilateral stimulation of the subthalamic nucleus in Parkinson disease: a double-blind 12-month evaluation study. *J Neurosurg* **101**: 36–42.
- Giladi N (2008). Medical treatment of freezing of gait. *Mov Disord* **23**(Suppl 2): S482–S488.
- Godwin-Austen RB (1973). The long term therapeutic effect of levodopa in the treatment of parkinsonism. *Adv Neurol* **3**: 23–27.
- Goetz CG, Damier P, Hickey C, Laska E, Muller T, Olanow CW *et al* (2007). Striatum as a treatment for dyskinesias in Parkinson's disease: a double-blind placebo-controlled trial. *Mov Disord* **22**: 179–186.
- Goetz CG, Laska E, Hickey C, Damier P, Müller T, Nutt J *et al* (2008). Placebo influences on dyskinesias in Parkinson's disease. *Mov Disord* **23**: 700–707.
- Goff LK, Jouve L, Melon C, Salin P (2009). Rationale for targeting the thalamic centre-median parafascicular complex in the surgical treatment of Parkinson's disease. *Parkinsonism Relat Disord* **15**(Suppl 3): S167–S170.
- Goldstein DS, Sewell L (2009). Olfactory dysfunction in pure autonomic failure: implications for the pathogenesis of Lewy body diseases. *Parkinsonism Relat Disord* **15**: 516–520.
- Gottwald MD, Aminoff MJ (2008). New frontiers in the pharmacological management of Parkinson's disease. *Drugs Today (Barc)* **44**: 531–545.
- Gradinaru V, Mogri M, Thompson KR, Henderson JM, Deisseroth K (2009). Optical deconstruction of parkinsonian neural circuitry. *Science* **324**: 354–359.
- Greene JG (2008). Excitatory amino acid antagonists. In: Factor SA, Weiner WJ (eds). *Parkinson's Disease-Diagnostic and Clinical Management*. Demos: New York. pp 545–555.
- Gregoire L, Morin N, Ouattara B, Gasparini F, Bilbe G, Johns D *et al* (2011). The acute antiparkinsonian and antidyskinetic effect of AFQ056, a novel metabotropic glutamate receptor type 5 antagonist, in L-Dopa-treated parkinsonian monkeys. *Parkinsonism Relat Disord* **17**: 270–276.
- Grondin R, Bedard PJ, Hadj Tahar A, Gregoire L, Mori A, Kase H (1999). Antiparkinsonian effect of a new selective adenosine A2A receptor antagonist in MPTP-treated monkeys. *Neurology* **52**: 1673–1677.
- Gunzler SA, Nutt JG (2008). Motor fluctuations with dyskinesia. In: Factor SA, Weiner WJ (eds). *Parkinson's Disease-Diagnostic and Clinical Management*. Demos: New York. pp 575–584.
- Haehner A, Boesveldt S, Berendse HW, Mackay-Sim A, Fleischmann J, Silburn PA *et al* (2009). Prevalence of smell loss in Parkinson's disease—a multicenter study. *Parkinsonism Relat Disord* **15**: 490–494.
- Haehner A, Hummel T, Hummel C, Sommer U, Junghanns S, Reichmann H (2007). Olfactory loss may be a first sign of idiopathic Parkinson's disease. *Mov Disord* **22**: 839–842.
- Haehner A, Hummel T, Reichmann H (2009). Olfactory dysfunction as a diagnostic marker for Parkinson's disease. *Expert Rev Neurother* **9**: 1773–1779.
- Halbig TD, Gruber D, Kopp UA, Schneider GH, Trottenberg T, Kupsch A (2005). Pallidal stimulation in dystonia: effects on cognition, mood, and quality of life. *J Neurol Neurosurg Psychiatry* **76**: 1713–1716.
- Hanson JE, Smith Y (1999). Group I metabotropic glutamate receptors at GABAergic synapses in monkeys. *J Neurosci* **19**: 6488–6496.
- Hardy J, Cai H, Cookson MR, Gwinn-Hardy K, Singleton A (2006). Genetics of Parkinson's disease and parkinsonism. *Ann Neurol* **60**: 389–398.
- Hargus G, Cooper O, Deleidi M, Levy A, Lee K, Marlow E *et al* (2010). Differentiated Parkinson patient-derived induced pluripotent stem cell grow in the adult rodent brain and reduce motor asymmetry in parkinsonian rats. *Proc Natl Acad Sci USA* **107**: 15921–15927.
- Hariz MI, Johansson F, Shamsgovara P, Johansson E, Hariz GM, Fagerlund M (2000). Bilateral subthalamic nucleus stimulation in a parkinsonian patient with preoperative deficits in speech and cognition: persistent improvement in mobility but increased dependency: a case study. *Mov Disord* **15**: 136–139.
- Hasselmo ME (2006). The role of acetylcholine in learning and memory. *Curr Opin Neurobiol* **16**: 710–715.
- Hauptmann C, Tass PA (2010). Restoration of segregated, physiological neuronal connectivity by desynchronizing stimulation. *J Neural Eng* **7**: 056008.
- Hauser RA, Cantillon M, Pourcher E, Micheli F, Mok V, Onofri M *et al* (2011). Preladenant in patients with Parkinson's disease and motor fluctuations: a phase 2, double-blind, randomised trial. *Lancet Neurol* **10**: 221–229.
- Hauser RA, Schwarzschild MA (2005). Adenosine A2A receptor antagonists for Parkinson's disease: rationale, therapeutic potential and clinical experience. *Drugs Aging* **22**: 471–482.
- Hawkes C (2003). Olfaction in neurodegenerative disorder. *Mov Disord* **18**: 364–372.
- Hawkes CH, Shephard BC, Daniel SE (1997). Olfactory dysfunction in Parkinson's disease. *J Neurol Neurosurg Psychiatry* **62**: 436–446.
- Healy DG, Falchi M, O'Sullivan SS, Bonifati V, Durr A, Bressman S *et al* (2008). Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. *Lancet Neurol* **7**: 583–590.
- Hely MA, Morris JG, Reid WG, Trafficante R (2005). Sydney Multicenter Study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. *Mov Disord* **20**: 190–199. **Extensive survey showing the high prevalence of nonmotor symptoms that are unresponsive to dopamine therapy in PD.**
- Hernan MA, Takkouche B, Caamano-Isorna F, Gestal-Otero JJ (2002). A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Ann Neurol* **52**: 276–284.
- Herzog CD, Dass B, Gasmi M, Bakay R, Stansell JE, Tuszynski M *et al* (2008). Transgene expression, bioactivity, and safety of CERE-120 (AAV2-neurturin) following delivery to the monkey striatum. *Mol Ther* **16**: 1737–1744.
- Herzog CD, Dass B, Holden JE, Stansell III J, Gasmi M, Tuszynski MH *et al* (2007). Striatal delivery of CERE-120, an AAV2 vector encoding human neurturin, enhances activity of the dopaminergic nigrostriatal system in aged monkeys. *Mov Disord* **22**: 1124–1132.
- Herzog J, Reiff J, Krack P, Witt K, Schrader B, Muller D *et al* (2003a). Manic episode with psychotic symptoms induced by subthalamic nucleus stimulation in a patient with Parkinson's disease. *Mov Disord* **18**: 1382–1384.
- Herzog J, Volkmann J, Krack P, Kopper F, Pötter M, Lorenz D *et al* (2003b). Two-year follow-up of subthalamic deep brain stimulation in Parkinson's disease. *Mov Disord* **18**: 1332–1337.
- Higginson CI, Wheelock VL, Levine D, King DS, Pappas CT, Sigvardt KA (2009). The clinical significance of neuropsychological changes following bilateral subthalamic nucleus deep brain stimulation for Parkinson's disease. *J Clin Exp Neuropsychol* **31**: 65–72.
- Hirsch EC, Hunot S (2009). Neuroinflammation in Parkinson's disease: a target for neuroprotection? *Lancet Neurol* **8**: 382–397. **A comprehensive review of evidence that neuroinflammation contributes to PD pathogenesis.**
- Hodgson RA, Bedard PJ, Varty GB, Kazdoba TM, Di Paolo T, Grzelak ME *et al* (2010). Preladenant, a selective A(2A) receptor antagonist, is active in primate models of movement disorders. *Exp Neurol* **225**: 384–390.
- Hodgson RA, Bertorelli R, Varty GB, Lachowicz JE, Forlani A, Fredduzzi S *et al* (2009). Characterization of the potent and highly selective A2A receptor antagonists preladenant and SCH 412348 [7-[2-[4-(2,4-difluorophenyl)-1-piperazinyl]ethyl]-2-(2-furanyl)-7H-pyrazolo [4,3-c][1,2,4]triazolo[1,5-c]pyrimidin-5-amine] in rodent models of movement disorders and depression. *J Pharmacol Exp Ther* **330**: 294–303.
- Holloway RG, Shoulson I, Fahn S, Kieburz K, Lang A, Marek K *et al*, Parkinson Study Group (2004). Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. *Arch Neurol* **61**: 1044–1053.
- Hopkins CR, Lindsley CW, Niswender CM (2009). mGluR4-positive allosteric modulation as potential treatment for Parkinson's disease. *Future Med Chem* **1**: 501–513.
- Hornykiewicz O (2002a). Dopamine miracle: from brain homogenate to dopamine replacement. *Mov Disord* **17**: 501–508.
- Hornykiewicz O (2002b). L-DOPA: from a biologically inactive amino acid to a successful therapeutic agent. *Amino Acids* **23**: 65–70.
- Hubert GW, Paquet M, Smith Y (2001). Differential subcellular localization of mGluR1a and mGluR5 in the rat and monkey Substantia nigra. *J Neurosci* **21**: 1838–1847.
- Hughes AJ, Bishop S, Kleedorfer B, Turjanski N, Fernandez W, Lees AJ *et al* (1993). Subcutaneous apomorphine in Parkinson's disease: response to chronic administration for up to five years. *Mov Disord* **8**: 165–170.
- Huisman E, Uylings HB, Hoogland PV (2004). A 100% increase of dopaminergic cells in the olfactory bulb may explain hyposmia in Parkinson's disease. *Mov Disord* **19**: 687–692.
- Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G (1997). 'Sniffin sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. *Chem Senses* **22**: 39–52.
- Isacson O (2009). Cell therapy ahead for Parkinson's disease. *Science* **326**: 1060.
- Isacson O, Kordower JF (2008). Future of cell and gene therapies for Parkinson's disease. *Ann Neurol* **64**(Suppl 2): S122–S138.
- Isacson O, Mendez I (2010). Being too inclusive about synuclein inclusions. *Nat Med* **16**: 960–961.
- Jarraya B, Boulet S, Ralph GS, Jan C, Bonvento G, Azzouz M *et al* (2009). Dopamine gene therapy for Parkinson's disease in a nonhuman primate without associated dyskinesia. *Sci Transl Med* **1**: 2ra4.

- Jenner P, Mori A, Hauser R, Morelli M, Fredholm BB, Chen JF (2009). Adenosine, adenosine A2A antagonists, and Parkinson's disease. *Parkinsonism Relat Disord* **15**: 406–413.
- Jiménez-Jiménez FJ, Mateo D, Giménez-Roldán S (1992). Premorbid smoking, alcohol consumption, and coffee drinking habits in Parkinson's disease: a case-control study. *Mov Disord* **7**: 339–344.
- Johnson KA, Conn PJ, Niswender CM (2009). Glutamate receptors as therapeutic targets for Parkinson's disease. *CNS Neurol Disord Drug Targets* **8**: 475–491.
- Johnston TH, Fox SH, McIlldowie MJ, Piggott MJ, Brochie JM (2010). Reduction of L-DOPA-induced dyskinesia by the selective metabotropic glutamate receptor 5 antagonist 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned macaque model of Parkinson's disease. *J Pharmacol Exp Ther* **333**: 865–873.
- Jouve L, Salin P, Melon C, Kerkerian-Le Goff L (2010). Deep brain stimulation of the center median-parafascicular complex of the thalamus has efficient anti-parkinsonian action associated with widespread cellular responses in the basal ganglia network in a rat model of Parkinson's disease. *J Neurosci* **30**: 9919–9928.
- Just H, Ostergaard K (2002). Health-related quality of life in patients with advanced Parkinson's disease treated with deep brain stimulation of the subthalamic nuclei. *Mov Disord* **17**: 539–545.
- Kachroo A, Orlando LR, Grandy DK, Chen JF, Young AB, Schwarzschild MA (2005). Interactions between metabotropic glutamate 5 and adenosine A2A receptors in normal and parkinsonian mice. *J Neurosci* **25**: 10414–10419.
- Kagi G, Bhatia KP, Tolosa E (2010). The role of DAT-SPECT in movement disorders. *J Neurol Neurosurg Psychiatry* **81**: 5–12.
- Kanda T, Jackson MJ, Smith LA, Pearce RK, Nakamura J, Kase H et al (1998). Adenosine A2A antagonist: a novel antiparkinsonian agent that does not provoke dyskinesia in parkinsonian monkeys. *Ann Neurol* **43**: 507–513.
- Kapli MG, Feigin A, Tang C, Fitzsimons HL, Mattis P, Lawlor PA et al (2007). Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson's disease: an open label, phase I trial. *Lancet* **369**: 2097–2105.
- Kapp W (1992). The history of drugs for the treatment of Parkinson's disease. *J Neural Transm* **38**: 1–6.
- Kasten M, Kertelge L, Bruggemann N, van der Vegt J, Schmidt A, Tadic V et al (2010). Nonmotor symptoms in genetic Parkinson's disease. *Arch Neurol* **67**: 670–676.
- Katzenschlagher R, Manson AJ, Evans A, Watt H, Lees AJ (2004). Low dose quetiapine for drug induced dyskinesias in Parkinson's disease: a double blind cross over study. *J Neurol Neurosurg Psychiatry* **75**: 295–297.
- Khan NL, Brooks DJ, Pavese N, Sweeney MG, Wood NW, Lees AJ et al (2002). Progression of nigrostriatal dysfunction in a parkin kindred: an [18F]dopa PET and clinical study. *Brain* **125**: 2248–2256.
- Kim HJ (2011). Stem cell potential in Parkinson's disease and molecular factors for the generation of dopamine neurons. *Biochim Biophys Acta* **1812**: 1–11.
- Kitagawa M, Murata J, Uesugi H, Kikuchi S, Saito H, Tashiro K et al (2005). Two-year follow-up of chronic stimulation of the posterior subthalamic white matter for tremor-dominant Parkinson's disease. *Neurosurgery* **56**: 281–289; discussion 281–289.
- Klein C, Schlossmacher MG (2007). Parkinson disease, 10 years after its genetic revolution: multiple clues to a complex disorder. *Neurology* **69**: 2093–2104.
- Kojima J, Yamaji Y, Matsumura M, Nambu A, Inase M, Tokuno H et al (1997). Excitotoxic lesions of the pedunculopontine tegmental nucleus produce contralateral hemiparkinsonism in the monkey. *Neurosci Lett* **226**: 111–114.
- Koller WC (1986). Pharmacologic treatment of parkinsonian tremor. *Arch Neurol* **43**: 126–127.
- Kordower JH, Chu Y, Hauser RA, Freeman TB, Olanow CW (2008a). Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. *Nat Med* **14**: 504–506. **Case reports of evidence for Lewy body pathology in transplanted dopaminergic neurons in the striatum of parkinsonian patients.**
- Kordower JH, Chu Y, Hauser RA, Olanow CW, Freeman TB (2008b). Transplanted dopaminergic neurons develop PD pathologic changes: a second case report. *Mov Disord* **23**: 2303–2306.
- Kordower JH, Emborg ME, Bloch J, Ma SY, Chu Y, Leventhal L et al (2000). Neurodegeneration prevented by lentiviral vector delivery of GDNF in primate models of Parkinson's disease. *Science* **290**: 767–773.
- Kordower JH, Herzog CD, Dass B, Bakay RA, Stansell III J, Gasmi M et al (2006). Delivery of neurturin by AAV2 (CERE-120)-mediated gene transfer provides structural and functional neuroprotection and neurorestoration in MPTP-treated monkeys. *Ann Neurol* **60**: 706–715.
- Kotzbauer PT, Lampe PA, Heuckeroth RO, Golden JP, Creedon DJ, Johnson Jr EM et al (1996). Neurturin, a relative of glial-cell-line-derived neurotrophic factor. *Nature* **384**: 467–470.
- Krack P, Vercueil L (2001). Review of the functional surgical treatment of dystonia. *Eur J Neurol* **8**: 389–399.
- Krauss JK, Pohle T, Weigel R, Burgunder JM (2002). Deep brain stimulation of the centre median-parafascicular complex in patients with movement disorders. *J Neurol Neurosurg Psychiatry* **72**: 546–548.
- Kulisevsky J, Berthier ML, Gironell A, Pascual-Sedano B, Molet J, Pares P (2002). Mania following deep brain stimulation for Parkinson's disease. *Neurology* **59**: 1421–1424.
- Kumar R, Krack P, Pollak P (1999a). Transient acute depression induced by high-frequency deep-brain stimulation. *N Engl J Med* **341**: 1003–1004; discussion 1004.
- Kumar R, Lozano AM, Sime E, Halket E, Lang AE (1999b). Comparative effects of unilateral and bilateral subthalamic nucleus deep brain stimulation. *Neurology* **53**: 561–566.
- Kuwajima M, Dehoff MH, Furuichi T, Worley PF, Hall RA, Smith Y (2007). Localization and expression of group I metabotropic glutamate receptors in the mouse striatum, globus pallidus, and subthalamic nucleus: regulatory effects of MPTP treatment and constitutive Homer deletion. *J Neurosci* **27**: 6249–6260.
- Kuwajima M, Hall RA, Aiba A, Smith Y (2004). Subcellular and subsynaptic localization of group I metabotropic glutamate receptors in the monkey subthalamic nucleus. *J Comp Neurol* **474**: 589–602.
- Laitinen LV, Bergenheim AT, Hariz MI (1992). Ventroposterolateral pallidotomy can abolish all parkinsonian symptoms. *Stereotact Funct Neurosurg* **58**: 14–21. **Clinical evidence that launched the rejuvenation of the use of pallidotomy as treatment for Parkinson's disease.**
- Lane EL, Bjorklund A, Dunnett SB, Winkler C (2010). Neural grafting in Parkinson's disease: unraveling the mechanisms underlying graft-induced dyskinesia. *Prog Brain Res* **184**: 295–309.
- Lane EL, Winkler C, Brundin P, Cenci MA (2006). The impact of graft size on the development of dyskinesia following intrastratial grafting of embryonic dopamine neurons in the rat. *Neurobiol Dis* **22**: 334–345.
- Lang AE (2009). When and how should treatment be started in Parkinson disease? *Neurology* **72**: S39–S43.
- Lang AE, Gill S, Patel NK, Lozano A, Nutt JG, Penn R et al (2006). Randomized controlled trial of intraputamenal glial cell line-derived neurotrophic factor infusion in Parkinson disease. *Ann Neurol* **59**: 459–466.
- Lang AE, Langston JW, Stoessl AJ, Brodsky M, Brooks DJ, Dhawan V et al (2006). GDNF in treatment of Parkinson's disease: response to editorial. *Lancet Neurol* **5**: 200–202.
- Lang AE, Mikulis D (2009). A new sensitive imaging biomarker for Parkinson disease? *Neurology* **72**: 1374–1375.
- Langmead CJ, Watson J, Reavill C (2008). Muscarinic acetylcholine receptors as CNS drug targets. *Pharmacol Ther* **117**: 232–243.
- Langston JW (2006). The Parkinson's complex: parkinsonism is just the tip of the iceberg. *Ann Neurol* **59**: 591–596.
- Langston JW, Ballard Jr PA (1983). Parkinson's disease in a chemist working with 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine. *N Engl J Med* **309**: 310–315.
- Lefaucheur JP (2009). Treatment of Parkinson's disease by cortical stimulation. *Expert Rev Neurother* **9**: 1755–1771.
- Leroi I, Brandt J, Reich SG, Lyketsos CG, Grill S, Thompson R et al (2004). Randomized placebo-controlled trial of donepezil in cognitive impairment in Parkinson's disease. *Int J Geriatr Psychiatry* **19**: 1–8.
- Leroi I, Overshott R, Byrne EJ, Daniel E, Burns A (2009). Randomized controlled trial of memantine in dementia associated with Parkinson's disease. *Mov Disord* **24**: 1217–1221.
- Lim SY, Lang AE (2010). The nonmotor symptoms of Parkinson's disease—an overview. *Mov Disord* **25**(Suppl 1): S123–S130.
- Levi-Montalcini R, Hamburger V (1951). Selective growth stimulating effects of mouse sarcoma on the sensory and sympathetic nervous system of the chick embryo. *J Exp Zool* **116**: 321–361.
- LeWitt PA (2004). Subcutaneously administered apomorphine: pharmacokinetics and metabolism. *Neurology* **62**: S8–S11.
- LeWitt PA, Guttman M, Tetud JW, Tuite PJ, Mori A, Chaikin P et al (2008). Adenosine A2A receptor antagonist istradefylline (KW-6002) reduces "off" time in Parkinson's disease: a double-blind, randomized, multicenter clinical trial (6002-US-005). *Ann Neurol* **63**: 295–302.
- LeWitt PA, Rezaei AR, Leehey MA, Ojemann SG, Flaherty AW, Eskandar EN et al (2011). AAV2-GAD gene therapy for advanced Parkinson's disease: a double-blind, sham-surgery controlled, randomised trial. *Lancet Neurol* **10**: 309–319. **First report of the results of a double-blind placebo controlled trial for gene therapy in PD.**
- Lewy FH (1912). Paralysis agitans. Pathologische anatomie. In: Lewandowsky M (ed). *Handbook der Neurologie*. Springer: Berlin. pp 920–933.
- Lezcano E, Gomez-Esteban JC, Zarranz JJ, Lambarri I, Madoz P, Bilbao G et al (2004). Improvement in quality of life in patients with advanced Parkinson's

- disease following bilateral deep-brain stimulation in subthalamic nucleus. *Eur J Neurol* **11**: 451–454.
- Li JY, Christophersen NS, Hall V, Soulet D, Brundin P (2008a). Critical issues of clinical human embryonic stem cell therapy for brain repair. *Trends Neurosci* **31**: 146–153. **Concise assessment of the potential promises and problems stem cell therapy faces as treatment for Parkinson's disease.**
- Li JY, Englund E, Holtón JL, Soulet D, Hagell P, Lees AJ et al (2008b). Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. *Nat Med* **14**: 501–503.
- Li JY, Englund E, Widner H, Rehnström S, Björklund A, Lindvall O et al (2010). Characterization of Lewy body pathology in 12- and 16-year-old intrastriatal mesencephalic grafts surviving in a patient with Parkinson's disease. *Mov Disord* **25**: 1091–1096.
- Li S, Arbutnot GW, Jutras MJ, Goldberg JA, Jaeger D (2007). Resonant antitonic cortical circuit activation as a consequence of high-frequency subthalamic deep-brain stimulation. *J Neurophysiol* **98**: 3525–3537.
- Liberini P, Parola S, Spano PF, Antonini L (2000). Olfaction in Parkinson's disease: methods of assessment and clinical relevance. *J Neurol* **247**: 88–96.
- Lilleeng B, Dietrichs E (2008). Unmasking psychiatric symptoms after STN deep brain stimulation in Parkinson's disease. *Acta Neurol Scand Suppl* **188**: 41–45.
- Limousin P, Pollak P, Benazzouz A, Hoffmann D, Broussolle E, Perret JE et al (1995a). Bilateral subthalamic nucleus stimulation for severe Parkinson's disease. *Mov Disord* **10**: 672–674. **Early evidence that deep brain stimulation of the STN alleviates motor symptoms in PD.**
- Limousin P, Pollak P, Benazzouz A, Hoffmann D, Le Bas JF, Broussolle E et al (1995b). Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet* **345**: 91–95.
- Lin LF, Doherty DH, Lile JD, Bektesh S, Collins F (1993). GDNF: a glial cell line-derived neurotrophic factor for midbrain dopaminergic neurons. *Science* **260**: 1130–1132.
- Lindsay CW, Niswender CM, Engers DW, Hopkins CR (2009). Recent progress in the development of mGluR4 positive allosteric modulators for the treatment of Parkinson's disease. *Curr Top Med Chem* **9**: 949–963.
- Lindvall O, Rehnström S, Brundin P, Gustavii B, Åstedt B, Widner H et al (1989). Human fetal dopamine neurons grafted into the striatum in two patients with severe Parkinson's disease. A detailed account of methodology and a 6-month follow-up. *Arch Neurol* **46**: 615–631.
- Lloyd K, Hornykiewicz O (1970). Parkinson's disease: activity of L-dopa decarboxylase in discrete brain regions. *Science* **170**: 1212–1213.
- Lopez S, Turle-Lorenzo N, Acher F, De Leonibus E, Mele A, Amalric M (2007). Targeting group III metabotropic glutamate receptors produces complex behavioral effects in rodent models of Parkinson's disease. *J Neurosci* **27**: 6701–6711.
- Lopez S, Turle-Lorenzo N, Johnston TH, Brochie JM, Schann S, Neuvill P et al (2008). Functional interaction between adenosine A2A and group III metabotropic glutamate receptors to reduce parkinsonian symptoms in rats. *Neuropharmacology* **55**: 483–490.
- Lundblad M, Vaudano E, Cenci MA (2003). Cellular and behavioural effects of the adenosine A2a receptor antagonist KW-6002 in a rat model of L-DOPA-induced dyskinesia. *J Neurochem* **84**: 1398–1410.
- Luo J, Kaplitt MG, Fitzsimons HL, Zuzga DS, Liu Y, Oshinsky ML et al (2002). Subthalamic GAD gene therapy in Parkinson's disease rat model. *Science* **298**: 425–429.
- Lyons KE, Pahwa R (2005). Long-term benefits in quality of life provided by bilateral subthalamic stimulation in patients with Parkinson disease. *J Neurosurg* **103**: 252–255.
- Lyons KE, Wilkinson SB, Tröster AI, Pahwa R (2002). Long-term efficacy of globus pallidus stimulation for the treatment of Parkinson's disease. *Stereotact Funct Neurosurg* **79**: 214–220.
- Madrazo I, León V, Torres C, Aguilera MC, Varela G, Alvarez F et al (1988). Transplantation of fetal substantia nigra and adrenal medulla to the caudate nucleus in two patients with Parkinson's disease. *N Engl J Med* **318**: 51–60.
- Marek K, Jennings D (2009). Can we image premotor Parkinson disease? *Neurology* **72**: S21–S26.
- Marin C, Bonastre M, Aguilar E, Jimenez A (2011). The metabotropic glutamate receptor antagonist 2-methyl-6-(phenylethynyl) pyridine decreases striatal VGlut2 expression in association with an attenuation of L-dopa-induced dyskinesias. *Synapse* **65**: 1080–1086.
- Marino MJ, Conn PJ (2006). Glutamate-based therapeutic approaches: allosteric modulators of metabotropic glutamate receptors. *Curr Opin Pharmacol* **6**: 98–102.
- Marino MJ, Williams Jr DL, O'Brien JA, Valenti O, McDonald TP, Clements MK et al (2003). Allosteric modulation of group III metabotropic glutamate receptor 4: a potential approach of Parkinson's disease treatment. *Proc Natl Acad Sci* **100**: 13668–13673.
- Marino MJ, Wittmann M, Bradley SR, Hubert GW, Smith Y, Conn PJ (2001). Activation of group I metabotropic glutamate receptors produces a direct excitation and disinhibition of GABAergic projection neurons in the substantia nigra pars reticulata. *J Neurosci* **21**: 7001–7012.
- Marks Jr WJ, Bartus RT, Siffert J, Davis CS, Lozano A, Boulis N et al (2010). Gene delivery of AAV2-neurturin for Parkinson's disease: a double-blind, randomised, controlled trial. *Lancet Neurol* **9**: 1164–1172.
- Marks Jr WJ, Ostrem JL, Verhagen L, Starr PA, Larson PS, Bakay RA et al (2008). Safety and tolerability of intraputamin delivery of CERE-120 (adeno-associated virus serotype 2-neurturin) to patients with idiopathic Parkinson's disease: an open-label, phase I trial. *Lancet Neurol* **7**: 400–408.
- Martin AJ, Larson PS, Ostrem JL, Keith Sootsman W, Talke P, Weber OM et al (2005). Placement of deep brain stimulator electrodes using real-time high-field interventional magnetic resonance imaging. *Magn Reson Med* **54**: 1107–1114.
- Martinez-Martin P, Valdeoriola F, Tolosa E, Pilleri M, Molinuevo JL, Rumia J et al (2002). Bilateral subthalamic nucleus stimulation and quality of life in advanced Parkinson's disease. *Mov Disord* **17**: 372–377.
- Masilamoni G, Bogenpohl JW, Alagille D, Delevich K, Tamagnan G, Votaw JR et al (2011). Metabotropic glutamate receptor 5 antagonist protects dopaminergic and noradrenergic neurons from degeneration in MPTP-treated monkeys. *Brain* **134**: 2057–2073.
- May LT, Avlani VA, Langmead CJ, Herdon HJ, Wood MD, Sexton PM et al (2007). Structure-function studies of allosteric agonism at M2 muscarinic acetylcholine receptors. *Mol Pharmacol* **72**: 463–476.
- Mazzone P, Insola A, Lozano A, Galati S, Scarnati E, Peppe A et al (2007). Peripeduncular and pedunculopontine nuclei: a dispute on a clinically relevant target. *Neuroreport* **18**: 1407–1408.
- Mazzone P, Sposato S, Insola A, Dilazaro V, Scarnati E (2008). Stereotactic surgery of nucleus tegmenti pedunculopontine [corrected]. *Br J Neurosurg* **22**(Suppl 1): S33–S40.
- McCulloch CC, Kay DM, Factor SA, Samii A, Nutt JG, Higgins DS et al (2008). Exploring gene-environment interactions in Parkinson's disease. *Hum Genet* **123**: 257–265.
- McKinnon JH, Demaerschalk BM, Caviness JN, Wellik KE, Adler CH, Wingerchuk DM (2007). Sniffing out Parkinson disease: can olfactory testing differentiate parkinsonian disorders? *Neurologist* **13**: 382–385.
- Mela F, Marti M, Dekundy A, Danysz W, Morari M, Cenci MA (2007). Antagonism of metabotropic glutamate receptor type 5 attenuates L-DOPA-induced dyskinesia and its molecular and neurochemical correlates in a rat model of Parkinson's disease. *J Neurochem* **101**: 483–497.
- Mena-Segovia J, Bolam JP, Magill PJ (2004). Pedunculopontine nucleus and basal ganglia: distant relatives or part of the same family? *Trends Neurosci* **27**: 585–588.
- Mendez I, Viñuela A, Astradsson A, Mukhida K, Hallett P, Robertson H et al (2008). Dopamine neurons implanted into people survive without pathology for 14 years. *Nat Med* **14**: 507–509.
- Menon R, Stacy MA (2008). Adenosine A2A receptor antagonists. In: Factor SA, Weiner WJ (eds). *Parkinson's Disease-Diagnostic and Clinical Management*. Demos: New York. pp 557–562.
- Menza M, Dobkin RD, Marin H, Mark MH, Gara M, Buyske S et al (2009). A controlled trial of antidepressants in patients with Parkinson disease and depression. *Neurology* **72**: 886–892.
- Merello M, Nouzeilles MI, Cammarota A, Leiguarda R (1999). Effect of memantine (NMDA antagonist) on Parkinson's disease: a double-blind crossover randomized study. *Clin Neuropharmacol* **22**: 273–276.
- Merello M, Tenca E, Pérez Lloret S, Martín ME, Bruno V, Cavanagh S et al (2008). Prospective randomized 1-year follow-up comparison of bilateral subthalamicotomy versus bilateral subthalamic stimulation and the combination of both in Parkinson's disease patients: a pilot study. *Br J Neurosurg* **22**: 415–422.
- Meyers R (1940). Surgical procedure for postencephalitic tremor, with notes on the physiology of premotor fibres. *Arch Neurol Psychiatry* **44**: 455–459.
- Miyasaki JM, Martin W, Suchowersky O, Weiner WJ, Lang AE (2002). Practice parameter: initiation of treatment for Parkinson's disease: an evidence-based review: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* **58**: 11–17.
- Mizuno Y, Hasegawa K, Kondo T, Kuno S, Yamamoto M (2010). Clinical efficacy of istradefylline (KW-6002) in Parkinson's disease: a randomized, controlled study. *Mov Disord* **25**: 1437–1443.
- Montastruc JL, Rascol O, Senard JM, Rascol A (1992). A pilot study of N-methyl-D-aspartate (NMDA) antagonist in Parkinson's disease. *J Neurol Neurosurg Psychiatry* **55**: 630–631.
- Montel SR, Bungener C (2009). Coping and quality of life of patients with Parkinson disease who have undergone deep brain stimulation of the subthalamic nucleus. *Surg Neurol* **72**: 105–110; discussion 110–111.

- Morelli M, Carta AR, Jenner P (2009). Adenosine A2A receptors and Parkinson's disease. *Handb Exp Pharmacol* 589–615. **A review of the anatomical, neurochemical and functional evidence supporting the use of adenosine A2A receptor antagonists as antiparkinsonian therapy.**
- Morelli M, Carta AR, Kachroo A, Schwarzschild MA (2010). Pathophysiological roles for purines: adenosine, caffeine and urate. *Prog Brain Res* 183: 183–208.
- Morelli M, Di Paolo T, Wardas J, Calon F, Xiao D, Schwarzschild MA (2007). Role of adenosine A2A receptors in parkinsonian motor impairment and L-DOPA-induced motor complications. *Prog Neurobiol* 83: 293–309.
- Morley JF, Duda JE (2010). Olfaction as a biomarker in Parkinson's disease. *Biomark Med* 4: 661–670.
- Moro E, Lozano AM, Pollak P, Agid Y, Rehncrona S, Volkmann J et al (2010). Long-term results of a multicenter study on subthalamic and pallidal stimulation in Parkinson's disease. *Mov Disord* 25: 578–586.
- Morrison CE, Borod JC, Perrine K, Beric A, Brin MF, Rezai A et al (2004). Neuropsychological functioning following bilateral subthalamic nucleus stimulation in Parkinson's disease. *Archives of Clinical Neuropsychology* 19: 165–181.
- Muller A, Mungersdorf M, Reichmann H, Strehle G, Hummel T (2002a). Olfactory function in Parkinsonian syndromes. *J Clin Neurosci* 9: 521–524.
- Muller A, Reichmann H, Livermore A, Hummel T (2002b). Olfactory function in idiopathic Parkinson's disease (IPD): results from cross-sectional studies in IPD patients and long-term follow-up of de-novo IPD patients. *J Neural Transm* 109: 805–811.
- Muller CM, de Vos RA, Maurage CA, Thal DR, Tolnay M, Braak H (2005). Staging of sporadic Parkinson disease-related alpha-synuclein pathology: inter- and intrarater reliability. *J Neuropathol Exp Neurol* 64: 623–628.
- Nagatsu I, Kondo Y, Inagaki S, Kojima H, Nagatsu T (1979). Immunofluorescent and biochemical studies on tyrosine hydroxylase and dopamine-beta-hydroxylase of the bullfrog sciatic nerves. *Histochemistry* 61: 103–109.
- Nakanishi S, Nakajima Y, Masu M, Ueda Y, Nakahara K, Watanabe D et al (1998). Glutamate receptors: brain function and signal transduction. *Brain Res Rev* 26: 230–235.
- Nandi D, Aziz TZ, Giladi N, Winter J, Stein JF (2002a). Reversal of akinesia in experimental parkinsonism by GABA antagonist microinjections in the pedunculopontine nucleus. *Brain* 125: 2418–2430.
- Nandi D, Liu X, Winter JL, Aziz TZ, Stein JF (2002b). Deep brain stimulation of the pedunculopontine region in the normal non-human primate. *J Clin Neurosci* 9: 170–174.
- Nash JE, Hill MP, Brotchie JM (1999). Antiparkinsonian actions of blockade of NR2B-containing NMDA receptors in the reserpine-treated rat. *Exp Neurol* 155: 42–48.
- Nash JE, Fox SH, Henry B, Hill MP, Peggs D, McGuire S et al (2000). Antiparkinsonian actions of indenprodil in the MPTP-lesioned marmoset model of Parkinson's disease. *Exp Neurol* 165: 136–142.
- Nicoletti F, Bockaert J, Collingridge GL, Conn PJ, Ferraguti F, Schoepp DD et al (2011). Metabotropic glutamate receptors: From the workbench to the bedside. *Neuropharmacology* 60: 1017–1041. **A review of the preclinical studies that led to the development of mGluR-related drug therapies for brain diseases.**
- Nilsson D, Nyholm D, Aquilonius SM (2001). Duodenal levodopa infusion in Parkinson's disease—long-term experience. *Acta Neurol Scand* 104: 343–348.
- Nisipeanu PF, Korczyn AD (2008). Dopamine agonists. In: Factor SA, Weiner WJ (eds). *Parkinson's Disease-Diagnostic and Clinical Management*. Demos: New York. pp 515–532.
- Niswender CM, Conn PJ (2010). Metabotropic glutamate receptors: physiology, pharmacology, and disease. *Annu Rev Pharmacol Toxicol* 50: 295–322. **A comprehensive review of the physiology, pharmacology and therapeutic relevance of metabotropic glutamate receptors as drug targets for brain disorders.**
- Niswender CM, Johnson KA, Weaver CD, Jones CK, Xiang Z, Luo Q et al (2008). Discovery, characterization, and antiparkinsonian effect of novel positive allosteric modulators of metabotropic glutamate receptor 4. *Mol Pharmacol* 74: 1345–1358.
- Nutt JG (2000). Clinical pharmacology of levodopa-induced dyskinesia. *Ann Neurol* 47: S160–S164; discussion S164–S166.
- Nutt JG, Burchiel KJ, Comella CL, Jankovic J, Lang AE, Laws Jr ER et al (2003). Randomized, double-blind trial of glial cell line-derived neurotrophic factor (GDNF) in PD. *Neurology* 60: 69–73.
- Nutt JG, Obeso JA, Stocchi F (2000). Continuous dopamine-receptor stimulation in advanced Parkinson's disease. *Trends Neurosci* 23: S109–S115.
- Nyholm D, Aquilonius SM (2004). Levodopa infusion therapy in Parkinson disease: state of the art in 2004. *Clin Neuropharmacol* 27: 245–256.
- Obeso JA, Guridi J, DeLong M (1997). Surgery for Parkinson's disease. *J Neurol Neurosurg Psychiatry* 62: 2–8.
- Obeso JA, Olanow CW, Nutt JG (2000). Levodopa motor complications in Parkinson's disease. *Trends Neurosci* 23: S2–S7. **A detailed assessment of the main motor side effects of chronic L-DOPA therapy in PD.**
- Obeso JA, Schapira AH (2009). Compensatory mechanisms in Parkinson's disease. *Mov Disord* 24: 153–154.
- Odin P, Wolters E, Antonini A (2008). Continuous dopaminergic stimulation achieved by duodenal levodopa infusion. *Neural Sci* 29(Suppl 5): S387–S388.
- Oh JD, Bibbiani F, Chase TN (2002). Quetiapine attenuates levodopa-induced motor complications in rodent and primate parkinsonian models. *Exp Neurol* 177: 557–564.
- Oh JD, Chase TN (2002). Glutamate-mediated striatal dysregulation and the pathogenesis of motor response complications in Parkinson's disease. *Amino Acids* 23: 133–139.
- Okun MS, Fernandez HH, Wu SS, Kirsch-Darrow L, Bowers D, Bova F et al (2009). Cognition and mood in Parkinson's disease in subthalamic nucleus vs globus pallidus interna deep brain stimulation: the COMPARE trial. *Ann Neurol* 65: 586–595.
- Okun MS, Green J, Saben R, Gross R, Foote KD, Vitek JL (2003). Mood changes with deep brain stimulation of STN and GPI: results of a pilot study. *J Neurol Neurosurg Psychiatry* 74: 1584–1586.
- Olanow CW (1990). Oxidation reactions in Parkinson's disease. *Neurology* 40(Suppl 3): S32–S37.
- Olanow CW (2008). Levodopa/dopamine replacement strategies in Parkinson's disease—future directions. *Mov Disord* 23(Suppl 3): S613–S622.
- Olanow CW (2009). Can we achieve neuroprotection with currently available anti-parkinsonian interventions? *Neurology* 72: S59–S64.
- Olanow CW, Goetz CG, Kordower JH, Stoessl AJ, Sossi V, Brin MF et al (2003). A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. *Ann Neurol* 54: 403–414. **Results of a randomized double blind placebo-controlled trial showing the lack of efficacy of dopaminergic neurons striatal transplantation in PD.**
- Olanow CW, Agid Y, Mizuno Y, Albanese A, Bonuccelli U, Damier P et al (2004). Levodopa in the treatment of Parkinson's disease: current controversies. *Mov Disord* 19: 997–1005.
- Olanow CW, Obeso JA, Stocchi F (2006a). Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. *Lancet Neurol* 5: 677–687.
- Olanow CW, Obeso JA, Stocchi F (2006b). Drug insight: Continuous dopaminergic stimulation in the treatment of Parkinson's disease. *Nat Clin Pract Neurol* 2: 382–392.
- Ondo W, Jankovic J, Schwartz K, Almaguer M, Simpson RK (1998). Unilateral thalamic deep brain stimulation for refractory essential tremor and Parkinson's disease tremor. *Neurology* 51: 1063–1069.
- Ondo WG, Sethi KD, Kricorian G (2007). Selegiline orally disintegrating tablets in patients with Parkinson disease and “wearing off” symptoms. *Clin Neuropharmacol* 30: 295–300.
- Ondo WG, Shinawi L, Davidson A, Lai D (2011). Memantine for non-motor features of Parkinson's disease: a double-blind placebo controlled exploratory pilot trial. *Parkinsonism Relat Disord* 17: 156–159.
- Ondo WG, Tintner R, Young KD, Lai D, Ringholz G (2005). Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease. *Mov Disord* 20: 958–963.
- Ossowska K, Konieczny J, Wardas J, Golembiowska K, Wolfarth S, Pilc A (2002). The role of striatal metabotropic glutamate receptors in Parkinson's disease. *Amino Acids* 23: 193–198.
- Ossowska K, Konieczny J, Wolfarth S, Pilc A (2005). MTEP, a new selective antagonist of the metabotropic glutamate receptor subtype 5 (mGluR5), produces antiparkinsonian-like effects in rats. *Neuropharmacology* 49: 447–455.
- Quattara B, Gasparini F, Morissette M, Gregoire L, Samadi P, Gomez-Mancilla B et al (2010). Effect of L-Dopa on metabotropic glutamate receptor 5 in the brain of parkinsonian monkeys. *J Neurochem* 113: 715–724.
- Quattara B, Gregoire L, Morissette M, Gasparini F, Vranesic I, Bilbe G et al (2011). Metabotropic glutamate receptor type 5 in levodopa-induced motor complications. *Neurobiol Aging* 32: 1286–1295.
- Ouchi Y, Yoshikawa E, Sekine Y, Futatsubashi M, Kanno T, Ogasu T et al (2005). Microglial activation and dopamine terminal loss in early Parkinson's disease. *Ann Neurol* 57: 168–175.
- Ozelius LJ, Senthil G, Saunders-Pullman R, Ohmann E, Deligtisch A, Tagliati M et al (2006). LRRK2 G2019S as a cause of Parkinson's disease in Ashkenazi Jews. *N Engl J Med* 354: 424–425.
- Pagni CA, Albanese A, Bentivoglio A, Broggi G, Canavero S, Cioni B et al (2008). Results by motor cortex stimulation in treatment of focal dystonia, Parkinson's disease and post-ictal spasticity. The experience of the Italian Study Group of the Italian Neurosurgical Society. *Acta Neurochir Suppl* 101: 13–21.

- Pankratz N, Foroud T (2007). Genetics of Parkinson disease. *Genet Med* **9**: 801–811.
- Papa SM, Chase TN (1996). Levodopa-induced dyskinesias improved by a glutamate antagonist in Parkinsonian monkeys. *Ann Neurol* **39**: 574–578.
- Paquet M, Smith Y (2003). Group I metabotropic glutamate receptors in the monkey striatum: subsynaptic association with glutamatergic and dopaminergic afferents. *J Neurosci* **23**: 7659–7669.
- Parkin S, Nandi D, Giladi N, Joint C, Gregory R, Bain P et al (2001). Lesioning the subthalamic nucleus in the treatment of Parkinson's disease. *Stereotact Funct Neurosurg* **77**: 68–72.
- Parkinson J (1817). *An essay on the Shaking Palsy*. Whittingham and Rowland: London.
- Parkinson Study Group (1999). Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. *N Engl J Med* **340**: 757–763.
- Parkinson Study Group (2000). Pramipexole vs levodopa as initial treatment of Parkinson's disease: A randomized controlled trial. *JAMA* **284**: 1931–1938.
- Parkinson Study Group (2002). A controlled trial of rasagiline in early Parkinson disease: the TEMPO study. *Arch Neurol* **59**: 1937–1943.
- Parkinson Study Group (2005). A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. *Arch Neurol* **62**: 241–248.
- Patel NK, Heywood P, O'Sullivan K, McCarter R, Love S, Gill SS (2003). Unilateral subthalamotomy in the treatment of Parkinson's disease. *Brain* **126**: 1136–1145.
- Penn RD, Dalvi A, Slevin J, Young B, Gash D, Gerhardt G et al (2006). GDNF in treatment of Parkinson's disease: response to editorial. *Lancet Neurol* **5**: 202–203.
- Peppe A, Gasbarra A, Stefani A, Chiavalon C, Pierantozzi M, Ferri E et al (2008). Deep brain stimulation of CM/Pf of thalamus could be the new elective target for tremor in advanced Parkinson's disease. *Parkinsonism Relat Disord* **14**: 501–504.
- Peppe A, Pierantozzi M, Chiavalon C, Marchetti F, Caltagirone C, Musicco M et al (2010). Deep brain stimulation of the pedunculo-pontine tegmentum and subthalamic nucleus: effects on gait in Parkinson's disease. *Gait Posture* **32**: 512–518.
- Pereira EA, Muthusamy KA, De Pennington N, Joint CA, Aziz TZ (2008). Deep brain stimulation of the pedunculo-pontine nucleus in Parkinson's disease. Preliminary experience at Oxford. *Br J Neurosurg* **22**(Suppl 1): S41–S44.
- Piccini P, Whone A (2004). Functional brain imaging in the differential diagnosis of Parkinson's disease. *Lancet Neurol* **3**: 284–290.
- Pierantozzi M, Palmieri MG, Galati S, Stanzione P, Peppe A, Tropepi D et al (2008). Pedunculo-pontine nucleus deep brain stimulation changes spinal cord excitability in Parkinson's disease patients. *J Neural Transm* **115**: 731–735.
- Pin JP, Duvoisin R (1995). The metabotropic glutamate receptors: Structure and functions. *Neuropharmacology* **34**: 1–26.
- Plaha P, Ben-Shlomo Y, Patel NK, Gill SS (2006). Stimulation of the caudal zona incerta is superior to stimulation of the subthalamic nucleus in improving contralateral parkinsonism. *Brain* **129**: 1732–1747.
- Plaha P, Gill SS (2005). Bilateral deep brain stimulation of the pedunculo-pontine nucleus for Parkinson's disease. *Neuroreport* **16**: 1883–1887.
- Poewe W (2010). Parkinson disease: treatment of the nonmotor symptoms of Parkinson's disease. *Nat Rev Neurol* **6**: 417–418. **Comprehensive overview of the current status of treatment for nonmotor symptoms of PD.**
- Poewe W, Wolters E, Emre M, Onofri M, Hsu C, Tekin S et al (2006). Long-term benefits of rivastigmine in dementia associated with Parkinson's disease: an active treatment extension study. *Mov Disord* **21**: 456–461.
- Poisik OV, Mannaioni G, Traynelis S, Smith Y, Conn PJ (2003). Distinct functional roles of the metabotropic glutamate receptors 1 and 5 in the rat globus pallidus. *J Neurosci* **23**: 122–130.
- Poisik OV, Smith Y, Conn PJ (2007). D1- and D2-like dopamine receptors regulate signaling properties of group I metabotropic glutamate receptors in the globus pallidus. *Eur J Neurosci* **26**: 852–862.
- Politis M, Wu K, Loane C, Quinn NP, Brooks DJ, Rehnacrona S et al (2010). Serotonergic neurons mediate dyskinesia side effects in Parkinson's patients with neural transplants. *Sci Transl Med* **2**: 38ra46.
- Pollak P, Tison F, Rascol O, Destee A, Pere JJ, Senard JM et al (2004). Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up. *J Neurol Neurosurg Psychiatry* **75**: 689–695.
- Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A et al (1997). Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science* **276**: 2045–2047.
- Ponsen MM, Stoffers D, Booij J, van Eck-Smit BL, Wolters E, Berendse HW (2004). Idiopathic hyposmia as a preclinical sign of Parkinson's disease. *Ann Neurol* **56**: 173–181.
- Portman AT, van Laar T, Staal MJ, Rutgers AW, Journee HL, Leenders KL (2006). Chronic stimulation of the subthalamic nucleus increases daily on-time without dyskinesia in advanced Parkinson's disease. *Parkinsonism Relat Disord* **12**: 143–148.
- Powers KM, Kay DM, Factor SA, Zabetian CP, Higgins DS, Samii A et al (2008). Combined effects of smoking, coffee, and NSAIDs on Parkinson's disease risk. *Mov Disord* **23**: 88–95.
- Pruszek J, Isacson O (2009). Molecular and cellular determinants for generating ES-cell derived dopamine neurons for cell therapy. *Adv Exp Med Biol* **651**: 112–123.
- Raab W, Gigue W (1951). Concentration and distribution of "encephalin" in the brain of humans and animals. *Proc Soc Exp Biol Med* **180**: 1200.
- Rabey JM, Prokhorov T, Miniowitz A, Dobronevsky E, Klein C (2007). Effect of quetiapine in psychotic Parkinson's disease patients: a double-blind labeled study of 3 months' duration. *Mov Disord* **22**: 313–318.
- Rajput A, Zesiewicz TA, Hauser RA (2008). Monoamine oxidase inhibitors. In: Factor SA, Weiner WJ (eds). *Parkinson's Disease-Diagnostic and Clinical Management*. Demos: New York. pp. 499–513.
- Rangasamy SB, Soderstrom K, Bakay RA, Kordower JH (2010). Neurotrophic factor therapy for Parkinson's disease. *Prog Brain Res* **184**: 237–264.
- Rascol O (2009). 'Disease-modification' trials in Parkinson disease: target populations, endpoints and study design. *Neurology* **72**: S51–S58.
- Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE (2000). A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. *N Engl J Med* **342**: 1484–1491.
- Rascol O, Brooks DJ, Melamed E, Oertel W, Poewe W, Stocchi F et al (2005). Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. *Lancet* **365**: 947–954.
- Rauch F, Schwabe K, Krauss JK (2010). Effect of deep brain stimulation in the pedunculo-pontine nucleus on motor function in the rat 6-hydroxydopamine Parkinson model. *Behav Brain Res* **210**: 46–53.
- Ravina B, Putt M, Siderowf A, Farrar JT, Gillespie M, Crawley A et al (2005). Donepezil for dementia in Parkinson's disease: a randomised, double blind, placebo controlled, crossover study. *J Neurol Neurosurg Psychiatry* **76**: 934–939.
- Richard IH, McDermott M, McDonald WM (2010). A multicenter randomized, double-blind, placebo controlled trial of Paroxetine and Venlafaxine extended release for depression in Parkinson's disease. *2nd World Parkinson Congress Proceedings*, P19.18.
- Rinne JO (1987). Early combination of bromocriptine and levodopa in the treatment of Parkinson's disease: a 5-year follow-up. *Neurology* **37**: 826–828.
- Rinne JO, Portin R, Ruottinen H, Nurmi E, Bergman J, Haaparanta M et al (2000). Cognitive impairment and the brain dopaminergic system in Parkinson disease: [18F]fluorodopa positron emission tomographic study. *Arch Neurol* **57**: 470–475.
- Rodriguez JP, Walters SE, Watson P, Stell R, Mastaglia FL (2007a). Globus pallidus stimulation improves both motor and nonmotor aspects of quality of life in advanced Parkinson's disease. *Mov Disord* **22**: 1866–1870.
- Rodriguez JP, Walters SE, Watson P, Stell R, Mastaglia FL (2007b). Globus pallidus stimulation in advanced Parkinson's disease. *J Clin Neurosci* **14**: 208–215.
- Rodriguez AL, Grier MD, Jones CK, Herman EJ, Kane AS, Smith RL et al (2010). Discovery of novel allosteric modulators of metabotropic glutamate receptor subtype 5 reveals chemical and functional diversity and *in vivo* activity in rat behavioral models of anxiolytic and antipsychotic activity. *Mol Pharmacol* **78**: 1105–1123.
- Rodriguez-Oroz MC, Obeso JA, Lang AE, Houeto JL, Pollak P, Rehnacrona S et al (2005). Bilateral deep brain stimulation in Parkinson's disease. A multicenter study with 4 years follow-up. *Brain* **128**: 2240–2249.
- Rodriguez-Oroz MC, Zamarbide I, Guridi J, Palmero MR, Obeso JA (2004). Efficacy of deep brain stimulation of the subthalamic nucleus in Parkinson's disease 4 years after surgery: double blind and open label evaluation. *J Neurol Neurosurg Psychiatry* **75**: 1382–1385.
- Romito LM, Raja M, Daniele A, Contarino MF, Bentivoglio AR, Barbier A et al (2002). Transient mania with hypersexuality after surgery for high frequency stimulation of the subthalamic nucleus in Parkinson's disease. *Mov Disord* **17**: 1371–1374.
- Ross GW, Abbott RD, Petrovitch H, White LR, Tanner CM (2000). Relationship between caffeine intake and parkinson disease. *JAMA* **284**: 1378–1379.
- Ross GW, Petrovitch H, Abbott RD, Tanner CM, Popper J, Masaki K et al (2008). Association of olfactory dysfunction with risk for future Parkinson's disease. *Ann Neurol* **63**: 167–173.
- Rylander D, Recchia A, Mela F, Dekundy A, Danysz W, Cenci MA (2009). Pharmacological modulation of glutamate transmission in a rat model of L-DOPA-induced dyskinesia: effects on motor behavior and striatal nuclear signaling. *J Pharmacol Exp Ther* **330**: 227–235.

- Saint-Cyr JA, Trepanier LL, Kumar R, Lozano AM, Lang AE (2000). Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease. *Brain* **123**: 2091–2108.
- Samadi P, Gregoire L, Morissette M, Calon F, Hadj Tahar A, Dridi M et al (2008). mGluR5 metabotropic glutamate receptors and dyskinesias in MPTP monkeys. *Neurobiol Aging* **29**: 1040–1051.
- Sanders WR (1865). Case of an unusual form of nervous disease, dystaxia or pseudo-paralysis agitans, with remarks. *Edinburgh Med J* **10**: 987–997.
- Sanchez-Pernaute R, Lee H, Patterson M, Reske-Nielsen C, Yoshizaki T, Sonntag KC et al (2008). Pathogenetic dopamine neurons from primate embryonic stem cells restore function in experimental Parkinson's disease. *Brain* **131**: 2127–2139.
- Saunders-Pullman R, Lipton RB, Senthil G, Katz M, Costan-Toth C, Derby C et al (2006). Increased frequency of the LRRK2 G2019S mutation in an elderly Ashkenazi Jewish population is not associated with dementia. *Neurosci Lett* **402**: 92–96.
- Schapira AH (2004). Disease modification in Parkinson's disease. *Lancet Neurol* **3**: 362–368. **Discussion of the current status of neuroprotective therapies in PD.**
- Schapira AH (2009a). Etiology and pathogenesis of Parkinson disease. *Neurol Clin* **27**: 583–603, v.
- Schapira AH (2009b). Molecular and clinical pathways to neuroprotection of dopaminergic drugs in Parkinson disease. *Neurology* **72**: S44–S50.
- Schapira AH (2009c). Neurobiology and treatment of Parkinson's disease. *Trends Pharmacol Sci* **30**: 41–47.
- Schapira AH, Agid Y, Barone P, Jenner P, Lemke MR, Poewe W et al (2009). Perspectives on recent advances in the understanding and treatment of Parkinson's disease. *Eur J Neurol* **16**: 1090–1099.
- Schapira AH, Olanow CW (2004). Neuroprotection in Parkinson disease: mysteries, myths, and misconceptions. *JAMA* **291**: 358–364.
- Schoepp DD, Conn PJ (1993). Metabotropic glutamate receptors in brain function and pathology. *Trends Pharmacol Sci* **14**: 13–20.
- Schroeder U, Kuehler A, Hennenlotter A, Haslinger B, Tronnier VM, Krause M et al (2004). Facial expression recognition and subthalamic nucleus stimulation. *J Neurol Neurosurg Psychiatry* **75**: 648–650.
- Schubach WM, Chastan N, Welter ML, Houeto JL, Mesnage V, Bonnet AM et al (2005). Stimulation of the subthalamic nucleus in Parkinson's disease: a 5 year follow up. *J Neurol Neurosurg Psychiatry* **76**: 1640–1644.
- Schwab RS, England AC, Poskanzer DC, Young RR (1969). Amantadine in the treatment of Parkinson's disease. *JAMA* **208**: 1168–1170.
- Schwarzschild MA, Agnati L, Fuxe K, Chen JF, Morelli M (2006). Targeting adenosine A2A receptors in Parkinson's disease. *Trends Neurosci* **29**: 647–654.
- Sethi KD (2010). The impact of levodopa on quality of life in patients with Parkinson disease. *Neurologist* **16**: 76–83.
- Shah U, Hodgson R (2010). Recent progress in the discovery of adenosine A2A receptor antagonists for the treatment of Parkinson's disease. *Curr Opin Drug Discov Devel* **13**: 466–480.
- Shahlaie K, Larson PS, Starr PA (2011). Intraoperative computed tomography for deep brain stimulation surgery: technique and accuracy assessment. *Neurosurgery* **68**: 114–124; discussion 124.
- Shekhar A, Potter WZ, Lightfoot J, Lienemann J, Dube S, Mallinckrodt C et al (2008). Selective muscarinic receptor agonist xanomeline as a novel treatment approach for schizophrenia. *Am J Psychiatry* **165**: 1033–1039.
- Shimamoto SA, Larson PS, Ostrem JL, Glass GA, Turner RS, Starr PA (2010). Physiological identification of the human pedunculopontine nucleus. *J Neurol Neurosurg Psychiatry* **81**: 80–86.
- Siderowf A, Stern MB (2006). Preclinical diagnosis of Parkinson's disease: are we there yet? *Curr Neurol Neurosci Rep* **6**: 295–301.
- Siderowf A, Stern MB (2008). Premotor Parkinson's disease: clinical features, detection, and prospects for treatment. *Ann Neurol* **64**(Suppl 2): S139–S147.
- Simola N, Morelli M, Pinna A (2008). Adenosine A2A receptor antagonists and Parkinson's disease: state of the art and future directions. *Curr Pharm Des* **14**: 1475–1489.
- Simuni T, Jaggi JL, Mulholland H, Hurtig HI, Colcher A, Siderowf AD et al (2002). Bilateral stimulation of the subthalamic nucleus in patients with Parkinson disease: a study of efficacy and safety. *J Neurosurg* **96**: 666–672.
- Simuni T, Hurtig H (2008). Levodopa: a pharmacologic miracle four decades later. In: Factor SA, Weiner WJ (eds). *Parkinson's Disease-Diagnosis and Clinical Management*. Demos: New York, pp 471–490.
- Smeding HM, Esselink RA, Schmand B, Koning-Haaststra M, Nijhuis I, Wijndal EM et al (2005). Unilateral pallidotomy vs bilateral subthalamic nucleus stimulation in PD—a comparison of neuropsychological effects. *J Neurol* **252**: 176–182.
- Smeding HM, Speelman JD, Huizenga HM, Schuurman PR, Schmand B (2011). Predictors of cognitive and psychosocial outcome after STN DBS in Parkinson Disease. *J Neurol Neurosurg Psychiatry* **82**: 754–760.
- Smeding HM, Speelman JD, Koning-Haaststra M, Schuurman PR, Nijssen P, van Laar T et al (2006). Neuropsychological effects of bilateral STN stimulation in Parkinson disease: a controlled study. *Neurology* **66**: 1830–1836.
- Smith Y, Charara A, Hanson JE, Paquet M, Levey AI (2000). GABA(B) and group I metabotropic glutamate receptors in the striatopallidal complex in primates. *J Anat* **196**(Part 4): 555–576.
- Smith Y, Charara A, Paquet M, Kievel JZ, Pare JF, Hanson JE et al (2001). Ionotropic and metabotropic GABA and glutamate receptors in primate basal ganglia. *J Chem Neuroanat* **22**: 13–42.
- Soh SE, Morris ME, McGinley JL (2011). Determinants of health-related quality of life in Parkinson's disease: a systematic review. *Parkinsonism Relat Disord* **17**: 1–9.
- Sommer U, Hummel T, Cormann K, Mueller A, Frasnelli J, Kropp J et al (2004). Detection of presymptomatic Parkinson's disease: combining smell tests, transcranial sonography, and SPECT. *Mov Disord* **19**: 1196–1202.
- Spooren W, Lesage A, Lavreysen H, Gasparini F, Steckler T (2010). Metabotropic glutamate receptors: their therapeutic potential in anxiety. *Curr Top Behav Neurosci* **2**: 391–413.
- Stacy M, Silver D, Mendis T, Sutton J, Mori A, Chaikin P et al (2008). A 12-week, placebo-controlled study (6002-US-006) of istradefylline in Parkinson disease. *Neurology* **70**: 2233–2240.
- Starr MS (1995). Glutamate/dopamine D1/D2 balance in the basal ganglia and its relevance to Parkinson's disease. *Synapse* **19**: 264–293.
- Stefani A, Lozano AM, Peppe A, Stanzione P, Galati S, Tropepi D et al (2007). Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. *Brain* **130**: 1596–1607.
- Stefani A, Peppe A, Pierantozzi M, Galati S, Moschella V, Stanzione P et al (2009). Multi-target strategy for Parkinsonian patients: the role of deep brain stimulation in the centromedian-parafascicular complex. *Brain Res Bull* **78**: 113–118.
- Stefani A, Pierantozzi M, Ceravolo R, Brusa L, Galati S, Stanzione P (2010). Deep brain stimulation of pedunculopontine tegmental nucleus (PPTg) promotes cognitive and metabolic changes: a target-specific effect or response to a low-frequency pattern of stimulation? *Clin EEG Neurosci* **41**: 82–86.
- Stefurak T, Mikulis D, Mayberg H, Lang AE, Hevenor S, Pahapill P et al (2003). Deep brain stimulation for Parkinson's disease dissociates mood and motor circuits: a functional MRI case study. *Mov Disord* **18**: 1508–1516.
- Stern MB (2004). The preclinical detection of Parkinson's disease: ready for prime time? *Ann Neurol* **56**: 169–171.
- Stern MB, Doty RL, Dotti M, Corcoran P, Crawford D, McKeown DA et al (1994). Olfactory function in Parkinson's disease subtypes. *Neurology* **44**: 266–268.
- Stiasny-Kolster K, Doerr Y, Möller JC, Höffken H, Behr TM, Oertel WH et al (2005). Combination of idiopathic REM sleep behavior disorder and olfactory dysfunction as possible indicator for alpha-synucleinopathy demonstrated by dopamine transporter FP-CIT-SPECT. *Brain* **128**: 126–137.
- Stocchi F, Rascol O, Kiebert K, Poewe W, Jankovic J, Tolosa E et al (2010). Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: the STRIDE-PD study. *Ann Neurol* **68**: 18–27.
- Strafella AP, Lozano AM, Lang AE, Ko JH, Poon YY, Moro E (2007). Subdural motor cortex stimulation in Parkinson's disease does not modify movement-related rCBF pattern. *Mov Disord* **22**: 2113–2116.
- Su PC, Tseng HM, Liu HM, Yen RF, Liou HH (2002). Subthalamotomy for advanced Parkinson disease. *J Neurosurg* **97**: 598–606.
- Swanson CJ, Bures M, Johnson MP, Linden AM, Monn JA, Schoepp DD (2005). Metabotropic glutamate receptors as novel targets for anxiety and stress disorders. *Nat Rev Drug Discov* **4**: 131–144.
- Taba HA, Wu SS, Foote KD, Hass CJ, Fernandez HH, Malaty IA et al (2010). A closer look at unilateral versus bilateral deep brain stimulation: results of the National Institutes of Health COMPARE cohort. *J Neurosurg* **113**: 1224–1229.
- Tanganelli S, Sandager Nielsen K, Ferraro L, Antonelli T, Kehr J, Franco R et al (2004). Striatal plasticity at the network level. Focus on adenosine A2A and D2 interactions in models of Parkinson's Disease. *Parkinsonism Relat Disord* **10**: 273–280.
- Temel Y, Kessels A, Tan S, Topdag A, Boon P, Visser-Vandewalle V (2006). Behavioural changes after bilateral subthalamic stimulation in advanced Parkinson disease: a systematic review. *Parkinsonism Relat Disord* **12**: 265–272.
- Temel Y, Visser-Vandewalle V (2006). Targets for deep brain stimulation in Parkinson's disease. *Expert Opin Ther Targets* **10**: 355–362.
- Thomas A, Bonanni L, Gambi F, Di Iorio A, Onofri M (2010). Pathological gambling in Parkinson disease is reduced by amantadine. *Ann Neurol* **68**: 400–404.
- Tintner R, Manian P, Gauthier P, Jankovic J (2005). Pleuropulmonary fibrosis after long-term treatment with the dopamine agonist pergolide for Parkinson Disease. *Arch Neurol* **62**: 1290–1295.
- Tir M, Devos D, Blond S, Touzet G, Reyns N, Duhamel A et al (2007). Exhaustive, one-year follow-up of subthalamic nucleus deep brain stimulation in a large, single-center cohort of Parkinsonian patients. *Neurosurgery* **61**: 297–304.

- Tissingh G, Berendse HW, Bergmans P, DeWaard R, Drukarch B, Stoof JC *et al* (2001). Loss of olfaction in *de novo* and treated Parkinson's disease: possible implications for early diagnosis. *Mov Disord* **16**: 41–46.
- Tohgi H, Abe T, Takahashi S (1993). The effects of L-threo-3,4-dihydroxyphenylserine on the total norepinephrine and dopamine concentrations in the cerebrospinal fluid and freezing gait in parkinsonian patients. *J Neural Transm Park Dis Dement Sect* **5**: 27–34.
- Tolosa E (2007). Movement disorders: advances on many fronts. *Lancet Neurol* **6**: 7–8.
- Tolosa E, Compta Y, Gaig C (2007). The premotor phase of Parkinson's disease. *Parkinsonism Relat Disord* **13**(Suppl): S2–S7.
- Tomac A, Lindqvist E, Lin LF, Ogren SO, Young D, Hoffer BJ *et al* (1995a). Protection and repair of the nigrostriatal dopaminergic system by GDNF *in vivo*. *Nature* **373**: 335–339.
- Tomac A, Widenfalk J, Lin LF, Kohno T, Ebendal T, Hoffer BJ *et al* (1995b). Retrograde axonal transport of glial cell line-derived neurotrophic factor in the adult nigrostriatal system suggests a trophic role in the adult. *Proc Natl Acad Sci USA* **92**: 8274–8278.
- Tozzi A, de Iure A, Di Filippo M, Tantucci M, Costa C, Borsini F *et al* (2011). The distinct role of medium spiny neurons and cholinergic interneurons in the DA receptor interaction in the striatum: implications for Parkinson's disease. *J Neurosci* **31**: 1850–1862.
- Troster AI, Fields JA, Wilkinson S, Pahwa R, Koller WC, Lyons KE (2003). Effect of motor improvement on quality of life following subthalamic stimulation is mediated by changes in depressive symptomatology. *Stereotact Funct Neurosurg* **80**: 43–47.
- Valenti O, Marino MJ, Wittmann M, Lis E, DiLella AG, Kinney GG *et al* (2003). Group III metabotropic glutamate receptor-mediated modulation of the striatopallidal synapse. *J Neurosci* **23**: 7218–7226.
- Volkmann J, Allert N, Voges J, Sturm V, Schnitzler A, Freund HJ (2004). Long-term results of bilateral pallidal stimulation in Parkinson's disease. *Ann Neurol* **55**: 871–875.
- Voon V, Krack P, Lang AE, Lozano AM, Dujardin K, Schupbach M *et al* (2008). A multicentre study on suicide outcomes following subthalamic stimulation for Parkinson's disease. *Brain* **131**: 2720–2728.
- Wang J, You H, Liu JF, Ni DF, Zhang ZX, Guan J (2011). Association of olfactory bulb volume and olfactory sulcus depth with olfactory function in patients with Parkinson's disease. *AJNR Am J Neuroradiol* **32**: 677–681.
- Waters C (2008). Catechol-O-Methyltransferase inhibitors. In: Factor SA, Weiner WJ (eds). *Parkinson's disease-Diagnostic and Clinical Management*. Demos: New York. pp 533–543.
- Waters CH, Sethi KD, Hauser RA, Molho E, Bertoni JM, Zydys Selegiline Study Group (2004). Zydys selegiline reduces off time in Parkinson's disease patients with motor fluctuations: a 3-month, randomized, placebo-controlled study. *Mov Disord* **19**: 426–432.
- Watts RL (1997). The role of dopamine agonists in early Parkinson's disease. *Neurology* **49**: S34–S48.
- Weaver CD, Sheffler DJ, Lewis LM, Bridges TM, Williams R, Nalwyajko NT *et al* (2009a). Discovery and development of a potent and highly selective small molecule muscarinic acetylcholine receptor subtype I (mAChR 1 or M1) antagonist *in vitro* and *in vivo* probe. *Curr Top Med Chem* **9**: 1217–1226.
- Weaver F, Follett K, Hur K, Ippolito D, Stern M (2005). Deep brain stimulation in Parkinson disease: a metaanalysis of patient outcomes. *J Neurosurg* **103**: 956–967.
- Weaver FM, Follett K, Stern M, Hur K, Harris C, Marks Jr WJ *et al* (2009b). Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA* **301**: 63–73.
- Weinberger M, Hamani C, Hutchison WD, Moro E, Lozano AM, Dostrovsky JO (2008). Pedunculopontine nucleus microelectrode recordings in movement disorder patients. *Exp Brain Res* **188**: 165–174.
- Weintraub D, Mavandadi S, Mamikonyan E, Siderowf AD, Duda JE, Hurtig HI *et al* (2010). Atomoxetine for depression and other neuropsychiatric symptoms in Parkinson disease. *Neurology* **75**: 448–455.
- Wenning GK, Shephard B, Hawkes C, Petrukevitch A, Lees A, Quinn N (1995). Olfactory function in atypical parkinsonian syndromes. *Acta Neurol Scand* **91**: 247–250.
- Westin J, Nyholm D, Palhagen S, Willows T, Groth T, Dougherty M *et al* (2011). A pharmacokinetic-pharmacodynamic model for duodenal levodopa infusion. *Clin Neuropharmacol* **34**: 61–65.
- Wichmann T, DeLong MR (2003). Functional neuroanatomy of the basal ganglia in Parkinson's disease. *Adv Neurol* **91**: 9–18.
- Williams SS, Williams J, Combrinck M, Christie S, Smith AD, McShane R (2009). Olfactory impairment is more marked in patients with mild dementia with Lewy bodies than those with mild Alzheimer disease. *J Neurol Neurosurg Psychiatry* **80**: 667–670.
- Witt K, Pulkowski U, Herzog J, Lorenz D, Hamel W, Deuschl G *et al* (2004). Deep brain stimulation of the subthalamic nucleus improves cognitive flexibility but impairs response inhibition in Parkinson disease. *Arch Neurol* **61**: 697–700.
- Witt M, Bormann K, Gudziol V, Pehlke K, Barth K, Minovi A *et al* (2009). Biopsies of olfactory epithelium in patients with Parkinson's disease. *Mov Disord* **24**: 906–914.
- Wood LD (2010). Clinical review and treatment of select adverse effects of dopamine receptor agonists in Parkinson's disease. *Drugs Aging* **27**: 295–310.
- Wood LD, Neumiller JJ, Setter SM, Dobbins EK (2010). Clinical review of treatment options for select nonmotor symptoms of Parkinson's disease. *Am J Geriatr Pharmacother* **8**: 294–315.
- Xu L, Tan YY, Ding JQ, Chen SD (2010). The iPS technique provides hope for Parkinson's disease treatment. *Stem Cell Rev* **6**: 398–404.
- Zahodne LB, Okun MS, Foote KD, Fernandez HH, Rodriguez RL, Kirsch-Darrow L *et al* (2009a). Cognitive declines one year after unilateral deep brain stimulation surgery in Parkinson's disease: a controlled study using reliable change. *Clin Neuropsychol* **23**: 385–405.
- Zahodne LB, Okun MS, Foote KD, Fernandez HH, Rodriguez RL, Wu SS *et al* (2009b). Greater improvement in quality of life following unilateral deep brain stimulation surgery in the globus pallidus as compared to the subthalamic nucleus. *J Neurol* **256**: 1321–1329.
- Zhou Y, Rodriguez AL, Williams R, Weaver CD, Conn PJ, Lindsley CW (2009). Synthesis and SAR of novel, non-MPEP chemotype mGluR5 NAMs identified by functional HTS. *Bioorg Med Chem Lett* **19**: 6502–6506.
- Zrinzo L, Zrinzo LV (2008). Surgical anatomy of the pedunculopontine and peripeduncular nuclei. *Brit J Neurosurg* **22**(Suppl 1): S19–S24.
- Zrinzo L, Zrinzo LV, Tisch S, Limousin PD, Yousry TA, Afshar F *et al* (2008). Stereotactic localization of the human pedunculopontine nucleus: atlas-based coordinates and validation of a magnetic resonance imaging protocol for direct localization. *Brain* **131**: 1588–1598.