Milestones in Parkinson’s Disease Therapeutics
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ABSTRACT: In the mid-1980s, the treatment of Parkinson’s disease was quite exclusively centered on dopatherapy and was focusing on dopamine systems and motor symptoms. A few dopamine agonists and a monoamine oxidase B inhibitor (selegiline) were used as adjuncts in advanced Parkinson’s disease. In the early 2010s, levodopa remains the gold standard. New insights into the organization of the basal ganglia paved the way for deep brain stimulation, especially of the subthalamic nucleus, providing spectacular improvement of drug-refractory levodopa-induced motor complications. Novel dopamine agonists (pramipexole, ropinirole, rotigotine), catecholmethyltransferase inhibitors (entacapone), and monoamine oxidase B inhibitors (rasagiline) have also been developed to provide more continuous oral delivery of dopaminergic stimulation in order to improve motor outcomes. Using dopamine agonists early, before levodopa, proved to delay the onset of dyskinesia, although this is achieved at the price of potentially disabling daytime somnolence or impulse control disorders. The demonstration of an antidyskinetic effect of the glutamate antagonist amantadine opened the door for novel nondopaminergic approaches of Parkinson’s disease therapy. More recently, nonmotor symptoms (depression, dementia, and psychosis) have been the focus of the first randomized controlled trials in this field. Despite therapeutic advances, Parkinson’s disease continues to be a relentlessly progressive disorder leading to severe disability. Neuroprotective interventions able to modify the progression of Parkinson’s disease have stood out as a failed therapeutic goal over the last 2 decades, despite potentially encouraging results with compounds like rasagiline. Newer molecular targets, new animal models, novel clinical trial designs, and biomarkers to assess disease modification have created hope for future therapeutic interventions. © 2011 Movement Disorder Society

Key Words: Parkinson’s disease; treatment; levodopa; dopamine agonists; catecholmethyltransferase inhibitors; monoamine oxidase B inhibitors; deep brain stimulation

Since the late 1960s, the introduction of dopamine replacement via oral levodopa as a treatment to control the motor symptoms of Parkinson’s disease (PD) stands out as one of the most astounding successes of translational research in modern neuroscience. In the mid-1980s, after nearly 2 decades of routine clinical use of levodopa + dopa-decarboxylase (DDCI) inhibitors, the medical treatment of PD was quite exclusively centered on dopatherapy. The use of older drugs like antimuscarinics had dramatically declined, whereas that of the first ergolinic dopamine agonists (DAs) and monoamine oxidase B (MAO-B) inhibitors had entered the clinical arena as an adjunct to levodopa in advanced PD. In these times, clinical concepts as well as pharmacological research were still almost
exclusively focused on control of motor symptoms and the dopamine system. Major challenges were related to understanding and treating motor complications associated with chronic levodopa therapy. Pharmacologists had begun to unravel the multitude of dopamine receptors with the hope that selective targeting of dopamine receptor subtypes might lead to effective motor control with fewer side effects. The notion of “neuroprotection” was developing in laboratories but had never been tested in patients. Randomized controlled trials and evidence-based medicine had not reached modern standards, and novel assessment tools like the UPDRS and patient diaries had just emerged to assess novel antiparkinsonian medications. The fear of adverse reactions had not developed the concept of the “principle of cautiousness.” The antiparkinsonian market was small, sales were far from the current estimated $4 billion, and issues such as conflicts of interest were not of major concern.

At the present time, after another 25 years of sustained efforts in drug development, levodopa has remained the gold standard of symptomatic efficacy. At the same time, there have been advances in our understanding of the importance of levodopa pharmacokinetics (PKs) and drug delivery as critical factors for the development of motor complications. This has modified our use of levodopa and other dopaminergic medications to minimize motor complications. However, increased use of DAs has created new challenges including awareness of more recently recognized adverse drug reactions, raising interest in the underrecognized role of dopamine in wakefulness and impulse control.

The most significant breakthrough in the fight against motor complications has emerged from new insights into the organization of neuronal loops connecting the basal ganglia and frontal motor areas, paving the way for the introduction of deep brain stimulation. Recent years have also seen an increasing awareness of nonmotor symptoms as driving factors for disability in late-stage PD. Indeed, depression, dementia, and psychosis have been the focus of new randomized controlled trials (Table 1).

Despite therapeutic advances over the last 25 years, PD continues to be a relentlessly progressive disorder leading to severe motor disability, dementia, nursing home placement, and premature death for a majority of patients after 15 or more years of disease. Neuroprotective interventions able to modify the progression of PD have therefore stood out as a failed therapeutic goal over the last 2 decades. Recent insights into the molecular mechanisms leading to PD have provided novel targets for disease-modifying interventions as well as new approaches to experimental disease modeling. Further, newer clinical trial designs and surrogate markers to assess disease modification have created hope for therapeutic interventions that will prove to alter the course of PD.

### Milestones in the Medical Management of Parkinson’s Disease

**L-Dopa: Facing the Challenges of Motor Complications and Drug Delivery**

Soon after the introduction of levodopa to the routine treatment of PD in the 1970s, it became apparent that chronic treatment with this agent was associated with the development of motor complications. Fluctuations in motor performance were shown to reflect rises and falls of levodopa plasma levels following individual doses (wearing-off effect), whereas some
cases showed seemingly random and sudden switches between “on” and “off” states. At the same time, most of the patients exhibiting these motor fluctuations also developed various types of levodopa-induced involuntary movements with chorea accompanying “on” periods and painful dystonia of the distal lower limbs complicating “off” periods. More than 30 years after the original clinical descriptions of levodopa-related motor complications, their exact underlying pathophysiology still remains incompletely understood. However, a growing body of preclinical evidence together with clinical observations suggests that most levodopa-related motor complications are related to several factors: (1) the severity of dopamine denervation, as demonstrated by the rapid and severe occurrence of motor complications in monkeys and humans acutely intoxicated with MPTP; (2) the dose of levodopa, as demonstrated in the ELDOPA study that was the first clinical trial conducted to assess the efficacy and safety of different doses of the drug in a randomized, double-blind, placebo-controlled design; and (3) the discontinuous delivery of levodopa to the brain resulting in intermittent pulses of striatal dopamine receptor stimulation that in turn triggers neuroplastic changes in striatal pallidothalamocortical motor loops. Therefore, attempts have been made during the last 25 years to optimize levodopa delivery in order to provide more continuous dopamine stimulation (CDS) or at least more continuous dopamine delivery (CDD) and to “spare” the cumulative dose of levodopa with the use of other dopaminergic medications.

Two landmark proof-of-concept studies published in the mid-1980s provided the first clinical evidence that continuous delivery of levodopa via intravenous infusions is associated with dramatic improvement in motor oscillations in patients with advanced PD. Similar results were soon reported using continuous duodenal levodopa infusions. Although these early proof-of-concept studies using intravenous or duodenal constant rate infusions focused on the treatment of motor fluctuations, more recent work also showed that preexisting levodopa-induced dyskinesias can be markedly downregulated when switching to intrajejunal infusion schemes. Routine use of enteral levodopa infusions, however, was initially limited by the poor solubility of the drug. Within the last decade, the development of a new carboxymethylcellulose gel formulation enabled concentrations of levodopa of 20 mg/mL and short- and long-term studies using intraduodenal infusions via external pump systems and intraduodenal permanent catheters placed via percutaneous external gastrostomy have demonstrated both marked reductions in motor response oscillations and significant amelioration of preexisting levodopa-induced dyskinesias. Nevertheless, system-related complications such as kinking and occlusions or dislocation of catheters, local inflammation around the gastrostomy site, and mechanical pump problems are common complications during long-term use and, together with high costs, still limit the broad-scale use of this approach.

During the late 1980s, “controlled-release” oral formulations of levodopa (Sinemet CR and Madopar HBS) were developed in another attempt to increase the levodopa plasma elimination half-life and improve oral drug delivery. Unfortunately, such formulations did not really improve “off” problems in patients with established fluctuations. Moreover, the early use of the CR versus standard formulations failed to reduce the incidence of motor complications in the long term. It is likely that these disappointing results were related to insufficient improvement in levodopa PKs that did not achieve adequate CDD.

A more successful PKs improvement resulted from the development in the 1990s of catecholmethyltransferase (COMT) inhibitors as adjunct therapies, leading to an increase in both the half-life and bioavailability of single levodopa doses. Clinical trials with tolcapone and entacapone in patients with wearing-off fluctuations have consistently shown reductions in “off” time between 1 and 2.5 hours, with somewhat greater effect sizes with tolcapone than with entacapone. These trials, however, have also consistently shown increases in dyskinesias, requiring a reduction in total daily levodopa intake. Conversely, animal experiments provided evidence that the combined use of levodopa with the COMT inhibitor entacapone induced lesser degrees of dyskinesias compared with standard levodopa when administered to drug-naive animals. These observations suggested that combined treatment with levodopa and a COMT inhibitor might reduce the pulsatility of dopaminergic stimulation in the striatum. The STRIDE-PD trial was then initiated to investigate whether the early combination of standard levodopa/carbidopa with entacapone versus levodopa/carbidopa could delay the time to first occurrence of dyskinesias in levodopa-naive patients. After approximately 3 years of follow-up, patients treated with the triple combination had shorter delays and greater incidences of dyskinesias compared with those on standard levodopa/carbidopa. This finding contradicts the CDD hypothesis. It remains unclear whether this was caused by a failure to achieve sufficient CDD (4 times the administrations of levodopa/carbidopa/entacapone every 3.5 hours may still lead to plasma level fluctuations) or whether factors other than CDD are to be considered.

Therefore, after more than 40 years of routine clinical use, the optimum way of delivering levodopa to the brains of patients with PD still remains an elusive goal in current therapy, and clinical research and development into novel delivery routes including new oral sustained-release formulations are ongoing.
Optimizing Striatal Dopamine Substitution: The Early Use of DAs

Dopamine agonists (DAs) have longer plasma elimination half-lives than levodopa. Their use has therefore been considered an opportunity to improve CDD. By the late 1980s, ergot-derived DAs (bromocriptine, pergolide, lisuride, and cabergoline) already had an established role as adjuncts to levodopa in advanced PD because of their ability to reduce “off” time and, in many instances, allow a lowering of the levodopa dose, reducing dyskinesias.

Since 1985, the place of DAs in the treatment of PD has changed in 2 ways. First, the continuous subcutaneous infusion of DAs like apomorphine or lisuride was reported to improve “off” problems and dyskinesia in small uncontrolled series. Such observations provided further support to the concept of CDD, and in Europe the use of subcutaneous pumps of apomorphine is indeed marketed to treat PD patients with severe levodopa-induced motor complications. Second, the use of oral DAs has moved to earlier stages of PD. DAs proved to induce less dyskinesia than levodopa in levodopa-naive MPTP-intoxicated monkeys. Following early pilot uncontrolled observations in PD patients, the first levodopa-controlled trials were published in the mid-1980s, suggesting that patients starting on an agonist had a lower risk of subsequent motor complications than those starting on levodopa. This was subsequently confirmed within the last decade by double-blind trials demonstrating that “time to dyskinesia” was delayed in patients randomized to an agonist early as compared with levodopa. This consistent finding thereby changed our standard of care from the primary use of levodopa to the primary and early use of DAs, especially in younger-onset patients. Levodopa is now commonly held in reserve to supplement DAs when adequate control of symptoms cannot be achieved with an agonist alone. Whether the long-term treatment of PD is best achieved with the initial use of a DA followed by levodopa or with lower doses of initial levodopa with the early addition of DAs remains to be seen. Most experts now agree that withholding levodopa should never be at the expense of good symptomatic control, which may itself be a strong predictor of better long-term outcomes.

By the late 1990s, ergot DAs had been largely replaced by nonergot drugs like ropinirole and pramipexole because of reports of fibrotic adverse reactions, including cardiac valvular damage from pergolide and bromocriptine. Recently, controlled-release formulations of oral ropinirole and pramipexole and transdermal formulations of rotigotine have been developed, offering the convenience of a once-daily regimen. It remains unknown whether their longer elimination half-life provides any further benefit on CDD and dyskinesia.

In 2010, after more than a decade of widespread use of DAs in early PD, long-term clinical experience has taught us that the initial innovative and attractive finding of delaying time to dyskinesia with a DA is far from being the sole relevant outcome to consider. Indeed, our knowledge has extended to several other important issues:

- The large-scale use of DAs revealed that these drugs carry a greater risk than levodopa of previously unknown or underestimated and potentially troublesome adverse drug reactions including abnormal daytime somnolence, leg edema, and impulse control disorders.
- Levodopa must almost inevitably be added to a DA to keep control of parkinsonism after a few years of treatment, although the early use of a DA reduces the cumulative dose of levodopa and explains the long-term benefit of DAs on dyskinesia.
- The long-term disability and quality of life of patients initially randomized to an agonist or levodopa do not differ, although the impact of dyskinesia on quality of life can vary greatly from patient to patient.
- Motor complications, although occurring in the majority of PD patients, may no longer be as problematic as they were 30 years ago, as lower doses of levodopa are generally used, and novel medical and surgical therapies have emerged to manage such problems (see below).
- It is now realized that in most PD patients long-term disability (15 years) is driven by problems such as falls or dementia, and these are not influenced by early treatment with agonists.
- Finally, it is also now agreed that there is no clinical evidence supporting the theoretical rationale to avoid levodopa because of its potential oxidative “toxicity” toward dopamine neurons.

In summary, after 20 years of an increasing use of DAs in PD, their place remains a matter of debate. We first learned that using them early spares levodopa and reduces dyskinesia. This approach, commonly promoted by drug companies, has sometimes induced an inappropriate “levodopa phobia,” especially among patients. We now know that DAs can cause somnolence and impulse control disorders, and a novel “phobia,” this time toward DAs, is currently emerging, especially among physicians. In this context, after years of attempting to spare levodopa with DAs, it is possible that a future popular alternative will be using MAO-B inhibitors early to spare DAs!
From Symptomatic Therapies to the Concept of “Neuroprotection”: MAO-B Inhibitors and Beyond

Twenty-five years ago, oxidative stress was considered an important contributor to neurodegeneration in PD. With the recent discovery of MPTP toxicity and its blockade by MAO-B inhibitors, a clinical trial of an MAO-B inhibitor as a neuroprotective agent seemed logical, leading to the launch of the first major trial of a putative disease-modifying agent. The Deprenyl and Tocopheral Antioxidative Therapy of Parkinsonism trial (DATATOP) was positive in showing a significant delay in the need for levodopa treatment in patients treated with deprenyl versus placebo, but also illustrated that a mild symptomatic effect in a trial so designed could confound any neuroprotective interpretation, such that the debate whether this and subsequent trials of deprenyl support a “neuroprotective” effect is still ongoing. However, DATATOP provided a strong stimulus to develop and study numerous compounds for their potential to modify the course of PD and to further refine clinical trial methodology to better assess disease progression.

In the 1990s, rasagiline was another MAO-B inhibitor, with different metabolites than selegiline, to be successfully developed for PD therapy. From a symptomatic perspective, rasagiline 1 mg/day proved to be efficacious both as monotherapy in early PD and as an adjunct to levodopa to treat “off” episodes in more advanced patients, this last effect being comparable to that of entacapone. The good tolerability of rasagiline and its ease of use (1 dose, once daily, no titration) makes this drug an appealing option to start therapy in PD, whereas the use of selegiline has been largely abandoned, despite a lack of head-to-head comparisons of the 2 compounds. The current popularity of rasagiline is also related to the finding that the drug has neuroprotective properties in vitro and was the first putative disease-modifying agent to be tested with a randomized delayed-start design in PD. The recent ADAGIO trial showed that early therapy with 1 mg/day of rasagiline induced less cumulative disability over 18 months than the same therapy initiated 9 months later. The mechanisms underlying this effect remain unclear: enhanced survival/functioning of dopaminergic neurons (“neuroprotective” effect) or improved brain compensatory plasticity. Nevertheless, this result supports the concept that patients may benefit from being treated early in the course of PD and not when disability has progressed to more substantially affecting activities of daily living. It remains unknown whether the benefit reported in ADAGIO on rasagiline 1 mg/day after 18 months persists over longer follow-up and why another tested dose (2 mg/day) did not provide the same benefit. Therefore, the importance of these results for clinical practice remains controversial.

Definitive evidence for clinically meaningful disease modification remains an unsolved methodological issue, and most published trials remain negative or inconclusive. Other trial designs have been employed to look further. For example, in the long-term simple design, patients on PD medications are treated with an investigational agent or placebo and followed for upwards of 5 years with a composite of end points, including nondopaminergic features such as freezing, falls, and dementia. Future advances will also depend on better understanding of the mechanisms governing cell death in PD and better animal models, taking advantage of the recent progress in PD genetics. It is hoped that these approaches will open up new therapeutic targets and new molecules, addressing oxidative stress, excitotoxicity, mitochondrial dysfunction, inflammation, growth factors, apoptosis, autophagy, or proteosome dysfunction.

Motor Control Beyond Dopamine Replacement: The Antidyskinetic Properties of Amantadine

Within the past 25 years, animal models of PD have strongly emphasized how nondopaminergic mechanisms contribute to brain dysfunction in PD. This is caused by the direct degeneration of nondopaminergic cholinergic, adrenergic, and serotonergic nuclei and by the indirect functional impairment of nondopaminergic relays of cortico-subcortical loops as a result of basal ganglia dopamine denervation. This background constituted the rationale for attempts to develop new nondopaminergic antiparkinsonian medications targeting transmitter systems outside the striatal dopamine synapse (Fig. 1). This approach has raised great hopes, and the validity of the concept is supported by the long known antiparkinsonian efficacy of antimuscarnic drugs, although their use has largely declined in the levodopa era because of their poor safety profile.

Despite sustained pharmacological efforts, only amantadine, discovered to have antiparkinson effects in the 1960s, seems to relate to these novel mechanisms. Following the discovery of an increased phosphorylation state of the NMDA glutamate receptors in striatal spiny neurons of dyskinetic MPTP-intoxicated levodopa-treated monkeys, it was hypothesized that hyperactivity of glutamatergic transmission is a key mechanism underlying dyskinesia. Amantadine’s mechanism of action remains poorly understood, but it is one of the few noncompetitive NMDA antagonists that can be used in humans. This is why it was chosen to test the antiglutamate antidyskinetic concept in pilot proof-of-concept clinical trials during the late
1990s which confirmed its antidyskinetic effects in PD patients.\textsuperscript{89,90}

Other nondopaminergic drugs have been developed based on the same concept during the last decade, including the A2A adenosine antagonist istradefylline,\textsuperscript{91} the AMPA antagonist perampanel,\textsuperscript{92} and the 5HT1A agonist sarizotan (Fig. 1). Unfortunately, translation from animal models to clinical trials failed or provided inconsistent results. Poor model predictability, inadequate drug selectivity, or wrong dosages may account for these disappointing results.

**Advances in the Treatment of Nonmotor Symptoms**

PD continues to be clinically defined as a movement disorder, and for the past decades treatment research has almost exclusively targeted the cardinal motor symptoms or the complications induced by chronic levodopa therapy. However, the neuropathology of PD involves many brain areas beyond the nigrostriatal dopaminergic system including parts of the limbic area and neocortex, the diencephalon, and multiple brain stem areas not related to motor control, as well as the peripheral autonomic nervous system.\textsuperscript{94} Although exact clinico pathological correlations are not always clear, nonmotor symptoms in PD are likely related to the disseminated pathology in PD and include multiple functions like cognition, regulation of mood and hedonic tone, sleep–wake cycle regulation, and autonomic nervous system function, as well as sensory disorders and pain. In their various combinations, nonmotor symptoms may eventually become the chief source of disability of advanced PD. A recent 20-year follow-up of a prospective cohort of PD patients showed that more than 80% of survivors had cognitive decline, with dementia and hallucinosis present in 50%, depression in 50%, and between 30% and 40% of patients showing autonomic features like orthostatic hypotension or urinary incontinence.\textsuperscript{58,95}

Despite the impact of nonmotor features of PD on long-term disability, there is a striking paucity of randomized controlled clinical trials assessing interventions specifically targeting these features. When the MDS Task Force on evidence-based medicine reviewed all English-language publications of randomized controlled trials assessing interventions to treat the different symptoms of PD, only 2 level I studies were identified that had assessed interventions specifically targeting a nonmotor PD symptom in a PD cohort of greater than 10 patients for more than 4 weeks using an established and validated outcome instrument covering a review period ending in January 2002.\textsuperscript{1} Both these trials had established the efficacy of low-dose clozapine therapy to treat PD psychosis in a placebo-controlled design. Since then, no further trials of drugs...
to treat PD psychosis have matched clozapine’s efficacy. In particular, 3 placebo-controlled studies have failed to demonstrate the antipsychotic efficacy of quetiapine in PD patients despite a consistent body of evidence from open-label studies showing some degree of improvement in psychotic symptoms and a small randomized comparator trial with clozapine showing similar effect sizes for quetiapine.96

Since this MDS-sponsored review, several new randomized controlled trials have targeted PD dementia. The first large-scale randomized controlled trial ever focusing on nonmotor symptoms of PD has shown that the cholinesterase inhibitor rivastigmine provides a benefit in patients with mild to moderate dementia,97 and this was also later suggested for donepezil in another placebo-controlled randomized study.98 Two more recent placebo-controlled trials of the antiglutamatergic agent memantine in mixed populations of patients with PDD and DLB failed to show consistent benefits in patients with PDD.99,100 Nevertheless, cognitive dysfunction, dementia and psychosis continue to be major therapeutic challenges of advanced PD.

In 2010, the only large placebo-controlled, randomized trial targeting depressive symptoms in PD used the dopamine agonist pramipexole and reported small but statistically significant improvements that could not be fully explained by concomitant improvement in motor symptoms.101 In contrast, the evidence for efficacy of classical antidepressants remains sparse and only supports the efficacy of imipraminic agents like desipramine102 and nortriptyline,103 whereas the most commonly used group of agents—the SSRIs—lacks solid evidence for efficacy in PD depression from properly designed clinical trials. The most recent review of clinical trials on the treatment of the nonmotor symptoms of PD failed to identify any randomized, controlled clinical trial meeting class I criteria for interventions targeting constipation, urinary incontinence, sexual dysfunction, or orthostatic hypotension.104 Taken together, well-designed, controlled clinical trials of therapeutic interventions targeting the nonmotor symptoms of PD remain a key clinical research priority.

The Renaissance of PD Surgery

Although a variety of surgical approaches to PD were tried in the 1940s, it was only Cooper’s accidental thalamotomy in the 1950s105 that resulted in a standard ablative procedure for parkinsonian features in the prelevodopa era. Because of its excellent effect on tremor, it continued to be used sparingly. With the introduction of levodopa in the 1960s and the realization of its striking benefits, surgical treatments were temporarily largely abandoned.

A number of events led to the reemergence of surgery for PD in the last 25 years. First was the emergence of levodopa-related complications with long-term therapy and disease progression, particularly motor fluctuations and the emergence of drug-induced dyskinesias. Some patients with PD thus continued to be disabled despite best available medical treatment. Second, a number of advances occurred in the understanding of basal ganglia pathophysiology, aided in large part by the development of the MPTP model of parkinsonism in nonhuman primates.106 Such studies showed the important role of the subthalamic nucleus and the internal segment of the globus pallidus in the cardinal motor symptoms in PD and paved the way for experimental surgical therapeutics. Third, there were important advances in neurosurgical techniques, including better imaging with CT and MR, the refinement of neurophysiological mapping with microelectrode recordings,107–109 and the development of deep brain stimulation (DBS), first in the thalamus to reproduce the effects of thalamotomy for tremor and from there expansion to other basal ganglia targets. Early experiments by groups in Baltimore and Manchester showed that the overactivity of the globus pallidus interna (GPi) and subthalamic nucleus (STN) in parkinsonian models could be neutralized by precise lesioning,110,111 These seminal observations paved the way for high-frequency deep brain stimulation (DBS) in experimental animals112 and PD patients. At about the same time, in a landmark study published in 1992, Laitinen reintroduced pallidotomy,113 which had been resuscitated from the 1950s and 1960s to the world of Parkinson’s. A large number of pallidotomies were performed with excellent clinical results, particularly for unilateral procedures.107 In the 1990s pallidotomy was the most common surgical procedure for PD. In the decade starting in 2000, however, pallidotomy procedures have been overtaken by DBS, as the adverse effects of bilateral pallidotomy became too important to tolerate. Using the number of citations per decade in PUB MED with the words pallidotomy or deep brain stimulation revealed interesting trends, as shown in Table 2.

In the Western world, DBS has virtually eliminated the practice of ablative procedures and provided nothing less than dramatic improvement for many patients with advanced PD and complications of drug therapy. STN DBS was first reported to have a major impact on the symptoms of PD by Benabid and his colleagues114,115 and in the last decade, numerous studies have confirmed the major impact of this procedures on the symptoms of PD.116 The latest DBS study comparing DBS of both the GPi and STN suggests that both targets might offer similar motoric benefits,117 although this remains a matter of debate. In comparison, the best adjunctive medications developed in the
last 25 years improved “off” time in PD by 1–2 hours. DBS improves “off” time by 5–6 hours, allows a substantial reduction in medications in many patients, and often eliminates dyskinesias entirely. Although we will continue to refine our target choice and study novel targets for stimulation, DBS is indeed a major therapeutic milestone. The late David Marsden said he saw 2 miracles in PD in his career. The first was the introduction of levodopa and the second, the development of deep brain stimulation for PD (personal communication to Andres Lozano).

Future Perspectives

Cell-based therapies trying to restore the nigrostriatal dopamine projection have been at the forefront of neuroscientific research for more than 2 decades, but clinical trials using human fetal mesencephalic dopaminergic cells or other sources of dopaminergic cells so far have not stood the test of sham-surgery-controlled clinical trials.\(^1\) In addition, these approaches have resulted in uncontrollable off-medication dyskinesias, and Lewy body degeneration has been observed in grafted fetal neurons.\(^2\) Still, cell-based therapy may be one of the future approaches to physiological continuous dopamine replacement in PD if alternative sources, in particular stem cells, can be developed to a stage where routine clinical use will become safe and feasible.

The same may apply to gene therapy using local intracerebral injections of viral vectors carrying therapeutic genes. So far, small proof-of-concept studies have produced encouraging results for lentiviral delivery of glutamic acid decarboxylase into the STN as well as for viral delivery of dopamine-synthesizing enzymes to the putamen.\(^\) Although a phase II sham-controlled trial using intraputaminal viral delivery of neurturine to enhance function and survival of dopaminergic terminals was disappointing, this program is still ongoing.

Although cell-based and gene therapeutic approaches to PD therapy open up exciting perspectives for future treatment, long-term safety and efficacy remain important challenges, and there is currently no perspective for these approaches to significantly alter the progressive multiple system neuronal degeneration outside the nigrostriatal system, which is driving the progression of disability of this disorder. Therefore, the development of “neuroprotective” treatments via identification of novel molecular targets and drug candidates through improved animal models is the central challenges for future PD therapy.

To detect signals of efficacy and monitor disease-modifying effects, reliable surrogate markers for PD progression are badly needed. A central focus of current clinical PD research, therefore, is the identification of markers, both for disease progression and, more importantly, for the identification of at-risk subjects. In 2010, a variety of genomic, proteomic, neurophysiological, and imaging marker candidates emerged, with some of them, like hyposmia, carrying the potential for use as first-step screening instruments on a population basis. Large-scale, prospective studies in healthy subjects are needed to define the sensitivity and specificity of different PD risk markers with the aim of eventually defining a set of markers with sufficient predictive value to begin planning large neuropreventive interventional trials in PD risk populations. Such screening programs will likely involve multistep procedures, starting off with easily available and low-cost tests that can be used on a population basis, with more costly secondary screens involving imaging and other markers to further narrow these high-risk groups, which would then be candidates for neuropreventive interventions. PD-risk prediction and neuroprevention may well be another major milestone in PD therapy that could be reached within the next 25 years.

References


\(^\) Although a phase II sham-controlled trial using intraputaminal viral delivery of neurturine to enhance function and survival of dopaminergic terminals was disappointing, this program is still ongoing.
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