

Melvin D. Yahr Memorial Lecture

An Update on the Treatment of Parkinson's Disease

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Abstract

Although levodopa remains the most effective symptomatic drug for Parkinson's disease (PD), its use is limited by the emergence of motor fluctuations and dyskinesias, particularly in young-onset patients. Dopamine agonists, catechol-O-methyltransferase inhibitors and other anti-parkinsonian drugs have been found to diminish or prevent these complications and possibly to exert disease-modifying effects. The finding that the subthalamic nucleus (STN) and the globus pallidum internus (GPi) are abnormally active in PD has led to effective surgical treatments designed to improve patients' quality of life. The relative benefits of targeting STN or GPi with high-frequency stimulation are still being debated. Experimental therapeutics of PD include novel delivery systems, anti-apoptotic strategies and implantation of genetically engineered cells, and stem cells. Despite encouraging results from early pre-clinical and clinical studies, trials of human fetal grafts and intraventricular and intraparenchymal infusion of glial cell-line-derived neurotrophic factor have not shown clinically meaningful benefits. Future therapeutic strategies should focus not only on ameliorating the symptoms of PD, but also on neuroprotective or neurorescue therapies that can favorably modify the natural course of the disease and slow the progression of both motor and nonmotor manifestations of PD.

Key Words: Parkinson's disease, levodopa, dopamine agonists, dyskinesias.

Medical Treatment of Parkinson's Disease

THIS ARTICLE WILL FIRST SUMMARIZE current studies on medical approaches to treating Parkinson's disease (PD) and then present an update on neurosurgical treatments. Levodopa continues to be the most potent drug for controlling PD symptoms, particularly those related to bradykinesia, but the benefits may be outweighed by the emergence of motor complications, such as fluctuations and dyskinesias. To address the relative benefits and putative neurotoxicity of levodopa, a large multicenter study, the ELLDOPA (Earlier vs. Later LEVODOPA) trial, was designed to evaluate the effects of levodopa on the progression of PD (1). In this study, 361 patients never previously treated with nor requiring dopaminergic drugs were randomized to placebo or levodopa at 150, 300, or

600 mg/day for 40 weeks, followed by a 2-week washout. The total post-washout Unified Parkinson's Disease Rating Scale (UPDRS) score increased 7.8 points for placebo vs. 1.9 points for each of the two lowest doses and decreased 1.4 points for the highest dose ($p < 0.001$). Freezing was seen primarily in the placebo group, while wearing off and dyskinesias were more common in the highest-dose group (15 of 91 or 16.5% in the 600 mg group developed dyskinesia). A subset of patients ($n=135$) underwent single-photon emission tomography (SPECT) imaging using beta-CIT 2 beta-carbomethoxy-3 beta-(4-[(123)5]iodophenyl) tropane as a ligand for striatal dopamine transporter at baseline and at 9 months. No significant differences in loss of uptake were seen for any dose vs. those on placebo. However, when 21 of 142 scans without evidence of dopaminergic deficit (SWEDD) at baseline or at 9 months were excluded from the analysis, there was a significantly larger loss of uptake among all patients receiving levodopa and among high-dose patients vs. placebo. The decline of beta-CIT uptake in the striatum was significantly more pronounced in the levodopa groups than in the placebo group (-7.2% , -4% , -6% , and -1.4% in 600 mg/d, 300 mg/d, 150 mg/d, and placebo, respectively; $p=0.04$). Although

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Glossary

ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale
 ADL = activities of daily living
 AUC = area under the curve
 CALM-PD = comparison of the agonist pramipexole with levodopa on motor complications of Parkinson's disease
 CDS = continuous dopaminergic stimulation
 CIT = carbomethoxy-3ss-(4-iodophenyl)nortropan
 COMT = catechol-O-methyltransferase
 DA = dopamine
 DBS = deep brain stimulation
 DOPA = dihydroxy-phenylalanine
 ELLDOPA = Earlier vs. Later Levodopa
 FDA = Food and Drug Administration
 F-DOPA = ^{18}F -Dopa or [^{18}F]fluorodopa
 GABA = gamma-aminobutyric acid
 GDNF = glial cell-line-derived neurotrophic factor

GPe = globus pallidus externa
 GPi = globus pallidus interna
 Ki = influx rate constant
 L-DOPA = levodopa
 MAO-B = monoamine oxidase-type B
 MMSE = Mini-Mental State Examination
 MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
 NMDA = N-methyl-d-aspartate
 PADRECS = Parkinson's Disease Research, Education, and Clinic Center
 PD = Parkinson's disease
 PET = positron emission tomography
 SPECT = single photon emission tomography
 STN = subthalamic nucleus
 SWEDD = scans without evidence of dopaminergic deficit
 TH = tyrosine hydroxylase
 UPDRS = Unified Parkinson's Disease Rating Scale

the SPECT results are difficult to interpret, it is possible that they reflect a pharmacodynamic effect on the dopamine transporter rather than damaging effects on the dopaminergic neurons (2). There is a growing consensus among the experts that until the validity of the various neuroimaging studies in charting the course of the disease is well established, future clinical trials or neuroprotection should rely on clinical outcome measures (3, 4).

One of the most challenging problems in the management of PD is the treatment of levodopa motor and nonmotor complications (5). Although some studies have concluded that dyskinesias and motor fluctuations are rarely troublesome (6), other studies have shown that dyskinesias clearly have an adverse impact on a patient's quality of life (7). The "wearing off" effect, the most frequent form of motor fluctuation, appears to be related to the shortening of levodopa's half-life in the striatum as a result of the body's impaired capacity to store and buffer the striatal concentration of levodopa due to a loss of striatal dopaminergic terminals. This results in a more pulsatile, rather than continuous, delivery of levodopa, which has been postulated to lead to activation of post-synaptic signal transduction mechanisms, resulting in altered neuronal firing patterns in the globus pallidus interna—subthalamic nucleus—globus pallidus externa (GPe-STN-GPi) pathway, manifested clinically by motor fluctuations and dyskinesias (8).

The main strategies designed to decrease levodopa-induced dyskinesia include: (a) reducing each dosage of levodopa, (b) using drugs known to ameliorate dyskinesias, including amantadine,

clozapine, and fipamezole, and (c) surgery. Continuous infusion is one strategy that has been shown to "smooth out" motor fluctuations (9, 10). In addition to adjusting levodopa dosing, reducing or stopping anticholinergic drugs may also ameliorate levodopa-related dyskinesias. Dystonia, whether levodopa-related or part of the disease (11), often improves with the administration of baclofen, anticholinergic drugs, dopamine (DA) agonists, lithium, and local injections of botulinum toxin (12).

Motor fluctuations, particularly the wearing-off effect, are usually best treated by reducing each individual dose and increasing the frequency of administration of levodopa, or by prolonging levodopa response with the addition of a DA agonist or inhibition of catechol-O-methyltransferase (COMT) by drugs such as entacapone (Comtan) and tolcapone (Tasmar). The latter COMT inhibitor is not frequently used, because of rare reports of liver toxicity. As a result of the 2006 Food and Drug Administration (FDA) ruling, the monitoring for possible liver toxicity of tolcapone has been relaxed, and the newly approved labeling states that serum liver enzymes should be tested at baseline as well as periodically (i.e., every 2–4 weeks) for the first six months of therapy. In addition, after the first six months of therapy, periodic monitoring is recommended at intervals deemed clinically relevant. Entacapone, because of its short half-life, requires frequent administration (200 mg, up to 8 times per day); most patients take entacapone with each dose of levodopa. COMT inhibitors may increase levodopa-induced dyskine-

sia, requiring a substantial (>25%) reduction in daily levodopa dosage. In 2003, the FDA approved triple combination tablets (Stalevo) containing carbidopa, levodopa, and entacapone in the following doses: 12.5/50/200, 25/100/200, and 37.5/150/200 for end-of-dose wearing off. In a randomized, crossover study of 132 healthy subjects, the levodopa area under the curve (AUC) was essentially the same in the triple combination as compared to separate administration, indicating equivalent pharmacokinetics (13). Whether initiating a COMT inhibitor at the time levodopa is started, rather than waiting until motor complications occur, will delay levodopa-related motor complications is still unknown, but the hypothesis is currently being studied in clinical trials, including the STRIDE-PD trial (14).

In contrast to the traditional DA agonists (bromocriptine and pergolide), pramipexole and ropinirole are non-ergolines and, therefore, are expected to have a lower risk of complications such as peptic ulcer disease, vasoconstrictive effects, erythromelalgia, pulmonary and retroperitoneal fibrosis, and cardiac valvular disease (15). A study of 301 patients in early stages of PD, followed in a double-blinded fashion for a mean of 2 years after randomization to pramipexole or levodopa (Comparison of the Agonist Pramipexole with Levodopa on Motor Complications of Parkinson's Disease or CALM-PD), found marked reduction in the risk of motor complications in the pramipexole group (16). A 4-year follow-up of the CALM-PD cohort found that: (a) initial treatment with pramipexole was associated with a significant reduction in the risk of developing dyskinesias (24.5% vs 54.0%, hazard ratio 0.37, $p < 0.0001$) and wearing off (47.0% vs 62.7%, hazard ratio 0.68, $p = 0.02$), but there was no difference between the two groups in disabling dyskinesias; (b) initial levodopa treatment resulted in a significant reduction in the risk of freezing (25.3% vs 37.1%, hazard ratio 1.70, $p = 0.01$); (c) the improvement in mean total UPDRS was greater with levodopa than with pramipexole (2.0 ± 15.4 vs -3.2 ± 17.3 points, $p = 0.003$); (d) pramipexole treatment was associated with a higher risk of somnolence (36% vs 21%, $p = 0.005$) and edema (42% vs 15%, $p = 0.001$); and (e) there was no difference in quality of life (17). Furthermore, sequential beta-CIT SPECT scans show that the rate of loss of dopamine transporter density as measured by the decline in beta-CIT over the 46-month period of follow-up was about 40% lower in the group initially treated with pramipexole (16.0%) as compared to the levodopa group (25.5%) (18). The difference in slopes, however, is significant only between baseline and 22 months,

but not between 22 and 46 months. At 22 months patients treated with pramipexole and those on both pramipexole and levodopa had nearly identical (7%) declines in beta-CIT values from baseline as compared to 13.5% decline in patients treated with levodopa monotherapy. This suggests that the rate of loss of striatal beta-CIT may decrease as patients require more levodopa. This could be interpreted as indicating possible levodopa neurotoxicity, or that pramipexole and/or levodopa may have a direct effect on beta-CIT early in disease; there may be other reasons as well.

Ropinirole has also been demonstrated to be effective in early PD. In one study, 268 patients with early PD were randomized to either ropinirole ($n = 179$) or levodopa ($n = 89$) and followed for more than 5 years (19). After 5 years, approximately one half of the patients remained in the study (47% in the ropinirole group and 51% in the levodopa group) and 34% of those randomized to ropinirole remained on monotherapy (16.5 mg/day). The mean levodopa dose was 750 mg/day. Prior to the addition of levodopa, only 5% of the ropinirole-treated patients developed dyskinesia, in contrast to 36% of those treated with levodopa. After five years, only 20% of the patients on ropinirole or ropinirole/levodopa exhibited dyskinesias vs. 46% of those on levodopa. No significant differences were seen among groups for wearing off, freezing, or dopaminergic side effects, with the exception of hallucinations, which were more common in the ropinirole group. This study showed that the risk of developing dyskinesias was substantially lower with ropinirole monotherapy or with ropinirole plus levodopa supplementation. A follow-up study utilizing F-Dopa positron emission tomography (REAL-PET) showed a significantly slower decline in F-Dopa uptake in patients on ropinirole vs. levodopa. In this double-blind, European-Canadian, 2-year follow-up study, *de novo* patients not previously treated with dopaminergic drugs were randomized to ropinirole or Sinemet (20). The primary endpoint was a change in putamen 18F-Dopa uptake measured with 3-D positron emission tomography (PET), and secondary endpoints included incidence of dyskinesias. Of the 186 patients enrolled in the study, 21 were excluded because of normal 18F-Dopa PET. The mean dose at 2 years was 12.2 mg for ropinirole and 558 mg for levodopa. The 18F-Dopa uptake (K_i) in the putamen decreased an average of 13.4% in the ropinirole group ($n = 87$) and 20.3% in the levodopa group ($n = 75$), a 34% difference ($p = 0.022$). Using statistical parametric mapping analysis, the relative difference was 38% ($p < 0.025$). Although changes in the UPDRS motor

score on medication favored the L-DOPA group by six points ($p = ns$) there was significantly less dyskinesia with ropinirole: 26.7% vs 3.4% ($p < 0.001$) and it took about 8 times longer for the ropinirole patients than the levodopa patients to develop dyskinesia ($p < 0.001$). Various statistical analyses of the PET data showed significantly slower (30–35%) loss of dopamine terminal function in early PD patients treated with ropinirole compared with levodopa. Both pramipexole and ropinirole (and possibly other DA agonists) have been associated with irresistible sleep attacks and excessive daytime drowsiness (21). This drowsiness can be at least partially reversed with modafinil (22).

Apomorphine is a water-soluble DA and, therefore, is suitable for intravenous, subcutaneous, sublingual, or intranasal administration. Subcutaneous injections or continuous infusions have been found to be useful even in advanced PD, by reducing the “off” time without necessarily increasing dyskinesias (23).

There are several new DA agonists being investigated in Phase 2 or 3 clinical trials. Rotigotine CDS (constant delivery system; SPM 962; N-0923), a new 5-hydroxy-2-aminotetralin derivative, is a highly selective D2 agonist, delivered through a silicone-based transdermal patch. It has been found to produce dose-related improvement in the UPDRS (24). Administration via a transdermal patch bypasses metabolism by liver, and as a result of sustained delivery more steady plasma and brain levels can be achieved. This may result in a smoother response and less severe motor complications. Another novel DA agonist is sarizotan (EMD128130; Merck KGaA), which, based on *in vitro* binding studies, has a high affinity for D2, D3, and in particular D4 receptors, as well as 5-HT_{1A}. The drug has anti-psychotic effects and it reverses levodopa-induced dyskinesias in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkeys and other animal models of PD.

Psychiatric side effects of dopaminergic drugs, particularly agitation, visual hallucination, psychosis, paranoia, hypersexuality, and pathological gambling (25), may be controlled by reducing the dosage of these drugs (levodopa, dopamine agonists) and eliminating all other drugs that are not absolutely essential, such as selegiline, anticholinergics, and amantadine. Atypical antipsychotics offer the best strategy for controlling drug-induced psychosis without the need to adjust the dosage of dopaminergic drugs. Quetiapine fumarate (Seroquel), a dibenzothiazepine that blocks not only D1 and D2 receptors but also 5-HT_{1A} and 5-HT₂ receptors, has also been found to have a beneficial

effect on PD patients with hallucinations. In contrast to olanzapine, quetiapine usually does not worsen parkinsonism. The role of ziprasidone (Geodon), a potent blocker of D2 and D3 receptors as well as 5-HT_{2A}, 5-HT_{2C}, 5-HT_{1A}, 5-HT_{1D} and α_1 receptors, and aripiprazole (Abilify), a partial D2 and 5-HT_{1A} agonist and 5-HT₂ antagonist, in the treatment of PD-related psychosis is still unknown. Cholinesterase inhibitors such as donepezil (26), rivastigmine, and galantamine, and the N-methyl-D-aspartate (NMDA) antagonist memantine, have been found to improve cognitive and language function in patients with PD. In a study of rivastigmine in dementia associated with PD, involving 541 patients enrolled in a 24-week, randomized, multicenter, double-blind clinical trial, the mean Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) score, the primary efficacy variable, improved by 2.1 points in the rivastigmine group and by 0.7 in the placebo group ($p < 0.001$), and the Mini-Mental State Examination (MMSE) improved by 0.8 in the rivastigmine group and worsened by 0.2 in the placebo group ($p = 0.03$) (27). At the end of the study, 55.5% of all patients were receiving 9–12 mg of rivastigmine per day.

There are no proven neuroprotective drugs (28), although selegiline, a monoamine oxidase-type B (MAO-B) inhibitor, has been found to delay the need for levodopa therapy and may reduce the risk of freezing (29, 30). In clinical studies, rasagiline, another MAO-B inhibitor, provides a modest benefit as an adjunctive therapy for PD patients experiencing levodopa-related motor fluctuations. Using a “randomized, delayed-start” design to distinguish between short-term and long-term effects of the medication, 371 patients were randomized to 1 or 2 mg/d of rasagiline for 1 year, or placebo for 6 months followed by rasagiline, 2 mg/d, for 6 months (31). The mean adjusted difference between placebo/rasagiline, 2 mg/d, vs. rasagiline, 1 mg/d, for 1 year was -1.82 UPDRS units ($p = 0.05$). The drug was very well tolerated, and subjects treated with rasagiline 1 and 2 mg/d for 1 yr showed less functional decline than subjects whose treatment was delayed for 6 months. A double-blind, placebo-controlled trial showed that after a 10-week treatment with rasagiline, 12 of 43 of patients (28%) had an improvement in total UPDRS score of 30% or greater, compared with none in the placebo group ($p < 0.05$) (32). In an 18-week, double-blind trial of 687 patients randomized to receive once-daily rasagiline (1.0 mg), entacapone (200 mg with each dose of levodopa), or placebo (the LARGO trial), both rasagiline and entacapone reduced “off” time by 1.2 hours as compared with

placebo (0.4 hour reduction, $p \leq 0.0001$); the mean daily dose of levodopa was reduced by 24.3 mg/day on rasagiline and by 19.2 mg/day on entacapone, and was increased by 5.5 mg/day on placebo (33). Other variables showed that rasagiline was superior to placebo and to entacapone in reducing UPDRS motor score, and at least as effective as entacapone in reducing "off" time. In another study of patients with motor fluctuations, treatment with 1 or 0.5 mg/day of rasagiline was associated with a 29% (1.85 hour) and 23% (1.41 hour) reduction, respectively, in "off" time compared to baseline (34).*

One particularly promising therapeutic and potentially neuroprotective approach involves the use of neurotrophic factors, particularly the glial cell-line-derived neurotrophic factor (GDNF). This trophic factor has been reported to enhance the survival of midbrain dopaminergic neurons *in vitro* and to rescue degenerating neurons *in vivo* (35). The encouraging pre-clinical observations led to a pilot human, multicenter trial of intraventricular GDNF infusions in patients with moderately advanced PD. However, because of lack of observed efficacy and frequent occurrence of nausea, anorexia, tingling (Lhermitte sign), hallucinations, and depression, these trials were suspended (36). In a one-year follow-up of five patients with PD in whom GDNF was continuously infused directly into the putamen, there were no serious clinical side effects, a 39% improvement in the off-medication motor sub-score of the UPDRS, and a 61% improvement in the activities of daily living sub-score. Furthermore, levodopa-induced dyskinesias were reduced by 64% and, in contrast to fetal implants (see below), there were no off dyskinesias (37). This clinical improvement was accompanied by a 28% increase in putamen PET F-DOPA uptake and evidence of neuronal sprouting in an autopsied brain (35). A recently completed multicenter trial, however, has shown no benefit from GDNF, and further studies have been suspended because of evidence of development of GDNF antibodies in some patients and cerebellar toxicity in experimental primates (38–40).

Other agents that are being or soon will be investigated as potential neuroprotective drugs include aspirin and salicylate, modafinil, minocycline (41), and even green tea, which contains polyphenol (-)-epigallocatechin-3-gallate (42) and has been reported to block the uptake of MPP+. Only well-designed clinical trials will be able to address the question of whether therapeutic interventions with these agents can favorably alter the

natural course of the disease by promoting the survival and growth of degenerating neurons.

Another promising strategy in the treatment of PD is the use of adenosine antagonists. Adenosine A_{2A} receptors are colocalized with striatal dopamine D₂ receptors on gamma-aminobutyric acid (GABA)ergic medium spiny neurons, which project via the "indirect" striatopallidal pathway to the GPe. In a 12-week, double-blind, randomized, placebo-controlled, exploratory study, PD subjects with both motor fluctuations and peak-dose dyskinesias were randomized to treatment with placebo ($n = 29$), istradefylline up to 20 mg/day ($n = 26$), or istradefylline up to 40 mg/day ($n = 28$) (43). There was no prespecified primary outcome measure, and 19 outcome variables were analyzed. As assessed by home diaries, subjects assigned to istradefylline experienced a mean (\pm SE) reduction in the proportion of awake time spent in the "off" state of $7.1 \pm 2.0\%$ compared with an increase of $2.2 \pm 2.7\%$ in the placebo group ($p = 0.008$). There was a decrease in "off" time of 1.2 ± 0.3 hours in the istradefylline group compared with an increase of 0.5 ± 0.5 hour in the placebo group ($p = 0.004$). Dyskinesia severity was unchanged, but "on" time with dyskinesia increased in the istradefylline group compared with the placebo group (percent, $p = 0.002$; hours, $p = 0.001$). No differences were observed in change in UPDRS scores or Clinical Global Impression of Change. Istradefylline was generally well tolerated, and it reduced "off" time, as assessed by home diaries. Severity of dyskinesia was unchanged, but "on" time with dyskinesia increased.

Neurosurgical Treatment of Parkinson's Disease

Deep Brain Stimulation

It is beyond the scope of this article to comprehensively review the neurosurgical treatment of PD. Only a brief review, focusing on high-frequency deep brain stimulation (DBS) will be provided here. Several studies have demonstrated that DBS of the GPi and STN improves parkinsonian symptoms and prolongs the "on" time. In a multicenter, prospective, double-blind, crossover study of 143 patients with advanced PD who received bilateral high-frequency stimulation of STN or GPi, the UPDRS motor scores improved by 49% ($p < 0.001$) and 37% ($p < 0.001$) respectively in comparison to the non-stimulated state (44). Furthermore, 6 months following implantation as compared to baseline, the percent time "on" without dyskinesias increased from 27 to 74 ($p < 0.001$) and 28 to 64 ($p < 0.001$) with STN and GPi DBS, respectively. Adverse events included intracranial hemorrhage in seven and lead explantation in two.

*In 2006 rasagiline was approved by the FDA for initial monotherapy and as adjunct to levodopa.

While the levodopa dosage remained unchanged in the GPi group, the daily levodopa dose equivalents were reduced by 37% in the STN DBS group ($p < 0.001$). In a five-year prospective study of the first 49 patients, mean age 55 years, treated with bilateral STN DBS and assessed during “on” and “off” states at one, three and five year's, the Grenoble group found 54% improvement in “off” motor function as compared to baseline and 49% improvement in activities of daily living (ADL) (45). Speech was apparently the only motor function that did not improve. Except for improved dyskinesia and lower daily levodopa dose, there was no additional improvement in “on” motor function beyond one year, and the axial symptoms continued to deteriorate after the first year. Of the initial 49 patients, 7 did not complete the study, 3 died, 4 were lost to follow-up, 3 developed dementia after three years, one committed suicide and one had a large cerebral hemorrhage.

This and other studies provide evidence for the conclusion that STN DBS is no better than levodopa, but that it ameliorates levodopa-related motor complications and dyskinesias and off-period dystonia. Despite many reports concluding that GPi DBS is less effective than STN stimulation, there are only a few studies that have objectively compared these two approaches (46). Several studies have demonstrated greater anti-dyskinetic effects of GPi versus STN stimulation. Some studies have suggested that GPi DBS may be especially indicated in patients with a low threshold for dyskinesia (47), and GPi is considered the desirable target for treatment of dystonia and other hyperkinetic movement disorders. In their study involving 23 patients with PD complicated by marked levodopa-related motor fluctuations and dyskinesias, the investigators concluded that there were no significant differences in the overall benefits, although levodopa was decreased more in the STN group and dyskinesia improved more in the GPi group (48). Further controlled, randomized studies, however, are needed to determine which of the two methods is more effective and which patients should be considered the best candidates for either of the two procedures. Recently, the Veterans Administration initiated and sponsored a study designed to compare STN and GPi DBS in patients with PD as part of the Parkinson's Disease Research, Education, and Clinic Center (PADRECC) initiative. DBS of the STN has been found to be effective in controlling not only parkinsonian tremor (49), but also bradykinesia and handwriting, and possibly even gait difficulty and freezing (50).

Brain Grafting

Freed et al. (51) reported the results of the first double-blind, placebo-controlled trial of fetal graft transplantation for advanced PD. Forty patients, stratified by age into younger than and older than 60 years, with an approximately 7-year history of PD symptoms, were randomized to receive either 4 embryonic mesencephalons delivered via 4 needle passes to the left and right putamen or a sham operation (4 drill holes to the forehead without dural penetration). After one year, the “sham” patients were given the option to be implanted and were then followed in an open label manner; a total of 33 patients received an implant. Overall, there was no difference between the implanted vs sham patients with respect to the primary outcome variable, a global rating by the patients (from -3 , PD markedly worse, to $+3$, PD markedly improved). However, 5 of 33 (15%) patients who eventually received the implant experienced dyskinesias even during “off” periods (presumably as a result of release of DA from the fetal implant), which were successfully treated with GPi DBS in 3 of the 5 patients (52). In the second, National Institutes of Health (NIH)-funded, controlled trial of fetal transplants, 34 patients were randomized to receive bilateral grafting into the posterior putamen of 4 or 1 fetal tissues per side, or sham surgery (partial burr hole without penetration of the dura) (53). All patients received immunosuppression for six months after surgery and were followed for 24 months. Thirty-one patients completed the trial; 2 died during the trial, and 3 afterward, for causes unrelated to the procedure. There was no significant overall treatment effect, but patients with milder symptoms did show significant improvement ($p = 0.006$). Post-mortem examination was performed on all patients who died; in all transplanted patients the tyrosine hydroxylase (TH) staining indicated striatal innervation, particularly in those who received 4 tissues. PET results indicated a significant dose-dependent increase vs. baseline in fluorodopa uptake, with no change in placebo patients and an approximate one-third increase in patients receiving 4 tissues. Despite these histochemical and imaging improvements, no significant differences were seen in clinical measures. Increase (worsening) from baseline in the UPDRS motor score while off medication was 9.4 for placebo, 3.5 for 1 tissue, and -0.72 for 4 tissues ($p=0.096$ for 4 vs. placebo). Although treated patients improved for approximately 9 months, they then worsened. There was no difference between implanted and sham patients in “on” time without dyskinesias, total “off” time, ADL scores, or lev-

odopa dose required. No placebo patients, but 13 of 23 (56%) treated patients, developed off-medication dyskinesias. The authors concluded that “fetal nigral transplantation currently cannot be recommended as a therapy for PD based on these results.”

In addition to human embryonic tissue, other donor sources are currently being investigated, including retinal pigment epithelial cells (Spheramine). These cells, located in the inner layer of the neural retina, produce dopamine. When attached to cross-linked gelatin microcarriers (Spheramine) and implanted stereotactically into the striatum, the cells have improved parkinsonian symptoms in rodents, non-human primates and parkinsonian patients. A pilot, open-label study of 6 patients showed 48% improvement in the UPDRS motor score 12 months after implantation (54). A randomized, controlled trial is currently being conducted in selected centers in North America and Europe.

Discussion

The most important principle in the management of PD is to individualize therapy and to customize it to the needs of the patients. The selected therapy should be based on scientific rationale and evidence-based data (55). It should be designed not only to control symptoms, but also to slow the progression of the disease and prevent levodopa-related complications. Since younger patients are likely to require dopaminergic therapy for a longer period of time and they are at increased risk for the development of levodopa complications, levodopa-sparing strategies such as the use of MAO inhibitors and dopamine agonists are even more critical for this population (56). Certain symptoms of PD, such as dysarthria, dysphagia, freezing and other “axial” symptoms, usually do not respond to dopaminergic therapy and may be mediated by non-dopaminergic systems (57). Patients whose functioning is impaired because of levodopa-related motor complications that cannot be controlled with medical therapy may be candidates for surgical intervention (58). As we achieve better understanding of the mechanisms of neurodegeneration, more effective therapeutic strategies will probably become available.

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