FEATURE

The Parkinson's Journey: From Drug Discovery to Treatment of Early and Advancing Disease

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Efforts to find a treatment for Parkinson's disease (PD) began in the mid-1950s with the discovery of levodopa (L-dopa). Since then, advancements in treatment have included a variety of different modes of L-dopa administration as well as the development of other medical therapies, continuous infusions, and deep brain stimulation (DBS). This session featured presentations on the L-dopa story and treatment strategies for early and late PD.

L-DOPA: FROM IDEA TO TREATMENT

Arvid Carlsson, MD, Sahlgrenska Science Park, Gothenburg, Sweden, winner of the 2000 Nobel Prize in Physiology or Medicine, reviewed the history of treatment for PD, focusing on the discovery and development of L-dopa, the precursor of dopamine. The story of the characterization of L-dopa began in 1955, shortly after Prof. Carlsson joined Bernard B. Brodie, MD, at the Laboratory of Chemical Pharmacology of the National Heart Institute, Bethesda, Maryland, USA. There, members of Dr. Brodie's team discovered that administration of reserpine caused almost complete disappearance of serotonin from the brain and other tissues.

After working with Dr. Brodie, Prof. Carlsson collaborated with Nils-Ake Hillarp, PhD, MD, at the University of Lund, Lund, Sweden, where he studied the effects of reserpine in rabbits. From these experiments, the investigators learned that reserpine depleted catecholamines from heart and brain tissue and that movement was inhibited in reserpine-treated rabbits, mimicking the symptoms of PD. Treatment of these rabbits with the catecholamine precursor, 3,4-dihydroxyphenylalanine (dopa), caused a dramatic reversal of the symptoms within 15 minutes. These results, published in 1957, established that reserpine depletes serotonin and catecholamines in the body and dopa reverses that depletion.

Subsequent animal studies showed that it was not dopa itself, but dopamine, a monoamine formed from the precursor (dopa), that reversed reserpine's effects. Further investigations, published in 1958, demonstrated that dopamine accumulates in the basal ganglia of the brain, which are involved in motor function. These findings led to the conclusion that dopamine depletion induces PD and that treatment with L-dopa could restore dopamine levels, alleviating PD symptoms.

Prof. Carlsson presented his findings at a symposium on catecholamines at the National Institutes of Health in 1958. Two years later, at a London symposium, Prof. Carlsson's conclusions were rejected by Nobel laureate Sir Henry Dale and his colleagues, who argued that dopamine is a poison. This rejection spurred Profs. Hillarp and Carlsson, together with many colleagues, to develop fluorescent techniques for visualizing neurotransmitters in neurons. Within a few years, they established the presence of dopamine in the substantia nigra, mapped the major monoaminergic pathways, and determined the sites of action of major psychotropic drugs, including monoamine oxidase (MAO) inhibitors, chlorpromazine, reserpine, and imipramine.

In the early 1960s, Austrian researchers reported a marked reduction of dopamine in the brains of deceased PD patients. Following this, Walther Birkmayer demonstrated temporary improvement of akinesia in patients with PD after a single dose of L-dopa. Other laboratories, however, had varying results with L-dopa treatment in PD patients.

In the late 1960s, George Cotzias, MD, treated manganese miners who presented with symptoms similar to those of PD. Rather than giving L-dopa intravenously or orally in low doses, he treated PD patients with escalating oral doses until they were receiving much higher doses than had been given in previous studies. Prof. Carlsson and others replicated his findings in PD patients, and as a result, L-dopa became established as the gold standard for the treatment of PD. Prof. Carlsson

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concluded his presentation by recommending the book *Awakenings* by Oliver Sacks, which chronicled the L-dopa story and was made into a movie.

TREATMENT OF EARLY PARKINSON'S DISEASE

Heinz Reichmann, MD, University of Dresden, Dresden, Germany, outlined the initial treatment options for patients with PD: a dopamine agonist or MAO-B inhibitor for patients with mild motor disability and no cognitive impairment; a dopamine agonist for those with moderate or severe motor disability and no cognitive impairment; and L-dopa for patients with moderate or severe motor disability aged 70 years and older or who have significant comorbidity, including cognitive impairment. Treatment options might be different, however, with earlier diagnosis of PD and earlier initiation of treatment.

The lesions of PD are initially confined to the medulla oblongata and olfactory bulb (Stages 1 and 2), but they eventually progress to involve the substantia nigra and other nuclear gray areas of the midbrain and basal forebrain (somatomotor dysfunction; Stages 3 and 4). Eventually, the cerebral cortex is encroached on, resulting in increasing cognitive deterioration (Stages 5 and 6) [Braak H et al. *J Neurol* 2002]. Often, patients do not seek medical care when early symptoms appear, attributing them to the normal aging process.

Thus, unfortunately, by the time that many patients are diagnosed, the pathology has progressed significantly. Consider what can be done to identify these individuals earlier. In theory, improved diagnostic skills could lead clinicians to closely track patients presenting with the earliest symptoms, such as olfactory impairment or idiopathic rapid eye movement (REM)–sleep behavior disorder (RBD). One study of 44 patients with RBD reported that 20 (45%) eventually developed a neurological disorder, which typically occurred at a mean follow-up of 5.1 years after diagnosis [Iranzo A et al. *Lancet Neurol* 2006]. These neurological diagnoses included PD (n=9), Lewy body dementia (n=6), multiple system atrophy-C (n=1), and mild cognitive impairment (n=4).

According to Prof. Reichmann, timing of treatment initiation should be individualized. He reviewed the results of several studies on early versus delayed treatment (Table 1).

Other issues with treatment of Parkinson's disease include the development of dyskinesias with increased doses of L-dopa, patient noncompliance with treatment regimens, and on-and-off periods of symptom control due to inconsistent plasma drug concentrations with multiple dosing regimens. Alternative drug delivery methods have been evaluated to improve patient compliance and maintain consistent plasma drug levels. Among these are controlled-release oral therapy with ropinirole, subcutaneous apomorphine infusion, intrajejunal L-dopa infusion, and transdermal application (rotigotine transdermal patch).

Prof. Reichmann recommended using combination therapy with L-dopa (<600 mg/day) and a dopamine agonist. Initial treatment should be patient specific, however. Younger patients should be started on dopamine agonists, whereas older patients should be treated with L-dopa. Finally, patient safety and compliance should be key considerations when determining treatment strategies.

TREATMENT STRATEGIES FOR ADVANCING PARKINSON'S DISEASE

Lars Timmerman, MD, University Hospital Cologne, Cologne, Germany, presented data on treatment strategies for patients with advancing PD. He focused

Table 1. Studies of Early Versus Delayed Treatment for Parkinson's Disease

Study	Design and Patients	Results
PDLIFE [Grosset D et al. *J Neurol Neurosurg Psychiatry* 2007]	Prospective, audit-based, 18-month follow-up of 198 treatment-naïve PD patients	Significantly worse QoL in treatment-naïve patients vs patients on monotherapy with any anti-PD drug
TEMPO [Parkinson Study Group. *Arch Neurol* 2004]	Change in UPDRS with rasagiline 1 mg/day vs rasagiline 2 mg/day vs delayed rasagiline 2 mg/day; 371 patients	Patients treated for 12 months had significantly less functional decline than those whose treatment was delayed 6 months (1 mg/day vs delayed, p=0.05; 2 mg/day vs delayed, p=0.01).
TEMPO [Hauser RA et al. *Parkinsonism Relat Disord* 2005]	Long-term extension to 6 years, delayed start vs early start rasagiline; mean change in UPDRS	Overall difference between early and delayed-start groups, favoring early start, was 16% (p=0.006).
ADAGIO [Olanow CW et al. *N Engl J Med* 2009]	1176 treatment-naïve PD patients randomly assigned to rasagiline 1 or 2 mg/day for 72 weeks vs placebo for 36 weeks followed by rasagiline 1 or 2 mg/day for 36 weeks	Less worsening in UPDRS in 1 mg/day early-start vs delayed-start group (p=0.02); no significant change in 2 mg/day early-start vs delayed-start group
PROUD [Schapira AHV et al. *Lancet Neurol* 2013]	Early vs delayed start of pramipexole in 535 PD patients	No significant difference in adjusted mean UPDRS score between early and delayed pramipexole at 15 months (−0.4 points; 95% CI, −2.2 to 1.4; p=0.65); no disease-modifying effects with pramipexole

PD=Parkinson's disease; QoL=quality of life; UPDRS=Unified Parkinson's Disease Rating Scale.

Table 2. Studies of Continuous Drug Delivery in Patients With Advanced Parkinson's Disease

Study	Design and Patients	Results
Zibetti M et al. *Eur J Neurol* 2014	7-year follow-up of LCIG infusion therapy in advanced PD	QoL improved in >90% of patients Clinically significant improvement in motor function
Garcia Ruiz PJ et al. *Mov Disord* 2008	Long-term treatment with subcutaneous apomorphine infusion; mean follow-up of 19.93 months	Reduction from baseline in off-hours ($p<0.0001$), total and motor UPDRS ($p<0.0001$), dyskinesia severity ($p<0.0006$), and equivalent dose of anti-parkinsonian therapy ($p<0.0001$) AEs: skin nodules (68%), panniculitis (19%), and sedation (29%)
Katzenschlager R et al. *Mov Disord* 2005	Prospective study of dyskinesias with continuous subcutaneous apomorphine infusion; change from baseline to 6 months	Daily off-time reduced by 38%; on-time increased by 20% Dyskinesia duration reduced by 40%, and severity by 31% L-dopa dose reduced by 55%
Drapier S et al. *Parkinsonism Relat Disord* 2012	Continuous apomorphine in advanced PD patients with DBS contraindications; improvement from baseline to 12 months	VAS satisfaction, 52.8% Daily off-time reduced from 23.8% to 15.2% ($p=0.04$) Daily-on time improved from 32.7% to 48.4% ($p=0.004$)

AEs=adverse events; DBS=deep brain stimulation; LCIG=L-dopa–carbidopa intestinal gel pump; PD=Parkinson's disease; QoL=quality of life; UPDRS=Unified Parkinson's Disease Rating Scale; VAS=visual analog scale.

on continuous delivery therapies and DBS, particularly with respect to patient selection for these therapies and their use in clinical practice.

Treatment of PD with drug therapy is typically characterized by good symptom control in the early stage, but as the disease progresses, patients experience fluctuations in symptom control, with "wearing off" of the effect and increasing "off" periods as PD becomes more severe. Oral therapy options recommended by the German Neurological Society to counteract wearing off include frequent dosing with single-dose reduction, a long-acting dopamine agonist, a transdermal continuous dopamine agonist, catechol O-methyltransferase (COMT) inhibitors, MAO inhibitors, and amantadine [Eggert KM et al. *Leitlinien für Diagnostik und Therapie in der Neurologie.* 2012].

Continuous drug delivery options for advanced PD include the L-dopa–carbidopa intestinal gel (LCIG) pump system for continuous intrajejunal delivery and continuous subcutaneous apomorphine therapy. Table 2 summarizes results from studies evaluating these therapies in patients with advanced PD.

EuroInf [Reddy P et al. MDS 2013 (poster 596)] was a novel, case-controlled, comparative multicenter study that compared treatment with continuous apomorphine versus LCIG. Investigators reported a robust improvement in motor and quality-of-life (QoL) scores with a large effect size with both therapies on UPDRS 3 and 4. Sleep and fatigue were significantly improved by LCIG versus apomorphine ($p=0.017$), apomorphine significantly improved mood and apathy ($p=0.03$), and autonomic functions were moderately improved with LCIG and mildly improved with apomorphine. Both therapies had a large beneficial effect on QoL.

In Prof. Timmerman's opinion, LCIG pump therapy is suitable for the following patients: L-dopa responders of any age with insufficient response to oral combination therapies, with or without motor fluctuations, off-periods, and depression. Problems with LCIG are mostly technical or involve cost issues. Continuous apomorphine therapy is suitable for younger patients with good L-dopa response and motor complications, despite oral therapy. On-off fluctuations, dyskinesias, off-dystonia, and L-dopa-induced mild neuropsychiatric problems are not contraindications. Patients who might have problems include those who are underweight, are on anticoagulants, have tremor that is nonresponsive to dopaminergic therapy, and have dementia or hallucinations.

DBS involves high-frequency electrical stimulation of the subthalamic nucleus via implanted electrodes. A study of DBS versus medication in patients with advanced PD reported significant improvements in mobility ($p<0.001$), activities of daily living ($p<0.001$), emotional well-being ($p<0.001$), stigma ($p<0.001$), and bodily discomfort ($p=0.009$) [Deuschl G et al. *N Engl J Med* 2006]. Adverse events with DBS included suicide (n=1) and postoperative confusion (n=4).

A recent interim analysis demonstrated significant improvement of nonmotor deficits in PD patients treated with DBS [Dafsari HS et al. MDS 2014 (abstr SG 10)]. Schuepbach and colleagues [*N Engl J Med* 2013] reported significant improvement in QoL with DBS versus medical therapy in patients with earlier stages of PD ($p=0.002$). The VANTAGE trial [NCT01221948; Timmerman L et al. MDS 2013 (abstr 486)] of DBS showed 62.4% improved motor function from baseline (medications off) to 6 months (DBS on, medications off; $p<0.0001$).

Based on the evidence, Prof. Timmerman concluded this lecture with the assertion that subthalamic DBS is suitable for PD patients aged <75 years who have impaired QoL despite optimized therapy. DBS candidates should have an L-dopa response >30% or tremor (UPDRS >2), no dementia or severe psychiatric problems, minimal axial symptoms, and realistic expectations for therapy.