Levodopa therapy for Parkinson disease: A look backward and forward.

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ABSTRACT
Although levodopa is widely recognized as the most effective therapy for Parkinson disease (PD), its introduction 5 decades ago was preceded by several years of uncertainty and equivocal clinical results. The translation of basic neuroscience research by Arvid Carlsson and Oleh Hornykiewicz provided a logical pathway for treating PD with levodopa. Yet the pioneering clinicians who transformed PD therapeutics with this drug—among them Walther Birkmayer, Isamu Sano, Patrick McGeer, George Cotzias, Melvin Yahr, and others—faced many challenges in determining whether the concept and the method for replenishing deficient striatal dopamine was correct. This article reviews highlights in the early development of levodopa therapy. In addition, it provides an overview of emerging drug delivery strategies that show promise for improving levodopa's pharmacologic limitations.

GLOSSARY
CNS = central nervous system; PD = Parkinson disease; TOPA = 2,4,5-trihydroxyphenylalanine.

Among neurodegenerative diseases, Parkinson disease (PD) is unique in having several highly effective medications for suppressing its signs and symptoms. Heading the list of treatment options over the past 5 decades has been a remarkably effective medication: levodopa (3,4-dihydroxy-L-phenylalanine; also known as 1-DOPA).1–3 Its worldwide impact on reversing the disabilities of PD and improving quality of life has been enormous, though it arrived on the therapeutics scene amidst skepticism and, initially, unfulfilled promise.4,5 Eventually, after almost a decade of unconvincing clinical trials, levodopa finally proved itself to be a successful therapy.6,7 It provided the first opportunity for clinician and patient alike to recognize how much of the parkinsonian motor syndrome—resting tremor, slowed movement, decreased dexterity, rigidity, postural disturbance, and other impairments—are reversible consequences of striatal dopaminergic deficiency. Levodopa has also been one of the most cost-effective medications ever developed. Although, after nearly a half-century of use, this medication continues to be an enduring treatment for PD, it also behaves, as pioneering researcher Oleh Hornykiewicz recognized early on, as “…far from perfect as a drug.”8 Levodopa’s limitations at treating the full spectrum of parkinsonian signs and symptoms, as well as declining effectiveness, have been recognized in follow-up of PD populations for 10 years and longer.9

How levodopa came to be developed as a therapy is instructive for the modern reader in that it nicely illustrates a dictum of Louis Pasteur that “chance favors the prepared mind.” In fact, several “prepared minds” lent rational and imaginative thinking to the understanding of the distinctive pathology of the PD brain and how its biochemical changes might be reversed. Highlighting these revolutionary events was the development of an animal model (reserpine-induced akinesia), which was actually more of an analogy to parkinsonism than a rigorous recapitulation of all clinical features. A key part of the research leading to levodopa as a therapy...
was emerging knowledge about how amino acids could be transferred across the blood–brain barrier (unlike dopamine, which, as a charged molecule, is excluded). When Carlsson et al. first found levodopa could reverse the akinesia in reserpinized rabbits, dopamine was regarded as no more than an intermediate in the catecholamine synthesis pathway for norepinephrine and epinephrine. Following that experiment, the Swedish neuroscientist and Nobel Prize winner Arvid Carlsson showed that dopamine was present in the brain, was depleted with reserpine, and could be restored with levodopa. Later, as dopamine’s role in central nervous system (CNS) neurotransmission became recognized, levodopa achieved the status of “...the most natural substance...for treating...the striatal dopamine deficiency syndrome.”

Like the antituberculosis drug D-cycloserine, another modified amino acid, levodopa lacks the complexity of many drugs used in modern medicine. The Swiss biochemist Marcus Guggenheim isolated levodopa from a natural source, the broad bean (Vicia faba), and characterized this compound in 1913. With curiosity as to its biological roles, he heroically self-administered a 2.5-g oral dose. This promptly caused nausea and vomiting, side effects that even today are sometimes experienced by patients. In the 1940s, D,L-3,4-dihydroxyphenylalanine as a racemic mixture (levodopa is the proper name for just the levo species) was administered to humans in experiments that investigated its effects on blood pressure and its metabolism to form dopamine. Even though levodopa can be found in trace amounts in the human brain and elsewhere in the body, no other physiologic functions have been determined for it. Levodopa lacks a nucleic acid triplet codon and does not find its way into protein formation.

Although this compound was recognized as the starting source of catecholamine synthesis, interest in levodopa as a potential therapy for PD was nonexistent until after it was utilized in the animal research experiments mentioned above by Arvid Carlsson, who was investigating reserpine’s sedative effect. Reserpine, a naturally occurring alkaloid compound derived from the snakeroot plant, was originally used in traditional medicine in India. Swiss chemists extracted the active ingredient and developed its therapeutic use in the 1950s as a powerful antihypertensive agent. The attraction of reserpine for Carlsson was its ability to deplete brain stores of serotonin. His experiments with reserpine searched for its effects on other neurotransmitters as well. In collaboration with Nils Åke Hillarp, Carlsson found that reserpine depleted norepinephrine and epinephrine in the adrenal glands of rabbits. Could this have relevance for neurotransmitters in the brain? Carlsson endeavored to determine if the tranquilizer effect of reserpine in mice and rabbits was due to depletion of serotonin or the catecholamines. In the first of a series of landmark experiments on the brain that explored behavioral and neurochemical outcomes, he studied mice and rabbits rendered immobile by reserpine. Carlsson and colleagues discovered that this motor impairment could not be attributed to depleted serotonin. Administering 5-hydroxytryptophan, the immediate precursor of serotonin, had no effect on immobility. Carlsson had used 5-hydroxytryptophan in his experiments because he was aware that a charged molecule like serotonin was unable to cross the blood–brain barrier. Using similar reasoning, he next tested racemic 3,4-dihydroxyphenylalanine, which, as an amino acid, could be transported across the blood–brain barrier by means of a sodium-dependent L-stereospecific uptake mechanism. In contrast to the absence of effect conferred by the serotonin precursor, D,L-3,4-dihydroxyphenylalanine administration rapidly and almost completely reversed the animal’s inability to move. This profound (though transient) effect was enhanced by pretreating the animals with iproniazid, a monoamine oxidase inhibitor, supporting “the assumption that the effect of 3,4-dihydroxyphenylalanine was due to an amine formed from it.” Carlsson developed a sensitive fluorescent assay for dopamine, and his doctoral students were able to demonstrate in the brains of dogs that regional dopamine concentrations were highest in the caudate and putamen (the striatum). In this region, concentrations of norepinephrine were only at trace levels.

The identity of dopamine as a major brain neurotransmitter and integral to motor function (and subsequently to behavioral function)
led to the analogy that depleted dopamine concentrations might explain the pathophysiology of PD, which in some respects resembled the behavioral deficits of reserpinized animals. At this point, there was no understanding of why this might be, especially since norepinephrine concentrations did not rise when levodopa was administered. It required another breakthrough, recognition of the regulatory step in norepinephrine production imposed by dopamine-β-hydroxylase in norepinephrine-synthesizing neurons. Once this discovery was made, the diversity of catecholamine functions in the brain became better understood as the era of dopaminergic therapeutics opened for PD. Ironically, these developments also ushered in a long period of neglect for exploring norepinephrine as a therapeutic target for PD.

Offering a functional role to dopamine was revolutionary at the time, especially since the entire pathway of catecholamine synthesis starting from phenylalanine and tyrosine had yet to be worked out (though much earlier, Hermann Blaschko identified the steps used in creating epinephrine from levodopa). Recognizing the role of dopamine and the simplicity by which its function could be restored by levodopa administration marked a turning point in the eventual discoveries that led to harnessing this drug for the treatment of PD. The variable and inconclusive initial clinical results, however, led to this idea being largely unaccepted by many neurologists. A number of scientific questions remained unsettled. Many neuroscientists raised concerns that dopamine did not meet established criteria for a neurotransmitter and felt it was merely a precursor for the other catecholamines. Furthermore, high dosage of levodopa was suspected to be a possible neurotoxin (and responsible for killing some of the animals in some experiments). Although tyrosine was suspected to be the endogenous source for levodopa, the enzyme responsible for this synthesis was not known. The rate-limiting step, tyrosine hydroxylase, was finally identified in 1964. It was largely Carlsson’s work eventually convincing neuroscientists that dopamine behaved as a neurotransmitter in brain, subserving many of the motor activities mediated through the basal ganglia (where the brain’s highest dopamine concentrations were found).

Next in the pathway for developing dopaminergic therapy of PD were the contributions of Austrian neuropharmacologist Oleh Hornykiewicz. With an interest in measuring and understanding the roles of dopamine in the striatum, Hornykiewicz wondered whether observations made in reserpinized animals corresponded to findings in the PD brain. He obtained autopsied brain specimens from people who died of PD, postencephalitic parkinsonism, or Huntington disease, and without neurologic disease, and measured dopamine and norepinephrine in a number of brain regions. Ehringer and Hornykiewicz found a striking loss of dopamine in the parkinsonian brains, in contrast to Huntington disease and control brain; the loss was particularly striking in the striatum, where the dopamine content reduction was approximately 90%. Further research determined in the upper brainstem that a small group of pigmented neurons, the substantia nigra, also had major loss of dopamine. A functional connection between the substantia nigra and striatum was subsequently recognized by histochemical imaging of axonal projections that extend between these regions.

The therapeutic dimensions of these discoveries soon became obvious to Hornykiewicz, who collaborated with Austrian geriatrician Walther Birkmayer to undertake clinical trials with L-3,4-dihydroxyphenylalanine. This was given IV in acute experiments to patients with PD and those with parkinsonism due to von Economo encephalitis. These clinical trials, which were initiated in mid-1961, involved a group of 20 patients who received levodopa at doses between 50 and 150 mg. In some instances, there were striking results, with marked improvements in mobility for some of the patients who had long been bedridden or unable to walk. The benefits became evident quickly following the injections, and for some of the patients, lasted for up to 24 hours. Unknown to these investigators were similar experiments that had been conducted 1 year earlier by a research group in Japan led by Isamu Sano. Their clinical experiment followed a similar logic to the work of Carlsson, Hornykiewicz,
and Birkmayer, in that they capitalized on their own findings that dopamine concentrations in the brain were greatest in several basal ganglia regions. Since they also determined that striatal dopamine concentration in an autopsied PD brain was very much diminished, Sano went on to conduct a trial of racemic 3,4-dihydroxyphenylalanine. In this study, the 5 patients who received 200 mg IV demonstrated what the researchers described as minimal improvements of rigidity and tremor. The report of the study did not receive attention outside of Japan at the time and, presumably because of the limited clinical benefits, this research group did not pursue further experimentation.

Other research groups, aware of the findings in reserpinized rodents, also attempted to restore striatal dopamine concentrations and relieve parkinsonian signs and symptoms using the strategy of precursor therapy. In the 7 years following the publication of Carlsson’s report, and the work of Birkmayer and Hornykiewicz, small-scale clinical investigations were carried out in Germany, Italy, Canada, Sweden, Finland, and the United States. For the most part, these studies used IV administration of either the levo or the racemic forms of 3,4-dihydroxyphenylalanine and study designs that were either open-label or placebo-controlled. Overall, the clinical results from these studies were not impressive for achieving relief of parkinsonian features. During this period, considerable basic neuroscience progress enhanced knowledge about dopamine’s role in parkinsonism. However, the therapeutic approach of administering a dopamine precursor seemed to fail and there was considerable skepticism in the early 1960s.

Birkmayer and Hornykiewicz, who made use of the levo form of 3,4-dihydroxyphenylalanine in their 1961 experiments, attempted to replicate their findings in subsequent studies. They reported on 200 patients with parkinsonian symptoms who received 25-mg IV injections of levodopa that were administered once or twice weekly (together with an inhibitor of monoamine oxidase). The results of this approach were far less encouraging than what they previously reported. They found evidence for improvement in slowed movement for only 20% of the patients. While half of them showed some reduction in clinical signs and symptoms (such as impaired speech or posture), the remaining 30% were judged not to have experienced any improvements.

The first to use high oral dosages of D,L-3,4-dihydroxyphenylalanine in patients with PD were the Canadian neuropharmacologist Patrick McGeer and neurologist Ludmila Zeldowicz in 1964. Starting with doses of 250 mg/d, they built up the dose gradually by increments of 250 mg/d until a daily dosage of 5 g/d was reached. They treated 10 patients (6 PD, 3 postencephalitic parkinsonism, and 1 arteriosclerotic) for several days, and 1 patient received 3 g/d for 3 years. Two of the patients showed some benefit. IV levodopa (250 mg) was also given to 3 of the patients, of whom only one of the 3 (a postencephalitic patient) had a beneficial response. The authors concluded that levodopa had little to offer as a therapeutic agent in the treatment of parkinsonism.

The results of studies by both Birkmayer and McGeer were particularly discouraging and might have spelled the end of attempts to treat PD with levodopa. Many experts, including Melvin Yahr and Roger Duvoisin in the late 1960s, were unimpressed with the reported results using both D,L-3,4-dihydroxyphenylalanine and levodopa. From today’s perspective, after decades of experience in recognizing the diversity of parkinsonian signs and symptoms, disorders that mimic PD, the impact of placebo effect on clinical trials, the importance of controlled experiments, and the need for testing long duration of treatment, it seems no wonder that the small doses of administered levodopa or racemic 3,4-dihydroxyphenylalanine and the insufficient trials of higher doses were doomed to fail.

Fortunately, another mindset as to the therapeutic challenge in PD brought renewed interest in levodopa. The American pharmacologist George Cotzias initiated a series of experiments with treatment strategies that differed from an approach to restore striatal dopaminergic neurotransmission. Instead, Cotzias envisioned that the treatment for PD needed to target the absence of neuromelanin pigment in the substantia nigra. This neuropathologic finding, which was also
prominent in the parkinsonian and dystonic disorder induced in Chilean miners from chronic exposure to manganese, led Cotzias and colleagues to treat a group of patients with PD with intramuscular injections of melanocyte-stimulating hormone and oral administration of phenylalanine and 3,4-dihydroxyphenylalanine (the latter 2 amino acids in racemic forms). Although their treatment hypothesis was not to replenish dopamine in the brain, their trial with D,L-3,4-dihydroxyphenylalanine showed dramatic effectiveness, in contrast to melanocyte-stimulating hormone and phenylalanine (each of which exacerbated tremor). Among 16 patients receiving D,L-3,4-dihydroxyphenylalanine for treatment periods ranging from 33 to 347 days, 8 patients showed either complete or marked improvement of rigidity and tremor. The doses used ranged from 3 to 16 g/d in divided doses. An additional 2 patients showed some improvements, and no patients worsened. Among the adverse effects were nausea, vomiting, and postural lightheadedness. Cotzias and colleagues observed that side effects seem to be more prominent with rapid increase of daily drug intake. They also found that 25% of the patients developed a mild, transient granulocytopenia in correlation to intake of more than 200 g of the drug. The salient points that differentiated this study from previous clinical experience with levodopa or D,L-3,4-dihydroxyphenylalanine are the greatly increased daily intake that was used and the sustained periods of treatment. The slow buildup of dosage seems to be the critical factor permitting an adequate test for investigation of replacement therapy.

The outcome of the initial 1967 clinical study carried out by Cotzias et al. at Brookhaven National Laboratories led to the conclusion that further studies with levodopa, instead of the racemic mixture, seemed “highly warranted.” Two years later, Cotzias et al. reported on a group of 28 parkinsonian patients treated with levodopa. The patients were first given placebo and then had levodopa introduced in a regimen of substituting levodopa for placebo gradually in dosing of 3 times per day. Initially, they received 100 mg. Subsequent dosing, as tolerated, was increased by 200–300 mg every 2–4 days. The uptitration was discontinued if optimized clinical benefit was observed or if adverse effects developed. The uppermost dosage was 8 g/d if needed. The study was laborious, requiring several months of in-hospital treatment and evaluation. The results showed at least partial improvement for most of the patients, and 10 of the 28 had “dramatic” improvement, with another 10 classified as showing “marked” improvement. The investigators classified the remainder as having “moderate” or “modest” improvement in parkinsonian signs, and every feature of parkinsonism showed some response, although not uniformly across all of the patients. To achieve these effects, the average optimal dosage was 5.8 g per day (ranging from 4.2 to 7.5 g/d).

With the high doses of levodopa used in the study came adverse effects not previously encountered. Nausea and vomiting were common but could be prevented by the development of pharmacologic tolerance with the slow titration schedule. One of the patients showed psychic changes including irritability, anger, hostility, paranoia, and sleeplessness. Others showed improvements in mental functioning that were described as an effect of psychic “awakening” (the topic of an influential book about high-dose levodopa therapy of postencephalitic parkinsonism that was published in 1973 by Oliver Sacks, *Awakenings*, followed by a Hollywood movie with the same title in 1990, based on the book). As continued exposure to levodopa was observed by Cotzias et al., involuntary movements (dyskinesias) became evident in half of them (and in some instances took on relatively severe choreic or ballistic features). During the course of their second study, the L-aromatic amino acid decarboxylase inhibitor carbidopa was developed and became available for some participants in the clinical trial. This compound, blocking peripheral conversion of levodopa to dopamine, offered a synergistic action, permitting lower doses of levodopa to be used. On this basis, the optimized intake of levodopa tended to be much lower.

The 1969 publication of clinical trial results from the Brookhaven National Laboratories
propelled levodopa into the forefront of PD research, although these findings did not completely dispel the concerns of various experts. Additional clinical trials were needed to replicate and confirm key information that arose from the published studies. Since Cotzias’ notion that levodopa could restore neuromelanin seemed out of line with neuroscience thinking of that time, further studies were guided by increasing recognition that restoring dopaminergic neurotransmission was likely the basis for the benefits—as well is the limitations—of levodopa therapy.

Next to undertake clinical research was Yahr et al. at Columbia University, whose study with levodopa was double-blind and prospective. It included some patients who crossed over between placebo and active treatment. Comprising the clinical population were 56 patients with presumed idiopathic PD, 3 patients with postencephalitic parkinsonism, and 1 patient with probable progressive supranuclear palsy. This study, published in the same year as the second report by Cotzias et al., administered levodopa 3–5 times per day, starting with a daily intake of 750–1,000 mg. The maximal dose was 8 g/d, and in the study, the optimal effect for some patients was that dose or as low as 3 g/d. The study results confirmed the dramatic improvement of parkinsonism previously reported by Cotzias et al. In the study by Yahr et al., improvement was “marked” or “complete” for two-thirds of the patients. Only 4 of the patients were reported not to have any benefit. The greatest response rate was for rigidity and, to a lesser extent, for tremor and akinesia. Nausea and vomiting were common side effects, especially during the first days of treatment; these problems tended to be self-limited and were less frequent among patients also receiving anticholinergic drugs. Other adverse effects included symptomatic postural hypotension (affecting 14 of the patients) and self-limited anorexia (affecting 19 patients). Other problems included cardiac arrhythmias, various psychic manifestations, and dose-related dyskinesias (the latter affecting 37 of the patients, most frequently occurring after prolonged administration of relatively high doses of levodopa). The impact of the study was verification of levodopa as a remarkable symptomatic treatment for disabling parkinsonism, but also emphasizing that this therapy was not without limitations imposed by a variety of adverse effects.

The results of the trial by Yahr et al. opened the support of the pharmaceutical industry to make this compound available (using a newly developed chemical chirally-specific synthesis methodology that would one day help to win a Nobel Prize). Linked to the further development of levodopa was the coadministration of carbidopa or another inhibitor of peripheral L-aromatic amino acid decarboxylase, benserazide. Each greatly reduced many of the adverse effects and permitted easier introduction of the drug by clinicians.

Now almost a half-century after levodopa proved its worth for symptomatic relief of parkinsonism, it might seem hard to believe that the birth of such a useful therapy could be so slow and challenging. The next decade, after studies by Yahr et al., brought optimal therapeutics with levodopa into greater clarity. In 1970, levodopa achieved approval by the Food and Drug Administration in the United States. Its adoption as the major therapy for PD became worldwide shortly thereafter. Despite the development of drugs that mimic the actions of dopamine (dopaminergic agonists, of which more than 2 dozen have undergone clinical trials), levodopa therapy remains the most effective treatment for all stages of PD. The medical literature pertaining to levodopa therapeutics is extensive. The table provides a listing of major reviews and symposia pertaining to levodopa therapeutics in the first 2 decades following its initial development.

Overall, thousands of studies and other reports have documented the benefits and limitations of levodopa. It might seem that modern neuroscience, by now, should have developed a thorough understanding of how levodopa works. The latter question might seem curiously naive, since medical students are regularly educated with the dogma that this amino acid acts after it is decarboxylated into dopamine, replenishing the deficient neurotransmitter in the PD striatum. While there
is no question about this mechanism, the pharmacologic identity of levodopa, as shown in recent research findings, is more complex than this. Various clinical phenomena such as the development of dyskinesias and the loss of the long-duration response are not readily explained by the simple concept of levodopa as a dopamine precursor. A large clinical trial (the ELLDOPA study) raised questions as to the possibility that levodopa might have disease-modifying properties, though the study’s clinical and neuroimaging endpoints were at odds with each other.

Basic neuroscience research into the mode of action for levodopa has reported some unique physiologic actions. Levodopa serves as a Ca\(^{2+}\)-dependent “classic” neurotransmitter in several brain regions. It also acts in the CNS to downregulate L-aromatic amino acid decarboxylase. Another intriguing finding has been that levodopa is converted nonenzymatically to several biologically active compounds. One of these is 2,4,5-trihydroxyphenylalanine (TOPA), which, like its quinone conjugate, is an excitotoxin and can initiate various neuronal responses in dopaminergic pathways unrelated to stimulation of dopamine receptors (such as activating neuronal firing, inward current flux, and membrane depolarization). The actions induced by TOPA and TOPA-quinone could be blocked by administration of a glutamate antagonist. The relevance of these and other findings from studying levodopa pharmacology in the rodent brain merit further exploration in understanding clinical phenomena experienced by the patient with PD.

Looking forward to a future of improved levodopa therapy, many challenges need to be overcome. Once patients lose the initial long-duration response to this drug, its peripheral pharmacokinetics govern clinical responses. As a result, irregular absorption and the drug’s rapid peripheral clearance impose motor fluctuations, and patients can experience considerable “off” time despite regular dosing. Prolonged delay in uptake of this medication as well as sensitivity to dietary intake can add to the problems of living with PD. Peak effect involuntary movements and wearing-off dystonic phenomena as well as nonmotor fluctuation experiences are matters that patients (and their clinicians) can struggle with after just a few years of therapy.

Fortunately, the pharmaceutical industry has risen to the challenge of creating alternative ways to deliver levodopa in order to improve clinical responses. One example is infusion of a microsuspension of carbidopa-levodopa intestinal gel, introduced in Sweden in the 1990s. The pharmacokinetic principles underlying the variability in levodopa’s pharmacodynamics have become increasingly understood in the past decade. Products currently under development for more sustained levodopa effect include gastric retentive formulations, extended-release microspheres controlling drug release, a levodopa prodrug linked to nutritional molecules, and...
formulation for inhalation uptake through the lungs, and solubilized levodopa for continuous subcutaneous infusion. Each of these products is targeted against currently unmet needs with levodopa and might become realities in the next few years. It seems unlikely that levodopa will ever be replaced in the future, only improved upon.

DEDICATION The authors dedicate this article to the 2 surviving pioneering researchers who made the development of levodopa therapy possible: Avid Carlson and Oleh Hornykiewicz.

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