The Story of Levodopa: A Long and Arduous Journey

Kalyan B. Bhattacharyya
Department of Neurology, Apollo Superspecialty Hospital, Kolkata, West Bengal, India

Abstract

Levodopa (L-dopa) is the gold standard in the management of Parkinson’s disease (PD). It dates back to 1500 to 1000 BC when it was used in the Indian Ayurvedic and Chinese system of medicine. Certain beans such as velvet beans and broad beans contain L-dopa. The plant Mucuna pruriens (Mp) or velvet bean, cultivated in Eastern India and Southern China, contains L-dopa at a concentration of 5% and was used for the management of PD. Later, workers have documented the neuroprotective, neurorestorative, and immunomodulatory properties of Mp. Double-blind studies conducted in the Western world have proved the efficacy of Mp and reported some toxic side effects as well. In the Western world, the credit for isolating L-dopa from the seeds of Vicia faba or broad bean goes to Markus Guggenheim, a biochemist from Sweden in 1913. However, it has been used with success ever since Arvid Carlsson established the reversibility of reserpine-induced akinesia in rabbits in the late 1950s with the use of intravenous dopamine, and Oleh Hornykiewicz demonstrated its deficiency in the striatum in 1960–1961. George Cotzias used it in patients in a low and slow incremental fashion in 1967, and Melvin Yahr and his colleagues performed double-blind study on in-patients with success in 1969. Complications with its long-term use, particularly the on-off phenomenon, and dyskinesias appeared soon, and measures have been undertaken to reduce their incidence. Researches on alternative modes of delivery are carried out in various centers, and others are under investigation in the laboratories.

Keywords: Complications, later researches, Mucuna pruriens, newer drugs, Parkinson’s disease

INTRODUCTION

Levodopa (L-dopa) is the gold standard in the management of PD. The story of this wonder drug dates back to 1500 to 1000 BC in the Indian Ayurvedic system of medicine.\[1,2]\] The plant Mucuna pruriens (Mp), often known as the velvet bean, a climbing legume, was cultivated in southern China and eastern India.\[2]\] The genus Mucuna contains L-dopa in concentration of around 5% and has been used in ancient India for the management of PD.\[1,4]\] The system of Ayurvedic medicine conceptualized the human body as an amalgam of three basic elements, Vata, controlling the brain and the mind, Pitta, for the digestive system and metabolism, and Kapha, concerned with growth.\[5]\] In the Ayurvedic texts, there is mention of Kampavata, Kampavata, tremor due to Vata or problems in the brain or the mind, whose clinical features resemble those of PD.\[1]\] One symptom described includes Vishada, or depression, now recognized as a common presentation of PD, at times even antedating the motor symptoms.\[5]\] Another study carried out by Yadav et al.,\[6]\] compared the neuroprotective effect of Mp vis-à-vis estrogen, a known neuroprotective agent, for PD in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model. The effect was noticeably better in the first group. It downregulates nitric oxide production, neuroinflammation, and microglial activation which contribute to neuroprotection, presumably by the decrease in oxidative stress and prompting neuronal and glial crosstalk. Others have documented its neurorestorative properties on the nigrostriatal tract of 6-hydroxydopamine-lesioned rat models, and it significantly increased the cerebral mitochondrial complex-I activity.\[7]\] Rai et al.,\[8]\] suggested that Mp may work as an immunomodulatory agent. Nigrostriatal degeneration is caused by inflammation, and the cascade begins with the aggregation of misfolded α-synuclein. This leads to the activation of microglia and astrogliosis and the production of proinflammatory cytokines like tumor necrosis factor-alpha, interleukin-1 beta, IL-6, and other enzymes. Mp protects or even prevents the progression by altering these cytokines. A double-blind, randomized, controlled, crossover study by western workers like Cilia et al.,\[9]\] in 2017 concluded that only one high dose of Mp was similar in efficacy to levodopa used for some time, and the degree of motor improvement was greater at 90 and 180 min. Additionally, the latency to pass to the on-stage was shorter and was prolonged by about 45 min. Adverse effects like dyskinesias were also lesser in degree. It has also been shown that the incidence of dyskinesias was higher when a dopa-decarboxylase inhibitor was added to L-dopa and this may explain its lesser incidence with Mp which does not

Address for correspondence: Prof. Kalyan B. Bhattacharyya, Amrapali Point, Flat 1C, 59F, Bosepukur Road, Kolkata - 700 042, West Bengal, India.
E-mail: kalyanbrb@gmail.com

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contain it.\[10\] One report published in 2015 from Spain reported the toxic dopaminergic effects of *Vicia faba.*

‘A 73-year-old man had a 10-year history of PD. He was being treated with L-dopa plus carbidopa and cabergoline. Family members brought him to the emergency department. When he suddenly displayed involuntary movements, motor agitation, nausea, profuse sweating, and aggressiveness. Examination revealed choreic movements of the limbs, trunk, and neck, accompanied by cervical dystonia, profound sweating, tachycardia, anxiety, nausea without vomiting, and some level of verbal aggressiveness. Doctors asked the patient and his family about his eating habits. They responded that he had eaten broad beans.’\[11\]

Though L-dopa was first synthesized in 1911 by the Polish biochemist Casimir Funk (1884–1967), the credit for isolating it from the seeds of *Vicia faba* goes to Markus Guggenheim (1885–1970), a biochemist from Sweden in 1913.\[2,12\] Guggenheim himself consumed it and vomited violently. He shelved his idea and later, in his celebrated treatise, *Die biogenen Amine,* he devoted only two pages to his own discovery.\[13\] Sir Henry Dale, the peerless neuropharmacologist and the Nobel Laureate for the year 1936, suggested the name, *dopamine* (DA). In 1939, Peter Holtz (1902–1970) from Germany discovered the enzyme, *dopa decarboxylase,* in the mammalian kidneys which converts L-dopa to DA, the biologically active amine in the brain. This was followed in the same year by the works of Hermann Blaschko (1900–1993), a biochemist from Oxford, who worked on the biosynthesis of L-dopa from tyrosine and its conversion to DA and catecholamines;\[13\] Hasama in 1930 and Oleh Hornykiewicz in 1956 demonstrated that even a small dose of L-dopa led to postural hypotension, a common problem encountered in our day-to-day practice. Goodall isolated L-dopa from the adrenal medulla in 1950 and in the following year Raab et al., observed the presence of a catecholamine-like substance in the brain of many species, including humans.\[3,14,15\] Since then, L-dopa has been isolated by Weil-Malherbe, Montagu, and Bernheimer, among others, from pheochromocytoma, and tumors of the iris and choroid.\[3,16\]

**Systematic Study of L-dopa in the Western World in the 1960s**

After these primitive works on L-dopa in the Western world, Arvid Carlsson (1923–2018) from Sweden carried out some remarkable works in the 1950s and early 1960s. Carlsson had been investigating the mechanism of the antihypertensive effect of reserpine at the National Institute of Health, Bethesda, the USA. It was already documented that a dose of injection of reserpine lowered the level of serotonin in the brain, and it was speculated that its antihypertensive action was hyposerotonergic in effect.\[17\]

However, Carlsson felt that the action was brought about by catecholamines, and it was observed that L-dopa was present in the highest concentration in the basal ganglia. Following his return to Sweden, he set up his own laboratory at the University of Lund, and in 1957 he showed that following the administration of reserpine in rabbits there was complete disappearance of norepinephrine from the adrenal medulla and the brain. Additionally, the akinetic effect of reserpine resembled the clinical picture of parkinsonism which was quickly reversed by L-dopa. Incidentally, the precursor of serotonin, 5-hydroxytryptophan, had no such effect.

Below is the set of the famous photographs of the pair of rabbits, reserpinized and rendered immobile, [Figure 1] whereas the one below shows the alert ones with the use of L-dopa [Figure 2] by Arvid Carlsson, M Lindqvist, and T Magnusson, which Carlsson showed in his Nobel Lecture entitled, ‘A half-century of neurotransmitter research: impact on neurology and psychiatry’ at Stockholm in 2000.\[18\]

Carlsson wrote to Stanley Fahn and Andrew Lees, two legendary experts on PD in recent times, ‘I submitted it in 1957 together with my manuscript to Nature and the paper was accepted. The earliest publication of this picture is probably the one to be found in the proceedings of a meeting. But, the proceedings were published as late as 1960’…

Carlsson devised a fluorescent assay method to measure DA in the brain and observed that the striatum was rich in this substance.\[19\] Sano from Japan confirmed similar results in the human brain.\[20\] These experiments led Carlsson to conclude that reserpine depleted the DA store, and its deficiency was implicated in the development of the motor features, resembling PD. He presented his work entitled, ‘On the biochemistry and possible functions of dopamine and noradrenaline in the brain’ in London in 1960, but the reception was lukewarm. Andrew Lees, Eduardo Tolosa, and Warren Olanow wrote in a scholarly article in *Movement Disorders* in 2014, that the much-venerated Henry Dale was not convinced about Carlsson’s observations and commented that DA had not yet fulfilled the criterion for a neurotransmitter.\[21\] He felt that the actions were possibly

![Figure 1: Arvid Carlsson (1923–2018) ![](Image 378x74 to 495x250)
attributable to L-dopa being a ‘mysterious brain toxin and when combined with a monoamine oxidase inhibitor led to excitation and could be lethal.’[21]

When Carlsson’s attempt to establish his hypothesis met with criticisms, Falck et al.[22] from Sweden, carried out some histochemical works which confirmed the localization of monoamines in the brain and its pathways. In spite of the fact that in 1963, Hugh McLennan expressed an identical view that ‘no definitely ascribable adrenergic synapse has been detected in the vertebrate central nervous system’, Uvnas in 1965 stated in a symposium in Stockholm that catecholamines play a pivotal role in the central nervous system as a chemical mediator (personal communication from A. Carlsson to A. Lees).[21]

Undeterred, Carlsson met Lars Leksell (1907–1986) at Lund who was the inventor of radiosurgery. Like others, Leksell was not fully convinced, while the next endeavor to impress Tore Broman, Professor of neurology at Gothenburg, met with similarly frustrating results.[22]

In 1967, Carlsson watched a film that showed the results of the low and slow increment of L-dopa by George Cotzias in New York. On returning to Lund, he met Alvar Svenborg, a geriatrician, and finally, they were able to prove the dramatic results of L-dopa.[21] Thus, Carlsson’s life-long conviction that the loss of DA is the chief culprit in the genesis of PD was finally vindicated, and his contributions were recognized with the conferring the Nobel Prize in 2000. In his lecture at Stockholm during the 19th conference of the International Parkinson and Movement Disorders Society in June 2014, his take-home message was ‘Do not give in; stick it out.’[21]

Oleh Hornykiewicz (1926–2020), a young neuroscientist from Austria, returned to Vienna from Oxford in 1958 [Figure 3]. He worked on DA and observed its high concentration in the striatum. With his assistant Herbert Ehringer (1932–), he decided to study the DA content in the brain in patients with PD, postencephalitic parkinsonism, and Huntington’s disease (HD). They reported DA deficiency of 90% in PD and postencephalitic parkinsonism, whereas it was normal in HD.[24] He postulated that most of the major motor symptoms of PD were related to the deficiency of DA, and the symptoms appeared after an 80% reduction of DA in the nigral cells.[23,24]

The response to Hornykiewicz’s works was tepid. For instance, Derek Denny-Brown, the eminent neurologist from Boston, and Rolf Hassler, an anatomist from Frankfurt, repudiated his claims and denounced the idea of an ascending nigrostriatal dopaminergic system.[21]
Further explorations into the biochemistry and histopathology of dopamine and thereafter

In spite of the brilliant works by Carlsson and Hornykiewicz, the concept of DA and PD was muddled by the lack of any clear association between the reduction of nigral DA content and the loss of DA-ergic neurons in PD. In order to settle this incongruity, Carlsson wrote a letter to Nils Åke Hillarp, and they acquired a spectrophotofluorimeter that helped to visualize the localization of cellular biogenic amines. Their work was presented at a symposium in New York in 1965. They proposed that the DA-containing cell bodies were localized in the substantia nigra and they spread their fibers to the caudate nucleus and putamen. Around this time, Theodore Sourkes and Louis Poirier, a neurochemist and neuroanatomist, respectively, carried out experimental works in Montreal and showed that lesioning of the substantia nigra led to the deficiency of DA.

As stated before, Guggenheim carried out the first human experiment on the use of levodopa in the Western World in 1913. However, it is interesting to note that in 2010, Hornykiewicz, in a review article entitled, “A brief history of levodopa,” in the Journal of Neurology, wrote that it was first isolated from the beans of Vicia faba in 1910-1911, by Torquato Torquatirid. He did not allude to Mucuna pruriens practiced in ancient India and China, presumably because he had little access to Sanskrit and Chinese literature. Oster and Zorkin from Mount Sinai first injected L-dopa to human beings in 1942 only to observe that it led to hypotension and vomiting, as Guggenheim observed on himself. McGeer and his colleagues from Vancouver started using high doses of L-dopa to patients with Parkinsonism induced by reserpine or phenothiazines and observed mild improvement in the former group. Sano used 200 mg of L-dopa intravenously in 1960 and reported improvement which lasted only for a few minutes. In 1961, Hornykiewicz collected L-dopa and urged upon his associate, Walther Birckmayer (1910-1996), to carry out trials on 20 patients with PD and postencephalitic parkinsonism. They injected it in gradually incremental dosage in strengths of 50 mg, 100 mg, and 150 mg. In the third group, there was a marked improvement in hypokinesia. They treated more than 200 patients along with isocarboxazid, a MAO-inhibitor, and by 1964 the results showed that in about 20% of patients there was lasting relief for about 3 h. In an interview with B Sommer, a geriatric psychiatrist, he said, “. Bedridden patients who were unable to sit up, patients who could not stand up when seated, who when standing could not start walking, performed these activities with ease. The drug worked from the first dose, and its beneficial action from bradykinesia was reported to last from 3 to 24 hours. Pretreatment with the monoamine oxidase inhibitor isocarboxazid, considerably prolonged the anti-akinetis effect.”

The response to Hornykiewicz and Birckmayer’s works was equally indifferent. Derek Denny-Brown commented, ‘You have presented reasons against the common assumption that lesions in the substantia nigra are responsible for parkinsonism’, whereas Rolf Hassler from Frankfurt said, “The interpretation of your observations does not agree with many known facts about the direction of the nigrostriatal connections.” Mettler wrote, “The attribution of such a complex clinical syndrome to a rather small and homogeneous structure has not appeared logical,” whereas Bertler and Rosengren said, “The effect of L-dopa is too complex to permit a conclusion about disturbances of the striatal system in Parkinson’s disease.” Jasper’s comments were acerbic, and he wrote that “L-dopa is the right therapy for the wrong reason,” and even Arvid Carlsson was not far behind in snide remark and said, “. not possible to draw any conclusion about the relative importance of dopamine. for the central effects. Roger Duvoisin stated, “Despite enthusiastic claims of therapeutic benefit, no evidence has been presented that DOPA effects are in any way specific.” The issue was getting so convoluted with growing controversies, that in 1965, even Hornykiewicz had to concede that possibly L-dopa did not have a potential future.

Much later in 2010, when L-dopa was firmly established as the drug of choice in PD long ago, Hornykiewicz wrote, “. one would have expected unanimous support. This was indeed the case with the vast majority of clinical neurologists, but not the rule among the basic brain scientists. Among those strongly critical of DA and levodopa were the best minds of the contemporary neuroscience.”

André Barbeau (1931–1986) from Montreal observed a lower level of urinary DA in PD and started treating patients with L-dopa with improvement in some patients in 1961. Many similar works were undertaken in Europe and the USA where the investigators tried to assess the outcome but without much success.

Later, when DA was found to be useful for the management of PD, the world of neurology found it hard to accept the fact that when the Nobel Prize in 2000 was awarded to Carlsson, Hornykiewicz was overlooked. More than 250 eminent neurologists wrote to the Nobel Committee, expressing their disappointment. However, Hornykiewicz stated politely that scientists take to investigative studies not in order to win prizes and receive universal recognition though he regretted that the Nobel Committee was amiss in their assessment that Carlsson was the chief architect in discovering low DA content in the brain in PD. True to what he said, Hornykiewicz and his team were the scientists behind this fundamental discovery.

Use of the incremental high dose of L-dopa and George Cotzias: A remarkable breakthrough

In 1964, McGeer and Zeldowicz were the first neuroscientists to use oral L-dopa and increased it to 5 gm per day with time though the response was transient.

However, in 1967, it was George Cotzias (1918–1977, USA), who undeniably proved its efficacy [Figure 3]. He used
L-dopa in a small dosage, increased it slowly, and carried on the treatment for a long duration, ultimately attaining the dose of 12 gm per day. He published his observations in the New England Journal of Medicine in 1967, and thereafter, an exhaustive report titled, “Modification of parkinsonism: chronic treatment with L-dopa,” appeared in 1969 in the same journal, where he described the appearance of some involuntary movements.[33,34] He wrote that of the 28 patients studied, there were various grades of improvement which was sustained for 2 years. Thus, as Fahn wrote, “Despite the lack of benefit by McGeer, he had the right idea – building up the dose slowly to replace missing DA in the brain. In contrast, Cotzias gave to (supposedly) repigment the brain. So, Cotzias gave dopa for the wrong reason but got the right result, and the laurels go to him.”[35]

It is pertinent to question why Cotzias’ method of using the low and slowly incremental dosage of L-dopa was a success. A cogent argument was that he did not use it in order to dramatically increase the level of dopamine in the striatum; rather, his hope was to replenish the lost melanin in the substantia nigra, which he felt, was the cause of PD.[36] In his seminal paper in 1969, he wrote that one of the biochemical abnormalities in PD was the decrease in melanin in the substantia nigra and this might be interrelated because tyrosine is hydroxylated to dihydroxyphenylalanine, a precursor for the synthesis of melanin and catecholamines in the melanosomes. He surmised that the interrelation between melanogenesis and PD was of fundamental importance.[37] This view was endorsed by David Marsden of (1938–1998), one of the most influential experts in movement disorders in the latter half of the last century. In his Robert Wartenburg Lecture delivered before the American Academy of Neurology in 1982, he said, “I stepped sideways from the mainstream of medical education into the research laboratory to try to discover why the substantia nigra was black! In my naiveté, I thought that this must constitute some key to the function of this region of the brain and I even believed, that neuromelanin holds the key to the cause of Parkinson’s disease.”[38] However, in spite of the improvement in the symptoms of PD, the works of Cotzias were also not immediately recognized, as had been the case with the previous investigators. In fact, Melvin Yahr and Roger Duvoisin, unquestionable experts in PD, wrote in 1968, ‘Fahn S et al., (1967) have reported oral administration of L-dopa in dosages of up to 16 gm per day. However, there has also been an appreciable incidence of undesirable side effects. Though undoubtedly at this dosage a sustained effect can be obtained, the role of dopa is far from established.’[39]

Fahn made an interesting remark that when Cotzias presented his observations at a symposium in Montreal in 1967, Carlsson and he himself were present there and were impressed. By this time, Duvoisin and Yahr too had shed their doubts and endorsed the therapeutic effect of L-dopa. Thereafter, Duvoisin visited Cotzias’ laboratory to witness the patients under trial and returned to Columbia, content with the work.[35] Such was the impact of Cotzias’ work on the effect of L-dopa that Irving Cooper, the celebrated American neurosurgeon, who demonstrated amelioration of PD following accidental ligation of the anterior choroidal artery in 1953 declared that surgical procedures be postponed for at least 1 year.[35]

On the slow and incremental dose of L-dopa, Cotzias wrote, “We recognized that the oral route of administration must be used. We defined our needs as follows: to saturate, either or both the enzymes, dopa decarboxylase and the melanin-forming enzymes, i.e. tyrosinase, within the brain. This simplistic notion confirmed... with the method used by biochemists wishing to saturate an enzyme with substrate. They do this by gradually increasing the amounts of the substrate presented to the enzyme.”[21]

Melvin Yahr and Double-Blind Study on Dopamine

Melvin Yahr from Mount Sinai decided to carry out a double-blind study of L-dopa on PD patients [Figure 5]. He recruited 60 patients, (56 had PD, 3 of postencephalitic parkinsonism, and 1 suffering from progressive supranuclear palsy). They were hospitalized for a period of 4 to 12 weeks and were on 5 to 10 tablets per day. The placebo group received one tablet in a daily dosage of 750 mg to 1 gm. The placebo tablets were gradually replaced by 0.5 gm of L-dopa every 28 to 48 h until an optimal therapeutic response was observed, and a total dose of 8 gm per day was administered, or till side effects appeared. L-dopa was rapidly withdrawn in 9 patients, replaced by a placebo, and the patients were clinically examined by two independent observers every day. The patients were followed up for 4 to 12 months, and 49 subjects showed considerable improvement. Yahr et al.[39] concluded that L-dopa was an effective drug and was superior to all other modalities prevalent at that time.

Close on the heels of Cotzias many other workers performed open-label trials, met with success to a varying extent, and it was finally approved by the USA Food and Drug Administration in 1970. In 1973, Bernheimer et al.[40] noted morphological and neurochemical correlations in the dopamine level in PD treated with L-dopa and 2 years later, Lloyd and his
colleagues from Canada analyzed brain tissue in postmortem studies in PD subjects treated with L-dopa and controls. There was a 9- to 15-fold increase in L-dopa concentration in the substantia nigra in the former group.\[40,41\]

Late Complications of L-Dopa Therapy

The issue of the complications with the use of L-dopa therapy was recognized after a few years of its clinical use in the late 1960s. In 1969, barely 2 years after its introduction in clinical practice, Cotzias himself observed that in spite of the improvement of symptoms in a series of 28 patients, certain unwanted side-effects such as various involuntary movements and freezing of gait were beginning to appear.\[44\] In 1976, Marsden and Parkes surmised that early morning akinesia, freezing, and end-of-dose phenomenon were probably the result of the progression of the disease, peak dose dyskinesia due to excessive dosage of L-dopa, and yo-yoing was possibly the outcome of the total of these problems.\[45\] On-off fluctuations usually appear after 1 to 3 years of therapy in about 15% to 40% of subjects, though Barbeau et al., and others reported that after 5 to 10 years of treatment, more than 50% of the patients develop this complication.\[43\]

Other propositions include the formation of dopamine metabolites such as tetrahydroisopapaveroline, which may act as a partial dopamine agonist, blocking the action of L-dopa, or intake of protein in the diet, which competes with L-dopa uptake from the gut. These complications were commonly seen in the advanced stages of the disease and in young-onset subjects. In 2017, Obeso et al.,\[46\] and other experts on PD wrote in a classic paper that dyskinesias can be of various natures like on-period dyskinesias, off-dystonia, and diphasic dystonia. Peak-dose dyskinesia is characterized by involuntary head-bobbing stereotypy in the head and neck, choreiform movements in the trunk, or ballistic movements in the limbs. Diphasic dyskinesias present as parkinsonism-dyskinesia-improvement-dyskinesia-parkinsonism. Typically, dyskinetic movements appear as unilateral stereotypy in one leg. Thereafter, it spreads to the other leg within 15 min, followed by improvement in the symptoms.

This lasts for several hours and dyskinesias return as the blood level of L-dopa declines. Finally, there is the reappearance of the PD picture. Off-period dystonia usually appears in the early morning when the blood level of L-dopa wanes and is manifested as painful spasms of the muscles, inversion of the feet, and flexion of the toes. Another variety of rare dyskinesia is paroxysmal in nature which takes place irrespective of the “on” or “off” period, and it is known as the “yo-yo” response.\[44\]

Non-motor “off” period features include wearing-off anxiety, depression, and sweating.\[45\]

Apart from the severity of the disease and the duration of therapy, the other important factors for the genesis of these complications are the increasing dose of L-dopa and the nonphysiological and pulsatile nature of L-dopa administration.\[44\]

Newer modes of delivery of L-Dopa, like sustained-release preparations, intraduodenal infusions,\[40\] nasal and subcutaneous L-dopa,\[47\] micro tablets and electronic dose dispenser,\[48\] DM-1992,\[49\] accordion pill,\[50\] and other modalities have recently been tried out with some success.

In summary, Carlsson observed the ameliorating effect of L-dopa on reserpine-induced rabbit’s symptoms, Hornykiewicz demonstrated the deficiency of DA in the substantia nigra, Cotzias proved its efficacy by using in slow and incremental dosage, whereas Yahr replicated Cotzias’ work by double-blind studies in the inpatients. Indeed, these are the four masters, as Andrew Lees, Eduardo Tolosa, Warren Olanow, and Stanley Fahn, mentioned in two classic articles.\[51,52\] Later workers devised the controlled-release preparations, parenteral intraduodenal gel, intranasal, subcutaneous therapy, and other novel modalities, which helped further in the alleviation of the problems in PD patients. However, one shall be amiss if others such as Markus Guggenheim, Herbert Ehringer, Walther Birkmayer, and Roger, among others are not paid obeisance and remembered.

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Conflicts of interest

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