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THE EFFECT OF DOPAMINE AGONISTS ON PATIENTS WITH ADVANCED PARKINSON'S DISEASE SUBJECTED TO SUBTHALAMIC DEEP BRAIN STIMULATION

By

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Submitted in partial fulfillment of the requirements
for the **Doctor of Pharmacy** degree

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To all patients with Parkinson's disease

TABLE OF CONTENTS

PART II: A PROMISING THERAPEUTIC APPROACH UNDER INVESTIGATION: DOPAMINE AGONIST MONOTHERAPY AFTER SUBTHALAMIC STIMULATION IN ADVANCED PARKINSON'S DISEASE

ABBREVIATIONS

AADC = L-Amino-acid decarboxylase.
BBB = Blood-brain barrier.
BDNF = Brain-derived neurotrophic factors.
CAT = Catalase.
COMT = Catechol-O-Methyltransferase.
DBS = Deep brain stimulation.
DDI = Dopa decarboxylase inhibitor.
DOPAC = 3,4- Dihydroxyphenylacetic acid.
FDA = Food and Drug Administration.
GABA = Gamma-aminobutyric acid.
GDNF = Glial-derived neurotrophic factors.
GPe = Globus pallidus externa.
GPi = Globus pallidus interna.
GSH =Glutathione.
H&Y = Hoehn & Yahr scoring scale.
HVA = Homovanillic acid.
LD = Levodopa.
LDR = Long-duration response.
LEDD = Levodopa-equivalent daily dose.
LID = Levodopa-induced dyskinesia.
MAO_B = Monoamine Oxidase type B.
MPP^+ = 1- methyl-4 phenylpyperidine.
MPTP = 1- methyl-4-phenyl-1,2,3,6-tetrahydropyridine.
MSA = Multiple system atrophy.
NMDA = N-methyl-D-aspartate.
PD = Parkinson's disease.
PSP = Progressive supranuclear palsy.
SDR = Short-duration response.
SEM = Standard error of the mean.
SNPC = Substantia nigra pars compacta.
SNPR = Substantia nigra pars reticulata.
SOD = Superoxide dismutase.
STN = Subthalamic nucleus.
STN HFS = Subthalamic nucleus high frequency stimulation.
UCH-L1 = Ubiquitin carboxy-terminal hydroxylase L1.
UPDRS = Unified Parkinson's Disease Rating Scale.
VA = Ventral anterior.
Vim = Ventral intermediate nucleus.
VL = Ventrolateral.

LIST OF TABLES

LIST OF FIGURES

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THE EFFECT OF DOPAMINE AGONISTS ON PATIENTS
WITH ADVANCED PARKINSON'S DISEASE
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ABSTRACT

by

MAZEN G. JABRE

Parkinson's disease (PD) is a neurodegerative disorder predominantly characterized by the progressive loss of dopaminergic cells in the substantia nigra pars compacta (SNPC). Striatal dopamine concentration gets significantly reduced, and clinical symptoms, especially the motor handicap, prevail.

The management of this disease is symptomatic, mainly based on the use of levodopa. Due to the high incidence of adverse effects associated with its chronic use, alternative treaments based on the direct-acting dopamine agonists have been used. Deep brain stimulation has been proposed as an alternative effective treatment for advanced PD cases disabled by the high incidence of levodopa-induced motor complications.

High frequency stimulation of the subthalamic nucleus (STN HFS) alleviated the severe motor disabilities associated with PD; however, a postoperative pharmacological strategy has not been established yet. The following study reports and investigates the efficacy, safety and tolerability of a postoperative therapeutic approach mainly based on dopamine agonists.

We run a pilot, prospective, and open-label study on five patients with severe idiopathic PD who underwent STN HFS. Their postoperative management mainly consisted of dopamine agonist, while levodopa was considered as a rescue therapy. Efficacy, safety and tolerability outcome measures were determined 12 weeks after

surgery using the Unified Parkinson's Disease Rating Scale motor part (UPDRS-III), UPDRS part IV (complications of therapy) and the Hoehn and Yahr staging scale. Three months after surgery, all patients were effectively maintained on dopamine agonist-based therapy with an 88% improvement in UPDRS motor subscore ($p < 0.01$). Dyskinesias, motor fluctuations, and levodopa-equivalent daily dose requirements decreased by 82.35%, 82.14%, and 77%, respectively ($p<0.01$). The mean levodopa dose was reduced by 90% ($p < 0.01$), while the mean dopamine agonist dose was increased by 15% from preoperative level. Reported adverse events were mild and transient.

Our preliminary study suggests that STN HFS is a safe and effective approach in the treatment of advanced PD. Postoperative dopamine agonist monotherapy can potentially be proposed in controlling residual motor disability before adding levodopa.

INTRODUCTION

Parkinson's disease first description dates back to 1817 when James Parkinson saw several people on the streets of London who were walking slowly, taking short, shuffling steps, and trembling, and decided to be the pioneer in lucidly describing this disorder in his *Essay on the Shaking Palsy*. [1]

Parkinson's disease (PD) is a progressive neurodegenerative disorder that occurs in different word regions, all ethnic groups, and both sexes with a slightly more dominance among males (men to women ratio around 3:2). [2] The annual estimated incidence of new cases of PD is 20 per 100,000 [3] of the total population, with a mean age of onset of 55 years. [4] The rate of case prevalence increases with age to reach five cases per 1000 in the population older than 50 years and one per ten over the age of 80 years. [5,6] In the United States, it is the commonest neurodegenerative disease after Alzheimer's disease, [3] and the projected leading cause of death among the elderly by the year 2040. [7]

More than 180 years of its first description, the complete pathogenesis of this disorder remains a medical enigma, hampered by the complexity of neurological functions and biological findings, and its diagnosis mainly clinical often confused with other neurodegenerative disorders. Managing PD is symptomatic and its planning has always raised controversies among scientists trying always to delay the emergence of motor complications after years of pharmacological therapy. Once present, the quality of life acutely worsens and new medical challenges arise.

This manuscript will extensively review the medical literature shedding the light on current findings in PD, and present a newly settled clinical investigation questioning the possibility of a new genesis and better future in advanced PD.

PART I: PARKINSON'S DISEASE IN THEORY AND PRACTICE:CURRENT CONCEPTS AND THERAPEUTIC CONTROVERSIES AND LIMITATIONS

1. CLINICAL AND PATHOLOGICAL FINDINGS

1.1 Etiopathogenesis

Despite the universal propensity of PD, its prevalence has been linked to multiple extrinsic, intrinsic, and/or genetic risk factors, but the exact etiology remains unknown. Recreational exposure to 1-methyl-4-phenyl-1, 2,3,6-tetrahydropyridine (MPTP) for approximately 14 days engendered the permanent experience of the classical PD signs and symptoms. [8] Other environmental toxins with MPTP-like properties, such as some herbicides and pesticides, metals, such as copper, manganese, iron-copper/lead combinations have been significantly associated with PD. [9] Another study detected substantial amount of endogenous cytotoxic factors in the cerebrospinal fluid of PD patients. The nature of these factors remains, however, unidentified. [10]

In contrast, smoking has consistently been correlated with a reduced risk of PD [11] especially in patients with a relatively young age at the onset of disease. [12]

Recent studies have focused on the genetic component in idiopathic PD. Population-based epidemiological studies have found more than a two-fold increase in developing PD in first degree relatives of patients compared with controls. [13]

Mutations in the alpha-synuclein gene on chromosome 4, parkin gene on chromosome 6, and ubiquitin carboxy-terminal hydroxylase L1 (UCH-L1) gene have been more associated with an early onset PD. [3,14]

Whether PD is caused by any of the above cited speculated etiologies, or their combination remains unknown; nevertheless, it is always defined and clinically diagnosed by a specific set of symptoms.

1.2 Clinical Presentation and Diagnosis

The diagnosis of idiopathic Parkinson's disease is entirely clinical, primarily based on the presence of three cardinal motor symptoms that include tremor, rigidity, bradykinesia, and later on postural instability. [4,15]

Tremor is usually described as a classical intermittent and rhythmical 3- to 6-Hz distal resting tremor and even as an action or postural tremor. However, it is not confined to such classical pill-rolling, pronation-supination type but may appear as plain tremulousness or as a cerebellar type of tremor. [16] Most early cases of PD do have some form of obvious tremor making of it a differential feature; however, it's absence in around 30% of patients with PD, [17] and its presence in other diseases (*e.g.* multiple system atrophy [MSA], [18] progressive supranuclear palsy [PSP] [19]) make of it an optional extra.

Rigidity can be present early in the disease with slightly positive resistance on the affected side of the upper extremity, and follows in intensity the different phases of disease progression. [16] Moderately advanced cases will show onset of forearms dystonia in addition to rigidity, followed by a stooped, flexed, or "simian" posture heralding the onset of an advanced or severe disease.

Bradykinesia or akinesia is another unspecific clinical symptom that is present in most patients with PD. [20] It is characterized by the slowness in performing common voluntary movements (*e.g.* standing, walking, eating, writing, talking), and movement avarice presented as facial amimia, impaired arm swings, and movement blockage. The patient shows decreased amplitude of repetitive alternating movements, and clumsiness in his actions. Even though, this clinical sign is not unique to parkinsonians, upper body akinesia must be present for diagnosis. [4,15-17]

Postural instability is not usually an early sign of the disease, starting to feature only in stage 3 of the Hoehn and Yahr (H&Y) scale for grading clinical disability. [4] (See appendix, UPDRS part V)

Asymmetry in onset of clinical symptoms is another early but an unspecific criterion that has featured in stage 1 of H&Y scale (See appendix, UPDRS part V), yet it is sometimes skipped and the PD onset can be bilateral or generalized. [4]

These clinical criteria can also occur in, or as a result of other medical conditions and neurodegenerative diseases (*e.g.* MSA, PSP, corticobasal degeneration, vascular parkinsonism, dementia with Lewy bodies, drugs, Wilson's disease) resulting in a hurdle that could only be broken by a good and sustained response to levodopa therapy. [6]

Secondary features of PD include dementia (in 25 to 40% of patients), depression (about 40 % of cases [21]), hallucinations (in 2 to 6% of patients [22]), autonomic dysfunction in micturation reflex, [23] orthostatic hypotension, and seborrhea. Other motor features, that might be investigated for differential diagnosis, include blink rate, micrographia, motor freezing, blepharospam, and a distinctive hoarseness and monotonous voice. [15,16]

Since there are no clinical criteria that clearly differentiate PD from other neuropathological disorders, diagnosis remains preliminary for a substantial period of time (approximately five years) to ensure that the patient does not develop other symptoms suggestive of an alternative disorder.

1.3 Progression of Disability

The putative time course of nigral cell loss is considered to be cause-dependent. While environmental insult can rapidly result in the loss of nigral neurons, genetic mutations effect on the rate of cell death remains unknown. The interaction of these latter etiologies can in turn result in various presentation patterns. [3] In general, Parkinson's disease is characterized by an insidious onset with an estimated time lapse between the initiation of dopamine loss and the appearance of clinical symptoms (the prodromal phase) to be around five years. [24]

Hoehn and Yahr considered patients in stages 1,2, and 3, as minimally disabled, and patients in stages 4 and 5 as severely disabled. In their study on 672 cases of primary PD, they showed that the disease duration is positively linked to a more advanced grading. While the duration of illness at a specific stage has varied between patients, [4] Louis et al. [25] found an annual 1.5 % to 3% escalating rate of progression of parkinsonian signs, especially bradykinesia, rigidity, postural imbalance, but not tremor. This rate of progression was nonlinear, progressing at a faster rate early in the disease, with an average delay in reaching stage 5 of the Hoehn and Yahr scale in more than 10 years of untreated disease. [26-28] A slower rate of motor decline was noted with medical therapy; [27,28] Delayed onset of the disease, [29] and dementia [30] seemed to be associated with a faster progression of the disease and subsequent mortality.

In a number of postmortem studies, this progression in disability has been correlated with specific biochemical modulations and neuropathological features. [27]

1.4 Neuropathology and Biochemical Findings in Parkinson's Disease

A cardinal histological feature in PD is the substantial degeneration that involves multiple neurological loci, including the dopaminergic neurons of the substantia nigra pars compacta, some catecholaminergic and serotoninergic brain-stem nuclei, the cholinergic nucleus basalis of Meynert, hypothalamus, some cortical neurons, the olfactory bulb, and autonomic ganglia. [6] Fearnley and Lees [31] found an exponential increase in neuronal attrition with disease duration, especially involving dopaminergic neuronal loss in the caudal part of the substantia nigra pars

compacta, at a rate of 4.7% per decade. This loss tends to be mostly severe in the ventrolateral tier that project to the putamen, followed by the ventromedial, and then the dorsal regions that innervate caudate nuclei. This pattern of cellular loss is specific for PD and results in an uneven loss of dopamine in striatal nuclei, most prominently in the intermediate and dorsal subdivisions of the putamen, and in the onset of clinical symptoms, especially with akinesia and rigidity, [6,32,33] occurring whenever 60% to 80% of dopamine get lost. [34] Cognitive dysfunction becomes more pronounced with an increased dopamine loss in the caudate nucleus, [35] and the involvement of the nucleus basalis of Meynert, locus ceruleus, and the enterohinal cortex. [6]

The reduction of dopamine in other subcortical and cortical loci, including basal ganglia output nuclei (*e.g.* globus pallidus; substantia nigra pars reticulata [SNPR], and subthalamic nuclei [STN]), nucleus accumbens and the limbic cortex, might also be implicated in the emergence of motor disorders and psychological disturbances in PD. [36,37] Depression in PD has been attributed to the degeneration of aminergic brainstem nuclei (catecholaminergic and serotoninergic) and possibly the amygdaloid

nucleus. [21] Degeneration of the latter nuclei, along with the intermediolateral columns of the spinal cord and autonomic ganglia might also be at the origin of the prevalent autonomic dysfunction. [6]

Besides the loss of dopamine, noradrenaline and serotonin, postmortem studies on brains of patients with PD have shown additional disturbances in a number of neurotransmitters, including the loss of met-enkephalin, and substance P, and the increasing levels of GABA, glutamate, preproenkephalin, cholecystokinin-8, and neurotensin, among others, probably correlating with the progressive spread of the disease and the subsequent loss of neuronal perikarya in the respective nuclei. [37] However, their role in the genesis of motor and nonmotor clinical features remains uncertain.

An additional histopathological feature in PD involves the presence of Lewy body inclusions not only in neuronal cells of the substantia nigra, but also in the locus ceruleus, nucleus basalis of Meynert, vagal dorsal motor nucleus, and hypothalamus. These are ubiquitin-positive eosinophilic hyaline neuronal intracytoplasmic inclusions, the number of which usually increases with advancing age. Moreover, they are non-specific for PD as they occur in other neurodegenerative disorders (*e.g.* Alzheimer disease, motor neuron disease, subacute sclerosing panencephalitis, ataxia telangiectasia, corticobasal ganglionic degeneration, and Hallervorden-Spatz disease). [15] Such intriguing observations hurdle the underlying etiology of these Lewy bodies. Should they be considered as markers of advancing age and/or of PD? Would they underlie any other underlying neurodegenerative disease in its active or prodromal phases, or a combination of them, especially that we know that PD is primarily a disease of the elderly?

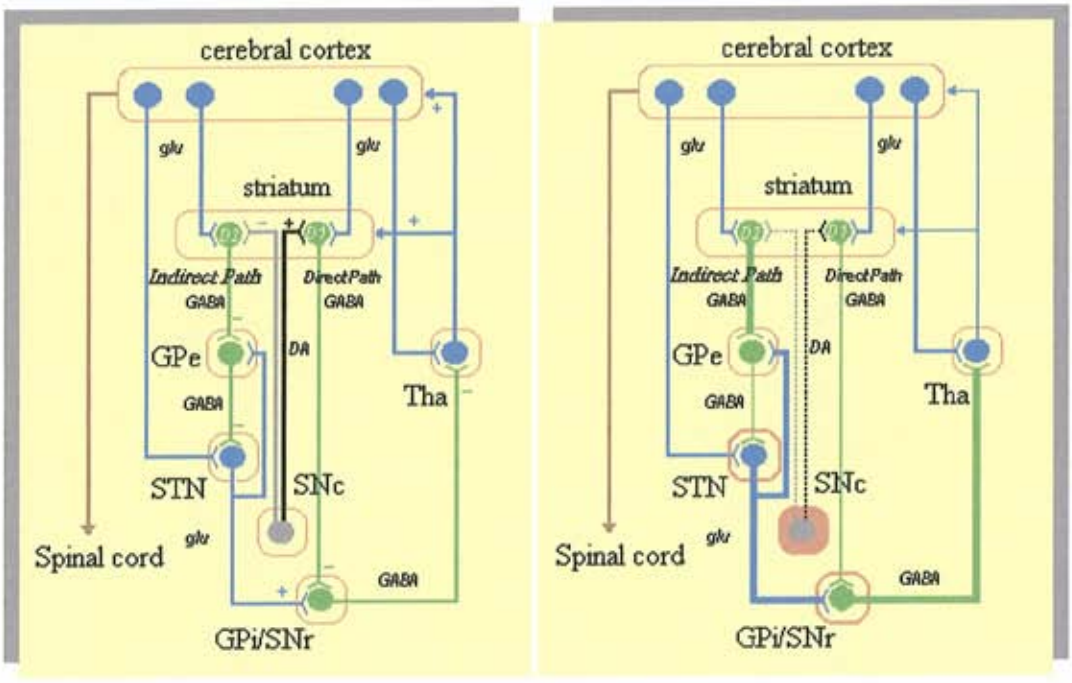
1.5 Mechanisms of Neuronal Death in Parkinson's Disease

The identification of histopathological and biochemical features of neuronal tissue in PD sheded the light over possible mechanisms of neuronal death. The detected mismatch between striatal dopamine loss and nigral dopamine and cell loss, in addition to the higher density of dopamine transporters found in mostly vulnerable nigral cells in primates, [38] suggest the dying-back process of neuronal death. The gradual functional loss of the nigrostiatal system has been correlated with the intrinsic property of dopaminergic neurons in the generation of dopamine transporters. [39] In fact, dopamine transporter system might be considered as a possible gate through which neurotoxins, including MPP^+ (from MPTP), enter nigrostriatal neurons causing primarily the progressive loss of synaptic neurotransmission leading to cellular death. [37] The accumulation of neurofilaments in Lewy bodies might further disrupt axonal function, favoring the proposed dying–back process. [40]

There is an accumulating evidence of MPP^+ role and/or genetically induced mitochondrial defect in energy production of nigral cells manifested by the loss of 30 to 40 percent of complex I (NADH- ubiquinone reductase) function. [41] Other studies have shown that the increased generation of oxygen radicals via iron metabolism, [42] the generation of nitric oxide free radicals via calcium-induced biochemical modulations, or of dopamine toxic byproducts in substantia nigra pars compacta, [43] might act as powerful neurotoxic oxidants, especially when accompanied with abnormally low levels of nigral anti-oxidant glutathione and neurotrophic factors; [6] these mechanisms ultimately increase the propensity of detected nigral cells apoptosis in neuronal tissue of dying patients with PD. [3, 44]

1.6 Functional Neuroanatomy and Pathophysiology of Parkinson's Disease

Under normal conditions, striatal nuclei (putamen and caudate nucleus) reside as a relay station between the afferent neuronal input [neocortex (glutamatergic), the centromedian parafascicular thalamic nuclei, the substantia nigra pars compacta (dopaminergic), as well as from other extrinsic serotoninergic and adenosinergic pathways and intrinsic cholinergic and somatostatinergic pathways], and the efferent transmission to basal ganglia (globus pallidus interna and externa - GPi, Gpe; substantia nigra pars reticulata - SNPR).[45, 46] (Figure 1, panel A)



Panel A Panel B

Figure 1. Functional model of the basal ganglia in normal condition (panel A) and in Parkinson's disease (panel B). Blue arrows indicate excitatory pathways, and green arrows inhibitory pathways. Dotted arrows indicate the loss of neuronal transmission. The width of the arrow indicates the level of neuronal activity. DA = Dopamine; D_1/D_2 = dopamine receptors; GABA = γ-aminobutyric acid; glu = glutamate; GPi = Globus pallidus interna; SNc = Substantia nigra pars compacta; SNr = Substantia nigra pars reticulata; STN = Subthalamic nucleus; Tha = Thalamus. (Adapted from 47)

The integrative role of sriatal nuclei gave them an important means in the modulation of motor function via γ- aminobutyric acid (GABAergic) neurotransmission. In fact, the striatum has been found to be enriched with D_1 and D_2 receptors, which respond differently to nigrostriatal dopaminergic input. The stimulation of striatal D_1 receptors elicits the direct inhibition of the striatopallidal and striatonigral pathways via GABAergic medium spiny neurons. Co-transmitters include substance P, dynorphin, and neurotensin.

On the other hand, dopamine effect on D_2 receptors mediates the more complex indirect neuronal pathway ultimately leading to the stimulation of the glutamatergic subthalamo-pallidal (GPi, GPe), and subthalmo-nigral (SNPR) pathways. Enkephalin and neurotensin serve as co-neuropeptides in this pathway. GABAergic efferents from GPi and SNPR constitute the principal basal output nuclei to the deep layers of the superior colliculus, the reticular formation of the mesencephalon, and to the ventral anterior (VA) and ventrolateral (VL) thalamic nuclei. Stimulated thalamic nuclei send their excitatory glutamatergic projections to the cortex to control normal motor function. Therefore, a balanced binary activation of the direct and indirect pathways results in a homeostatic response essential for the proper motor function. [45, 48] Johnels showed that dopaminergic projection of nigrostriatal cells on dorsal striatum control muscle tone, while the ventral striatum neurotransmission controls locomotion. [49]

In Parkinson's disease, the degeneration of more than 60 percent of the nigrostriatal dopaminergic pathway conceivably leads to the loss of balance between the direct and indirect pathways, resulting in heightened GABAergic output from the basal ganglia (GPi and SNPR). Indeed, the reduced level of dopamine in striatal synapses favors the activity of the indirect pathway via D_2 receptors, and the inhibition of the direct

pathway, resulting in the overactivity of subthalamic nuclei (STN) and excessive inhibition of thalamic and brain stem nuclei. (Figure 1, panel B) Inhibition of the thalamocortical pathway ultimately results in akinesia, rigidity, and tremor, while the shutdown of brain stem nuclei accounts for the experience of postural instability and shuffling gait. [50]

2. TREATMENT

The homeostatic role of dopamine in proper neuronal functioning and its loss in PD, led to the emergence of two basic therapeutic patterns (protective and symptmatic). While the neuroprotective therapy is mainly pharmacologic, the sypmtomatic therapy relies on pharmacologic and/or surgical strategies (functional and restorative therapies).

2.1 Neuroprotective Therapy

Much effort has been invested in the development of neuroprotective agents that can halt, delay, or slow the ongoing striatal neurodegenerative process. In depth understanding of the aforementioned underlying mechanisms of neuronal death deemed necessary for the generation of an optimal and rational causal treatment regimen.

2.1.1 Monoamine Oxidase Inhibition

Selegiline (formerly L-deprenyl), the levo-isomer of N-propyl-methamphetamine, is a selective irreversible monoamine oxidase type B inhibitor (MAO_BI). MAO_B generates hydrogen peroxide during dopamine metabolism, therefore, its inhibition should provide a protective role against oxidative stress. Selegiline's neuroprotective property [51] is still controversial and researchers thought that its effect is mainly symptomatic. [52] A very recent study [53] has indirectly showed that it can even contribute to the emergence of motor complications via its metabolite with amphetamine-like properties.

Rasagiline (TVP-1012) is another selective MAO_BI, which can provide symptomatic relief and speculated superior neuroprotective potency than selegiline. [54]

2.1.2 Anti-excitatory Agents

Excessive glutamatergic stimulation of neuronal cells has been associated with major intracellular calcium influx, and the generation of toxic oxygen free radicals, causing oxidative stress and neuronal loss. Normal neurons are protected by the ATP-dependent Mg^{++} blockage of NMDA channels, thus, smoothening the glutamatergic cytotoxic effect. A hypersecretion of glutamate can overcome such protective mechanism and induce alterations in calcium flux and cellular death. [55] Therefore, the theoretical intervention to block the excitatory glutamate effect via NMDA antagonism gains momentum and provided a potential neuroprotective strategy. [56]

2.1.3 Neurotrophic factors

Glial-derived neurotrophic factors (GDNF) and brain-derived neurotrophic factors (BDNF) have been positively linked to the enhancement of neuronal differentiation, survival, and protection. In PD, their replenishment has been associated with promising results. Preliminary studies [57, 58] have demonstrated GDNF beneficial role at the microscopic and systemic levels, when they permitted neuronal protection, regeneration and growth, as well as symptomatic benefit. Obviously, large clinical trials are still needed to confirm their therapeutic role.

2.1.4 Antioxidation

Cellular defense mechanisms are known to principally occur in two major phases. Phase I usually generates reactive species. Such metabolites would be later subjected to Phase II enzymes that catalyze genuine detoxification reactions involving molecular conjugation into more hydrophilic, easily eliminated compounds. The integral function of phase II enzymes seems to play a major role in neuronal metabolic defense against oxidative stress. Promotion of phase II enzymes expression has been achieved with the use of dithiolethiones, namely, Oltipraz and Anethole. These agents were able to upregulate phase II enzymes expression, and to act as regular free radicals scavengers in animal and human models. Providing a broad-spectrum neuronal defense mechanism with minimal side effects give these agents promising leads in PD neuroprotective therapy. [5]

2.1.5 Calcium Channel Blockers

Intracellular calcium imbalance has shown to act as a trigger for cellular apoptosis, possibly through activation of toxic reactions culminating in cellular damage. Calcium channel antagonists (*i.e.* Nimodipine, and Amlodipine) have spared cellular apoptosis, and prevented the development of MPTP-induced parkinsonism in animal models. However, large clinical studies are still needed to confirm such salutary effect in PD patients. [59]

2.2 Symptomatic Therapy

Parkinson's disease results from a deficiency in striatal dopamine mainly manifested as a motor deficit. Therefore, alleviating symptoms resides primarily either on the administration of dopaminergic agents that are capable of replenishing dopamine levels in the mesencephalon, or mimicking its pharmacological effect on striatal medium spiny neurons. The restoration of patients' functional ability and the amelioration of their quality of life is the primary endpoint.

2.2.1 Levodopa Therapy

Levodopa (LD) therapy has constituted the mainstay in the management of PD since the late 1960. [60] If dopamine is not able to cross the blood brain barrier (BBB) in appreciable amounts, its precursor- levodopa- can easily gain access to striatal tissue. In the body, levodopa is rapidly metabolized by the enzymes aromatic L-amino-acid dexarboxylase (AADC) and catechol-O-methyltransferase. (COMT), giving it a plasmatic half-life of about 60 minutes. To prevent its peripheral catabolism, LD is usually given with an AADC inhibitor (carbidopa or benserazide). Such combination increases LD concentration crossing the BBB, decreases the dose of LD needed, and limits its systemic side effects (*i.e.* nausea, vomiting, postural hypotension, cardiac arrhythmia, mental disturbances, and dyskinesia). (Figure 2) Virtually, all PD patients respond to levodopa therapy, if not, an alternative diagnosis should be thought of.

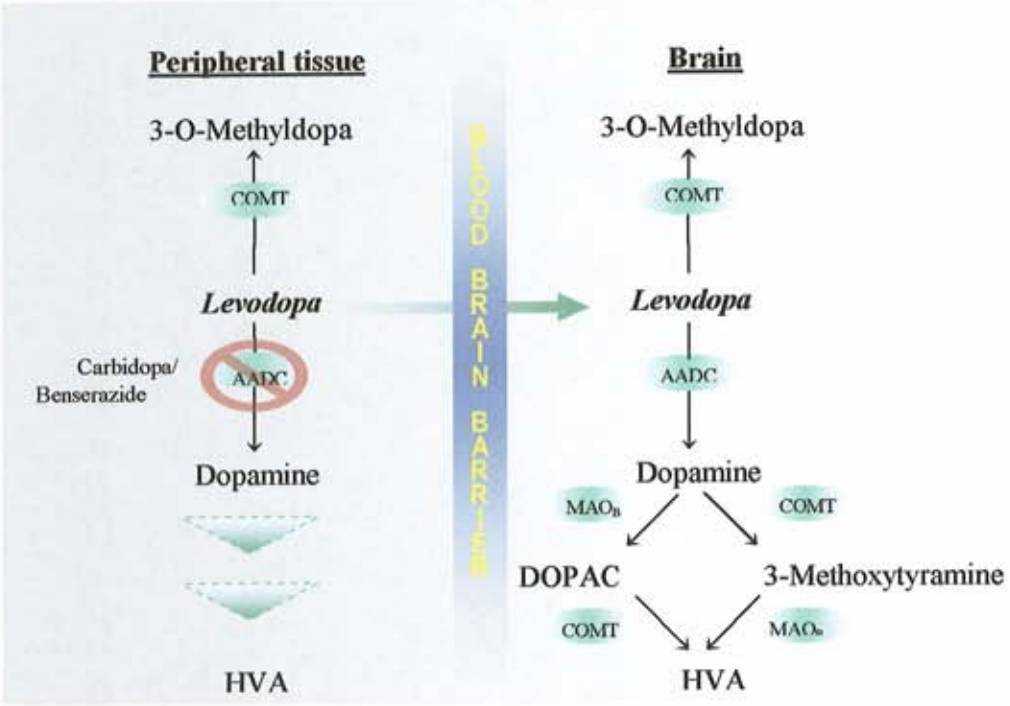


Figure 2. Metabolism of levodopa in the peripheral and brain tissues. The peripheral inhibition of AADC enzyme increases levodopa central bioavailability and reduces its side effects. AADC = L-Amino-acid decarboxylase; COMT = Catechol-O-Methyltransferase; DOPAC = 3,4-Dihydroxyphenylacetic acid; HVA = Homovanillic acid; MAO_B = Monoamine Oxidase type B.

A paradoxical transient worsening of motor functions, especially tremor, is usually experienced briefly after levodopa intake, denoting the beginning efficacy of the medication, and a time lapse of two weeks is usually necessary to observe the optimal therapeutic effect of any alteration in levodopa treatment. [61]

As the disease progresses, levodopa's pharmacodynamic property and duration of action markedly decrease with the progressive loss of nerve terminals and AADC level, as to necessitate its administration sometimes in 90 minutes intervals. [62]

Levodopa is a two-edged sword. While it is considered to be the most potent drug for controlling parkinsonian symptoms, there is much concern about the emergence of associated toxicity and motor complications.

Despite the forty years of experience with levodopa therapy, much controversy remains as to whether levodopa can adversely affect the progression of the disease through generation of potentially toxic reactive species and subsequent increase in oxidative stress. While *in vitro* studies demonstrated levodopa neurotoxicity, *in vivo* studies failed to provide to do so. Paradoxically, small doses of LD increased the antioxidative glutathione neuronal level providing a potential neuroprotective and even a neurotrophic effect in *in vitro* studies. [63-66]

On the other hand, it has been estimated from the Deprenyl and Tocopherol Antioxidant Therapy of Parkinsonism (DATATOP) study that two years were enough for the development of motor complications in the third of PD patients on LD therapy. [52] This rate could be increased to 50 or 90 percent after five to ten years of levodopa therapy, [67] with an estimated annual increasing rate of 10 per cent in motor fluctuations. [68]

Motor swings in PD patients can be considered to be treatment- and/or disease-related; They are usually classified according to their duration. Initially, the clinical response to levodopa tends to be stable (long-duration response [LDR] or "levodopa honeymoon"). As the disease progresses, patients start to experience an increase in the incidence of the usually predictable "wearing off" (short-duration response or [SDR]) effect characterized by a gradual perception (from minutes to an hour) of loss of motor plasticity, and a progressive shortening of the antiparkinsonian action of levodopa. This effect is temporarily correlated with the reduced ability of striatal dopaminergic cells to store dopamine, the limited dopamine storage in non-dopaminergic cells, and the waxing and waning of levodopa dose. [69] Therefore, we can speculate that the incidence rate of motor fluctuations can be successfully decreased with steady-state dopaminergic stimulation.

The experienced changes in levodopa over the course of PD does not seem to be related to peripheral pharmacokinetic changes, but rather to intracerebral ones. [70-72] The absence of such fluctuations usually denotes a non-idiopathic disease. [61]

The "on-off" fluctuations, or the "yo-yoing" effect, are more unpredictable in nature, characterized by their sudden occurrence, usually unrelated temporarily to antiparkinsonian medication. [50] It is noteworthy that the experienced "off" period is different from untreated PD condition; the former being proportional in severity to the time of "on" experience, the increase in levodopa dosage, [61] and more correlated with the progressive neuronal degeneration, as well as with the alterations detected in the postsynaptic dopamine receptors. [72,73]

Levodopa-treated patients experience also a heterogeneous variety of dyskinesias [61] that can range in intensity as to pass unnoticed in about 50 percent of patients in their first year of treatment. [69]

Sub-therapeutic dopaminergic stimulation, (*i.e.* during the "off" period or as the medication wears off), can cause fixed and painful dystonia which is usually relieved by increasing the "on" time).

Mobile choreodystonic dystonias are painless dopamine-induced dyskinesias that usually occur at peak dose and increase proportionally with LD dose. They can be critically managed by a glutamate antagonist or by reducing the individual levodopa dose without falling under the fixed threshold dose. [74] Levodopa therapeutic window will eventually vanish with time. Such dykinesia may overlap the entire medication "on" period as to mask any symptomatic relief. They are also named square-wave dyskinesias. Biphasic dyskinesias are usually experienced by early-onset

PD patients at the beginning and/or wearing "off" of medication. They are characterized by a very severe ballistic posturing and high resistance to treatment.[50, 61]

The etiology of such dyskinesias remains a point of debate, with many hypothetical considerations. Losing or altering the presynaptic integrity of striatal dopaminergic terminals [75] and/or the postsynaptic properties of neuronal transduction [76] associated with disease progression have been considered as contributors to the development of motor fluctuations, including dyskinesias. Whether such motor complications are the result of D_1 or D_2 agonism or antagonism, [70] dopamine autoreceptors subsensitivity, [53] a hypersensitivity reaction of postsynaptic dopaminergic receptors, [72, 77] D_1 receptors internalization (Muriel), or excessive glutamate excitation; [74] whether they are dependent on the intrinsic activity of anti-parkinsonian medications, [79] an imbalance between D_1 and D_2 receptors activity [80] or their combination, remain to be discovered.

Other complications of levodopa therapy include psychiatric disturbances possibly related to mesolimbic and mesocortical stimulation, mood, cognitive, and autonomic function fluctuations. [61]

To improve levodopa response, researchers tried to overcome the resulting pulsatile dopaminergic stimulation of the neostriatum after each levodopa dose. Pharmaceutical modifications included the formulation a LD sustained –release formulation, and oral solutions which were more efficacious, but were not able to eliminate motor fluctuations, [81-83] The CR Five-Year International Response Fluctuation Study (CR FIRST) compared the immediate- release with the sustained release of Sinemet® (levodopa/carbidopa) preparations and revealed an approximate 21% lower than expected in the rate of motor fluctuations for both groups. [82] This implies that motor

complications, including dyskinesias, involve a much more intricate mechanism than ever thought.

2.2.2 Dopamine Agonists

The development of aforementioned levodopa complications and the resulting morbidity has shed light on alternative therapeutic considerations. The usage of dopamine agonists as adjunctive therapy to levodopa permitted the reduction of the latter dose, thereby dropping, but not eliminating, the duration and severity of levodopa-induced dyskinesias (LID), and motor oscillations. [84] In fact, dopamine agonist add-on therapy was able to control peak dose dyskinesia by virtue of levodopa dose reduction, and bouts of biphasic forms by continuous dopaminergic stimulation.[85]

Studies have shown that the addition of bromocriptine, lisuride, pergolide, cabergoline, and the nonergot alkaloids ropinirole and pramipexole to primed levodopa therapy permitted levodopa dose reduction and a substantial smoothening of levodopa-induced motor complications. The variable efficacy of the different levodopa-dopamine agonist combinations could be mediated by dopamine receptors selectivity and the temporal extend of dopaminergic stimulation. [84] (Table 1) Nevertheless, this addition should preferably be initiated whenever levodopa dose is still lower than about 600 mg per day, or the patient will be more prone to dopamine agonists adverse effects. [62]

Table 1. Characteristics of dopamine agonists and their selective activity at receptor sites. *

Dopamine Agonist	$T_{max.}$ (min.)	t ½ (hrs)	D_1	D_2	D_3	D_4	5-$HT_{1/2}$	$\alpha_{1/2}$
Ergot derivatives								
Bromocriptine	70-100	4-8	0/-	+++	++	+	+	+
Pergolide	60-120	15-27	+	+++	+++	+	+	+
Cabergoline	60-240	65-110	0	+++	?	?	0	0
Lisuride	30-60	2	0/+	++	?	?	0/+	0/+
Non-ergot derivatives								
Ropinirole	80	6	0	++	+++	+	0	0
Pramipexole	60-180	10	0	++	+++	++	0	+
Piribedil	60	2	+	+++			0	
Apomorphine	>10	45 min	++	+++	?	?	0	0

* Tmax. = time to reach maximum concentration in blood; t ½ = half-life; 0 = no activity; + = minimal/mild activity; ++ = moderate activity; +++ = high activity; ? = unknown; - = antagonistic activity; 5-HT = serotonin. [67,86-89]

Another strategy involves the early combination therapy in which dopamine agonists are used in conjunction to levodopa in *de novo* treated patients. The addition of dopamine agonists permitted a continuous and direct stimulation of dopamine receptors preventing by this the stuttering motor responses to levodopa therapy, as the disease progresses. In fact, with a dopamine agonists, dopamine receptors keep on being stimulated as levodopa effect wanes, providing a continuous antiparkinsonian activity, better tolerability, and an additive "on" time with limited motor fluctuations. Olsson et al., [90] for instance, tried to evaluate and compare the combination of levodopa and bromocriptine versus levodopa alone therapy in newly diagnosed parkinsonians. Results revealed a levodopa dosage-sparing effect of 10 percent when bromocriptine permitted the maintenance of the initial levodopa dose during the first 12 months of treatment, while transiently increasing the frequency of adverse effects. Furthermore, the early combination therapy permitted significantly better clinical responses ($P = 0.043$). Interestingly, a significant lower degree of anxiety and

dyskinesia were noted in patients of levodopa/bromocriptine group. These results suggest a potential role of bromocriptine in positively affecting the clinical and prognostic implications of the disease, especially when it is early introduced in the therapeutic management; However, we could not assert that bromocriptine prevents, but rather delays or limits the development of long-term complications of the conventional levodopa regimen, when used concomitantly early in PD. [91]

A slightly different approach involves the priming of dopamine agonist monotherapy in PD that might be lately followed by the introduction of levodopa, thus delaying the motor complications that have often been associated with early LD therapy. [92-94]

In his meta-analysis of 13 studies on early treatment of PD patients with bromocriptine, Lieberman [95] provided evidence of the latter potential to delay the need for levodopa up to six years (mean of 2.3 years), with an improvement noted in 46 % of cases. When compared with early levodopa therapy, the positive therapeutic effect of levodopa was significantly higher (68% vs. 40%), as well as the rate of motor fluctuations (9% vs. 0.7%) and dyskinesias (13% vs. 0.2%), which might totally cloud levodopa symptomatic motor control.

In a prospective, randomized, controlled study performed by Montastruc et al., [94] tried to compare the incidence of long term motor complications occurrence in 60 patients with young onset previously untreated Parkinson's disease. Patients were divided into two groups: group B/D (N=31) in which bromocriptine monotherapy was used early in therapy followed by the addition of Levodopa, and group D (N=29) in which levodopa was used alone from the beginning. Patients were followed-up during five years. The primary end point was the detection of the first motor complications (biphasic dyskinesia, and on-off phenomenon). Results showed a significant lesser peak dose dyskinesias in the B/D group than in the group D. The number of wearing-

off incidences was similar in both groups. More and earlier motor complications were reported in group D than in group B/D. On the other hand, psychiatric side effects (hallucinations or confusion) were more prominent in group B/D (50% in group B/D vs. 8% in group D). Investigators concluded that the initial monotherapy with high dose bromocriptine, followed by levodopa delays the occurrence of long-term motor complications associated with levodopa therapy.

Recently, Barone et al.[92] conducted a randomized, double-blinded, multicenter, controlled study to test the efficacy of the early use of pergolide monotherapy in 105 PD patients assigned to receive either pergolide (N=53) or placebo (N=52). Investigators showed the efficacy of pergolide in 56.6% (30/53) of cases (defined as a ≥ 30 % decrease in UPDRS part III score at end point), and a placebo effect in 17.3 % (9/52) of responders (95% CI, 22.5 to 56.1%, $p < 0.001$). The mean dose of Pergolide was 2.06 mg/day. Eight patients withdrew from the study because of reported adverse effects (six with pergolide, and two with placebo). They finally concluded that the use of pergolide monotherapy was efficacious and well tolerated in controlling early-stage PD.

It is widely known that levodopa effect results from its enzymatic conversion to dopamine, and the subsequent stimulation of both striatal D_1 and D_2 receptors. The lower rate of motor fluctuations and dyskinesias associated with bromocriptine (a selective D_2 agonist) therapy implicates the potential role of D_1 receptors in the genesis of such complications. In contrast, D_1, rather than D_2 receptors, stimulation/inhibition seems to have the major impact on the electrophysiological status of the GPi and SNPR. As a matter of fact, Trugman et al.[96] were able to demonstrate that the pharmacological effect of pergolide (mixed D_1/D_2 agonist) on GPi and SNPR, can be integrally inhibited when the experimental rats were pretreated

with SCH-23390, a selective D_1 antagonist; However, a mild pharmacological attenuation was only recorded when a selective D_2 antagonist, eticlopride, was pre-administered. Similar results were also reported when the same pharmacological interference was practiced on levodopa treated rats. In contrast, STN inhibition was found to be exclusively mediated by a synergistic D_1/D_2 agonistic activity. [97]

Therefore, better therapeutic control would be theoretically achieved whenever a synergistic D_1/D_2 continuous stimulation could be achieved, mimicking then the physiologic dopaminergic activity. This can be ultimately achieved by the administration of a dopamine agonist with mixed dopaminergic stimulation (*e.g.* pergolide), or the combination of a low dose of levodopa with a D_2 receptor agonist (*e.g.* bromocriptine). However, a weaker symptomatic control was noted with dopamine agonist therapy when compared to levodopa clinical effect. [95] Levodopa would remain the gold standard in PD therapy with incomparable therapeutic efficacy. Its use as an adjunctive or "add-on" therapy to dopamine agonists can maintain a better improvement of parkinsonian symptoms, as the disease progresses, while limiting or delaying LD complications. [98]

The early use of dopamine agonists in the management of PD can also affect the prognosis of the disease. As a matter of fact, PD has been associated with multiple neurological findings due to oxidative stress and subsequent neurological damage. The intrinsic potential of dopamine agonists to directly stimulate dopaminergic receptors limits the postulated generation of free radicals by dopamine metabolism, either by their action on dopamine autoreceptors, limiting by this dopamine release and turnover, or indirectly by their levodopa-sparing potential.

It is known that dopamine can be metabolized and spontaneously auto-oxidized to generate hydrogen peroxide (H_2O_2) and reactive oxygen species ($^{\cdot}O_2$) (Figure 3). An

increase in dopamine turnover and iron in brain tissue associated with a decrease in the level of reduced glutathione (GSH), favor the generation of highly toxic hydroxyl radicals ($OH^{\cdot}$) which can induce lipid peroxidation, critical DNA damage, ultimately leading to cellular apoptosis. [99]

Dopamine auto-oxidation:

$$\text{Dopamine} + O_2 \longrightarrow SQ^{\cdot} + {}^{\cdot}O_2^{-} + H^{+}$$
$$\text{Dopamine} + {}^{\cdot}O_2^{-} + 2H^{+} \longrightarrow SQ^{\cdot} + H_2O_2$$

Dopamine enzymatic metabolism:

$$\text{Dopamine} + O_2 + H_2O \xrightarrow{MAO} \text{3,4, dihydroxyphenyl-acetaldehyde} + NH_3 + H_2O_2$$

Normal clearance of hydrogen peroxide:

$$H_2O_2 + 2\,GS \xrightarrow{GPX} GSSG + 2H_2O$$

Fenton reaction:

$$H_2O_2 + Fe^{2+} \longrightarrow OH^{-} + OH^{\cdot} + Fe^{3+}$$

Figure 3. Dopamine metabolism pathways. GSH = Reduced Glutathione; GPX = Glutathione Peroxidase; GSSG = Oxidized Glutathione; MAO = Monoamine Oxidase. (Adapted from 100)

Levodopa is also decarboxylated to generate dopamine, and theoretically complicate the situation when chronically administered- especially in high doses- to patients with PD. [65, 66] When combined with dopamine agonists early in therapy, a lower dose of levodopa is needed to achieve symptomatic relief. Priming dopamine agonists can further delay its introduction, lowering by this the cumulative coinciding cellular damage over the course of the illness.

On the other hand, the direct stimulatory effect of dopamine agonists on pre-and post-synaptic dopamine receptors permits not only a symptomatic relief, but also an inhibitory feedback on D_2 autoreceptors of the nigrostriatal neuronal cells, resulting in

a decrease in dopamine synthesis, release, and turnover. This will ultimately result in the decrease in the generation of reactive oxygen species. Unfortunately, such feedback efficacy will be lost in the advanced stages of the disease, as dopamine autoreceptors became subsensitive to dopaminergic stimulation. [53] Therefore, in the early stages of the disease, the introduction of dopamine agonists can potentially lower the threatening effect of dopamine on nigral cells, while providing therapeutic benefit.

Others studies have experimentally demonstrated the scavenging effect of dopamine agonists on generated oxidative species. Recent studies [101-104] demonstrated the quenching effects of pergolide and bromocriptine on generated cytotoxic hydroxyl ($HO^{\cdot}$) and nitric oxide radicals ($NO^{\cdot}$) by triggering the synthesis of radicals-scavenging proteins warranting neuroprotection for dopaminergic and non-dopaminergic cells. [105] Very recently, the new non-ergot dopamine agonists, pramipexole and ropinirole, were able to partly provide *in vitro* neuroprotection possibly via hydrogen peroxide (H_2O_2), or $HO^{\cdot}$ and $NO^{\cdot}$ radicals clearance, respectively. [106, 107] The nonselectivity of these released proteins warrants neuroprotection for dopaminergic, as well as for non-dopaminergic cells. [104] Other antioxidant mechanisms involve enzymatic induction such as the activation of glutathione (GSH), catalase (CAT), and superoxide dismutase (SOD) enzymes.[104,106,107]

The putative role of oxidative stress in the pathogenesis and progression of PD has gained momentum with the results of experimental models. However, Zou et al. [106] were able to *in vitro* demonstrate that dopamine –induced cytotoxicity and cellular apoptosis are actually mediated by a newly synthesized protein; Neuroprotection can

thus be assured by the addition of the transcription inhibitor actinomycin-D and the translation inhibitor cycloheximide to the cellular culture.

With this body of evidence, new questions arise: could we consider the elevated levels of free radicals as a mere result of dopamine metabolism, or consequential to the neuronal degeneration observed in PD? Was the cytoprotective role of dopamine agonists that was observed in experimental studies a reflection of their potential to clear the generated free radicals, or of their ability to block the synthesis and /or action of neurotoxic proteins? Can we consider that the generated/induced protein(s) after cellular treatment with dopamine agonists as potential antioxidant moieties or as neurotoxic proteins-inhibiting molecules?

The extrapolation of such experimental findings to the clinical arena is faced with multiple limitations, such as the determination of the needed neuroprotective dose of dopamine agonists, the exact level of neuronal exposure to these agonists in PD patients, and the difficulty in evaluating study subjects, since dopamine agonists can symptomatically control the disease. Indeed, *in vitro* exposure to high concentrations of ergoline derivatives has resulted in a paradoxical decrease in their pharmacoprotective effect. [104] Whether this latter effect was due to pharmacokinetic or pharmacodynamic reasons needs further investigations. Overall, no clinical trial was able to provide a clear-cut evidence of dopamine agonist neuroprotection.

Furthermore, the delay in the addition of levodopa to primed dopamine agonists may not be due to their neuroprotective role but to the natural course of the disease, which normally progresses to a higher stage in two to three years. [108]

Therefore, the exact role of dopamine agonists in PD remains an unsolved puzzlement that necessitates the conduction of large, double blind, placebo-controlled clinical

trials tightly controlled with sophisticated techniques to detect any forecasted neuronal modifications. However, the rational of their early use can still be backed-up by their potential to provide symptomatic relief of parkinsonian features while sparing earlier levodopa therapeutic complications.

2.2.3 Catechol-O-Methyltransferase Inhibitors

Catechol-O-methyltransferase (COMT) is an enzyme that takes part in the metabolism of a wide range of substrates that include neurotransmitters, and their derivatives, and catechol-structure containing xenobiotics and drugs. Because of its wide distribution in body tissues and its effect on levodopa metabolism, selective COMT inhibitors, such as the pyridine derivatives (CGP 28014) or the nitrocatechol type (tolcapone, entacapone, and nitecapone) have been developed. Their COMT inhibition is reversible and dose-dependent in nature. While tolcapone inhibits intracerebral and extracerebral COMT, CGP 28014, entacapone and nitecapone act mainly on extracerebral COMT. [109, 110] When given in combination with levodopa, COMT inhibitors were able to modify levodopa pharmacokinetic parameters as well as the potentiation of the latter clinical efficacy, especially when given in combination with a peripheral decarboxylase inhibitor (AADC), but without a significant increase in dyskinesias. [111, 112] Entacapone (200-mg per dose), for instance, when added to levodopa-AADC treatment of PD patients, was able to lower the Unified Parkinson's Disease Rating Scale (UPDRS) scores, [113] to lengthen motor response to levodopa therapy, [112, 114, 115] and reduce the mean daily total levodopa dose [114, 115] in acute and chronic therapeutic regimens. Entacapone requires a more frequent daily administration than tolcapone (200-mg, 4-6 times per day versus 100-400 mg three times per day for tolcapone). Similarly, Tolcapone has proved its efficacy in

positively affecting levodopa pharmacokinetic parameters and therapeutic outcome; [116] however, its use has been associated with cases of severe hepatocellular injury, including fulminant liver failure resulting in death. The Food and Drug Administration (FDA) and the manufacturer now recommend the use of tolcapone as an adjunct therapy in patients with Parkinson's disease on levodopa/carbidopa who are experiencing symptom fluctuations, and who are not responding satisfactorily to, or who are not appropriate candidates for other adjunctive therapies. It is still unknown whether entacapone will have the same problem of toxicity after its very recent FDA approval, and release in the US market.

2.2.4 Anticholinergic Agents

The disturbance in dopamine and acetylcholine neurotransmission in PD patients can lead to a state of relative cholinergic sensitivity that can contribute to the morbidity of the disease. [117] The introduction of anticholinergic drugs in the management of PD can therefore improve parkinsonian symptoms. Centrally acting anticholinergic drugs, such as trihexyphenidyl, benztropine mesylate, orphenadrine, biperiden, and procyclidine have been useful for the treatment of relatively younger PD patients with resting tremor, but they are of less value in the treatment of akinesia or impaired postural reflexes. [67] Because of anticholinergic side effects (*i.e.* memory impairment, acute confusion, dry mouth, blurred vision, constipation, nausea, urinary retention, tachycardia, etc), and the severe impairment of cholinergic systems in advanced stages, their use is often limited in elderly patients and patients with impaired cognition, and advanced PD cases. [118]

2.2.5 Amantadine

Amantadine is an antiviral drug fortuitously found to possess antiparkinsonian activity. It is known to be able to modulate dopamine uptake and release, and to have peripheral anticholinergic properties. However, its effect seems to be transient lasting about four to eight weeks after initiation of therapy. Its recognition as a NMDA receptor antagonist gives it a neuroprotective property, [56] as well as the potential of treating levodopa-induced dyskinesia (LID). [119]

Its use has been associated with the emergence of side effects, such as, confusion, insomnia, hallucination, livedo reticularis, and ankle edema. Amantadine seems to be more efficient in the management of akinesia and rigidity than tremor in PD patients.

Table 2. Pharmacological treatment of Parkinson's disease.[50, 62,67, 87, 120]

Class	Drug	Usual Daily Dosing	Important Side Effects
MAO_BI	Selegiline (Eldepryl®)	10 mg/d	Abdominal pain, , hallucinations, insomnia, headache.
Dopamine precursor	Levodopa (+ carbidopa, Sinemet®) (+ benserazide,Madopar®)	75 mg/d – 2 g/d	Nausea, vomiting, orthostatic hypotension, motor fluctuations, dysinesias, psychiatric disturbances.
Dopamine agonist	Bromocriptine (Parlodel ®)	5 – 40 mg/d	As for Levodopa, pedal edema, pleuropulmonary reaction, retroperitoneal fibrosis, erythromelalgia.
	Pergolide (Permax®, Celance ®)	2 – 4 mg/d	As for bromocriptine.
	Cabergoline (Cabsar®, Dostinex®)	0.5 – 6 mg/d	As for bromocriptine.
	Lisuride (Dopergin®)	1-5 mg/d	As for bromocriptine.
	Pramipexole (Mirapex®)	1.5 – 4.5 mg/d	As for brmocriptine but without pleuropulmonary reaction, retroperitoneal fibrosis, and erythromelalgia.
	Ropinirole (Requip®)	0.75 – 24 mg/d	As for pramipexole.
	Apomorphine	Varies.	As for levodopa, with local skin reactions including nodule formation.
COMT inhibitors	Tolacapone (Tasmar®)	300 – 1200 mg/d	Increases levodopa side effects, diarrhea, hepatotoxicity.

Table 2. Pharmacological treatment of Parkinson's disease- continued [50, 62, 67, 87, 118]

Class	Drug	Usual Daily Dosing	Important Side Effects
	Entacapone (Comtan®)	600 – 1200 mg/d	As for tolcapone. Effect on liver unknown.
Anti-cholinergic	Trihexyphenidyl (Artane®)	6 – 10 mg/d	Dry mouth, blurred vision, constipation, urinary retention, confusion, memory problems, and hallucinations.
	Benztropine (Cogentin®)	1-2 mg/d	As for trihexphenidyl.
Miscellaneous	Amantadine (Symmetrel ®)	200-300 mg/d	Confusion, visual hallucinations, nausea, dizziness, insomnia, livedo reticularis, ankle edema, hypotension.

2.2.6 Functional and Restorative Therapy

Over the past decades, a number of surgical procedures have been adopted in the treatment of parkinsonian symptoms but most of them have been abandoned with the introduction of levodopa in the late 1960's. Dopaminergic agents are then considered the utmost salvation for those afflicted with this disease. Nevertheless, as the disease progresses in morbidity, the efficacy of these agents becomes limited and their adverse effects often override their potential benefit. Recently, the deeper understandability of the functional anatomy and pathophysiology of PD permitted the resurgence of interest in a number of surgical procedures shown to provide benefit for advanced PD cases; These include: pallidotomy, deep brain stimulation, fetal nigral transplantation and gene therapy.

2.2.6.1 *Pallidotomy*

There is substantial evidence that the subthalamic nucleus get disinhibited in PD, leading to excessive glutamatergic firing to basal output nuclei, namely, GPi and SNPR. (Figure 1) Scientists have postulated the destruction of STN or GPi neurons as a potential means to increase thalamic and brain stem activity in PD patients. Previous experience with STN lesioning was associated with ballism, usually limited to the contralateral side of the body. [122] Laitinen et al. [123] reported that selective posteroventral pallidotomy produced major improvements in akinesia, rigidity, tremor, freezing, falls, speech, and LID; However, improvements were usually confined to the contralateral side of the lesion, and bilateral lesionning was associated with additional risks that include cognitive dysfunction, dyphagia, and dysarthria. [50, 67] Currently, this procedure is recommended as a potential bypass for severe LID, so that advanced PD cases can benefit from higher levodopa dose to further control their progressing disease. [47]

2.2.6.2 *Deep Brain Stimulation*

To obviate from the permanent neuronal damage engendering nuclei destruction and which can preclude further usage of potentially better alternative therapies, scientists have postulated the use of high-frequency stimulation of selected brain targets to control tremor and other parkinsonian symptoms, besides LIDs.

Deep brain stimulation (DBS) requires the surgical installation of electrodes into the desired target, connected via an extension wire that passes under the skin to a pulse generator, a pacemaker device placed in the upper pectoral area which can deliver

carefully selected pulses with defined parameters, modes, and polarities. The activation, deactivation, and manipulation of pulse generation can be easily customized using a magnet placed over the chest area where the generator is placed. (Figure 4) [54]

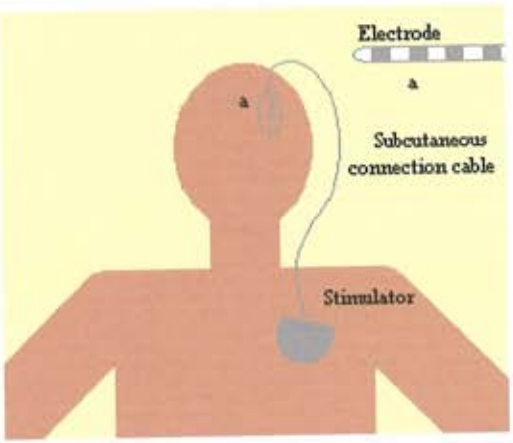


Figure 4. Deep brain stimulation. A quadripolar electrode is implanted into the target nucleus (thalamus, GPi, or STN). The electrode is then connected via a subcutaneous cable to an electric stimulator, which delivers a high-frequency current. (Adapted from 123)

Benabid's group in Grenoble-France [124] reported in 1991 their experience and promising results with high-frequency deep brain stimulation (DBS) of the ventral intermediate thalamic nucleus (Vim). This functional neurosurgery mainly abolished tremor in PD patients but did not significantly improve other parkinsonian features. Their results were comparable to those obtained with thalamotomy, promoting further investigation and experience in the use of deep brain stimulation, as an alternative surgical technique to control PD motor deficit.

Much attention has been recently focused on the STN and GPi high frequency DBS - rather than thalamic DBS - as potential means for the attenuation of the entire constellation of parkinsonian motor features, and LIDs, for advanced PD cases suffering from intractable motor symptoms.

Deep brain stimulation of the pallidum produced opposing effects, depending on the stimulated part within this structure. Stimulation of the dorsal pallidum (GPe) improved parkinsonian symptoms but induced dyskinesias, even when the patient was in the off-drug condition; whereas, stimulation of the posteroventral pallidum (GPi) reduced LIDs and rigidity, but significantly worsened gait and akinesia, even on "on drug" condition (Figure 5). [125, 126]

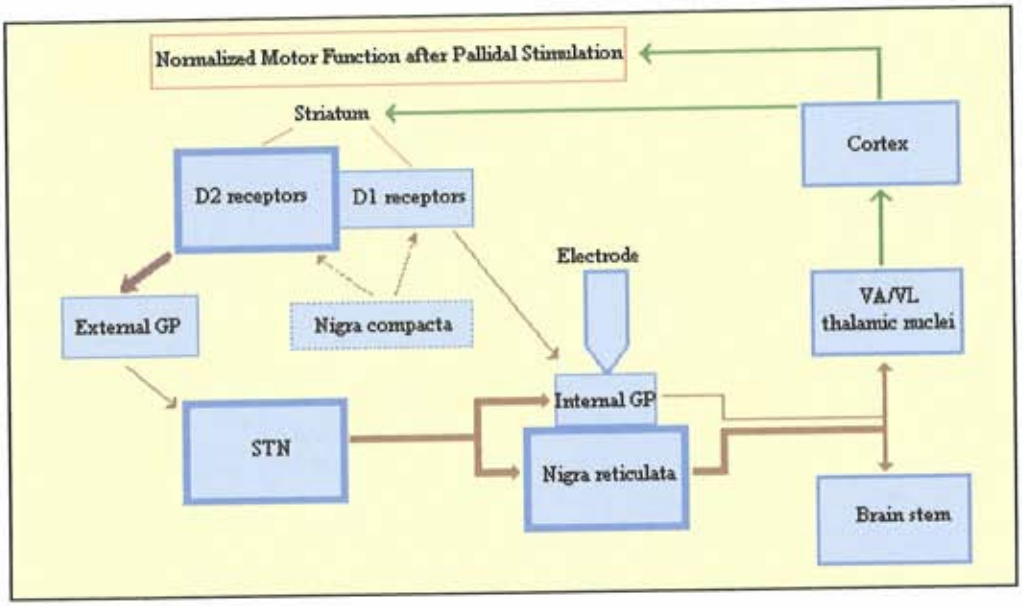


Figure 5. Neurological implications of GPi stimulation on basal ganglia activity. The high-frequency stimulation of the internal pallidum attenuates its hyperactivity and results in a marked improvement of motor function. Brown arrows indicate inhibitory pathways, and green arrows, excitatory pathways. The thickness of arrows indicates the firing activity of the respective pathway. The size and outlining of each box indicate the level of activity of the brain region. (Adapted from 50)

Subthalamic high frequency stimulation (STN HFS) influences both basal ganglia output nuclei, the SNPR and GPi. Therefore, we would assume a better antiparkinsonian motor control with bilateral STN HFS (Figure 6).

In idiopathic Parkinson's disease, the STN sustained no damage, and the resulting hyperactivity of its neurons highly suppresses the activity of thalamic nuclei via the activation of inhibitory relays. [127] The reduction of the STN hyperactivity state by lesioning, [128] pharmacologic, [129] and high-frequency stimulation techniques [130] in

animal models of PD, accompanied by a significant improvement in parkinsonian features, highlighted the role of the STN as a promising target in the management of PD in humans.

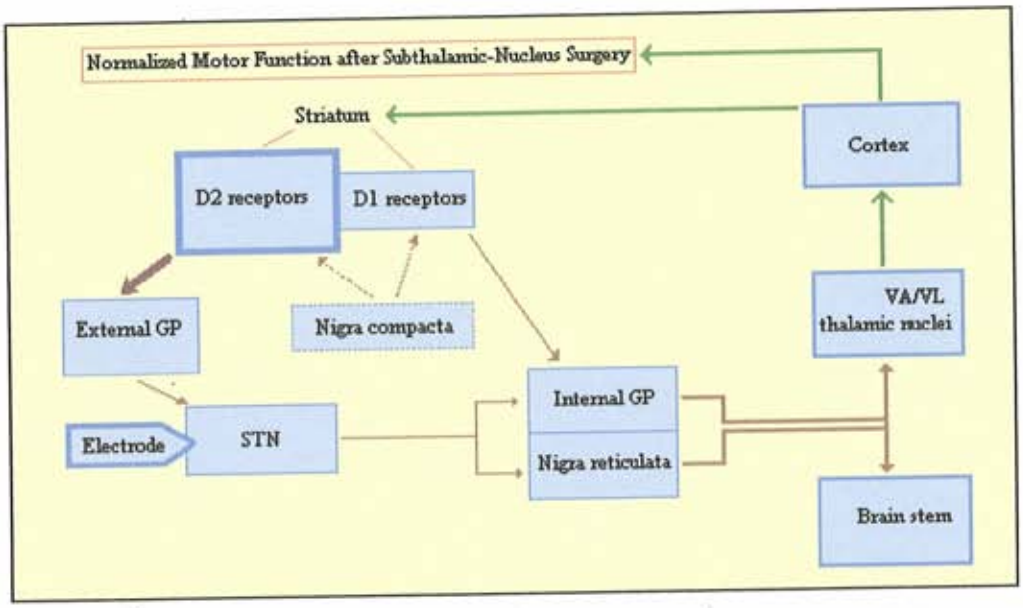


Figure 6. Neurological implications of STN HFS on basal ganglia activity. The high-frequency stimulation of the subthalamic nucleus attenuates its hyperactivity and results in the dysinhibition of the thalamocortical pathway. Brown arrows indicate inhibitory pathways, and green arrows, excitatory pathways. The thickness of arrows indicates the firing activity of the respective pathway. The size and outlining of each box indicate the level of activity of the brain region. (Adapted from 50)

Limousin et al. [131] studied the effect of STN HFS on 24 patients with severe idiopathic Parkinson's disease and motor complications. Twelve months after surgery, results revealed the safety and efficacy of STN HFS procedure in reducing the severity of parkinsonian motor disability and the mean dose of dopaminergic drugs by approximately 50%.

A further development and refinement of this technique permitted the direct visualization of the STN and limited the complications using a three-dimensional stereotactic magnetic resonance imaging coupled with electrophysiologic intra-operative guidance. [132] In their study, Bejjani and colleagues tested the effectiveness of this technique 6 months after surgery on 12 patients with advanced, levodopa-

reponsive idiopathic PD, and revealed a significant improvement in motor condition in the "off" and "on" medication states of 64% and 78%, respectively.

Interestingly, the improvement of all motor symptoms after bilateral STN HFS was highly comparable to the preoperative on-levodopa motor control. Thus, the levodopa test predicts the outcome of this procedure on selected PD patients. The antiparkinsonian treatment was reduced by 70% accompanied by a substantial attenuation of LIDs, and motor fluctuations.

Bilateral STN HFS produced a marked improvement of axial [133,134] and appendicular parkinsonism to a greater degree than that achieved with unilateral STN DBS, this thought to be due to the ipsilateral and contralateral synergistic effects of this procedure on PD neuropathology. [134] Nevertheless, the mode of action of STN HFS remains speculative and consistent with a rapid suppression of neuronal firing in SNPR and GPi. Currently, STN HFS is still considered an investigational procedure in the United States.

A systemic prospective appraisal comparing the effect of bilateral GPi and STN HFS in PD has not been carried out, yet, in a retrospective analysis conducted by Krack et al. [133] comparing the effects of chronic GPi and STN stimulation in 13 young-onset PD patients, chronic stimulation of the GPi was two-fold more effective than chronic STN HFS in lowering the severity of LID ($P < 0.05$); However, STN stimulation permitted a levodopa dose reduction of 56%- compared to a 29% increase with GPi stimulation – which permitted indirectly a further reduction in LIDs similar to that obtained with GPi HFS. The improvement in tremor, rigidity and LIDs was comparable in both groups but STN HFS had a better anti-akinetic effect. Such preliminary comparison greatly favours the stimulation of the STN, rather than GPi, for the treatment of advanced PD.

On the other hand, Burchiel et al. [136] revealed an indistinguishable efficacy in PD motor control between these two procedures, in their prospective small pilot study; Nevertheless, there is a clear need for a large-scale study to randomly assess DBS for GPi and STN DBS in advanced PD.

The effect of chronic STN stimulation revealed a sustained and significant improvement three years after surgery, [137] while GPi patients fail to bypass the second year post GPi stimulation before they started to show an increase in UPDRS score, despite the adjusted therapeutic parameters and doses. [138]

The following adverse effects have been noted in patients subjected to DBS: intracerebral hematoma, subcutaneous infection, transient confusion, hallucinations, temporospatial disorientation, abulia, dyskinesias, eyelid-opening apraxia, hypophonia, dyarthria, dysphagia, postural instability, and a transient aggravation of dyskinesias during the first posoperative weeks, mostly in those suffering from the most severe LIDs. This latter side effect can be controlled by adjusting the stimulation voltage and /or lowering the dopaminergic pharmacologic stimulation. [131, 139] Few cases of acute depression have been associated with the stimulation of a specific contact in STN stimulated patients when optimal stimulation settings were used. [132,37,138] The memory and overall cognitive performance were not greatly affected in PD patients subjected to either GPi or STN HFS. [142]

2.2.6.3 *Fetal Nigral Transplantation and Gene Therapy*

Besides performing a lesion or stimulating subcortical nuclei to lessen their overactivity, scientists tried to approach the pathological condition from another perspective when they tried to make up for the causative dopaminergic loss in the SNPC. The most promising restorative procedures currently under development involve human and porcine fetal nigral transplantation. Preliminary reports showed typical re-innervation of the striatum accompanied by clinical benefit and the resolution of symptoms in PD patients; however, it remains to define the optimal parameters for transplantation sites, and to establish the long-term safety and efficacy of these surgical procedures. [50]

Genetic manipulation of dopaminergic cells is another potential means for their preservation and/or metabolic modulation of enzymatic expressions needed in dopamine biosynthetic pathway.

PRELIMINARY CONCLUSION

Parkinson's disease is a neurodegenerative disorder and a debilitating illness that mainly affects motor performances during the latter third of patients' lifetime. Afflicted patients present mainly with progressive motor disabilities that negatively affect their daily living and quality of life; They mainly include resting tremor, plastic rigidity, bradykinesia, and later on, postural instability.

A cardinal histological feature in PD is the substantial attrition of dopaminergic substantia nigra pars compacta neurons. This results in striatal dopamine deficit. The subsequent overactivity of subthalamic nuclei results in an excessive inhibition of the thalamocortical pathway and the shutdown of brain stem nuclei, accounting for the typical PD semiology.

The homeostatic role of dopamine in proper neuronal functioning and its loss in PD, led to the emergence of multiple therapeutic strategies for the management of Parkinson's disease is either neuroprotective (pharmacologic) or symptomatic (pharmacologic and surgical).

Levodopa therapy remains the mainstay in the symptomatic treatment of PD. While it is considered to be the most potent drug for controlling parkinsonian symptoms, there is much concern about the emergence of complex motor behavior, namely motor fluctuations and dyskinesias, and a decrease in efficacy when chronically used.

Direct-acting dopamine agonists represent an alternative dopaminergic means for motor control. Although they showed a relatively lower efficacy than levodopa, they were successfully used as adjunctive to the latter, and introduced as early PD monotherapy. Such practice smoothed out and delayed the emergence of levodopa therapy-induced motor complications.

Patients refractory to conservative therapy are being surgically treated. Subthalamic high frequency stimulation (STN HFS) revealed its superiority over other stereotactic techniques. STN HFS improved parkinsonian motor disability, levodopa-induced dyskinesias, and motor fluctuations.

Overall, PD has been effectively managed with dopaminergic therapy, yet, the progressive nature of the disease associated with the limitations of the pharmacological treatment promoted the consideration of STN HFS in advanced PD cases.

PART II: A PROMISING THERAPEUTIC APPROACH UNDER INVESTIGATION: DOPAMINE AGONIST MONOTHERAPY AFTER SUBTHALAMIC STIMULATION IN ADVANCED PARKINSON'S DISEASE

1 BACKGROUND AND OBJECTIVES

Continuous subthalamic high frequency stimulation (STN HFS) is being used in the treatment of advanced Parkinson's disease (PD). [131, 133,139] Although the mechanism underlying its therapeutic benefit remains speculative, STN HFS demonstrated an improvement in disease staging, [133, 142-145] parkinsonian motor disability, [131,135,139, 143-148] as well as a reduction in levodopa-induced dyskinesias (LIDs) [132,139, 143,144,145,147,148] and motor fluctuations. [132,144,145,148] Antiparkinsonian daily dosages were reduced by 40 to 70 %, [131,132,143,144,145,148] and a complete withdrawal was noted in only zero to 17% of operated PD patients.

All reported studies presented the impact of STN HFS on postoperative pharmacological therapy as a reduction in equivalent levodopa dosages. [131,132,143,144,145,148] Although detailed data disclosed a substantial decrease in levodopa and dopamine agonists, [131,144,148] no study clearly proposed a strategy that preferentially relies on either levodopa or dopamine agonists use after STN HFS.

The introduction of dopamine agonists as add-on therapy permitted a decrease in levodopa needs. [94,149-152] Their early use in PD therapy delayed levodopa introduction[152] and reduced the rate of motor fluctuations and LIDs. [95] The trend towards early dopamine agonist monotherapy was, hence, further promoted. [92,153,154]

The advantages of using dopamine agonists early in the treatment of PD encourage the establishment of an innovative postoperative pharmacological approach based on the use of dopamine agonist monotherapy after surgery. The aim is to reduce

levodopa needs and avoid pulsatile dopaminergic insult, thus, reducing the risks of recurrence of motor fluctuations and levodopa-induced dyskinesias (LIDs).

In light of the advantages engendering dopamine agonist use in PD therapy, the inherent ability of STN stimulation in the juvenescence of parkinsonian condition, and the persistent need for antiparkinsonian treatment in more than 80% of operated cases, the following study reports the results of five PD patients with STN HFS and goes further to investigate the potentials of a postoperative pharmacological approach based on the use of dopamine agonists monotherapy after STN HFS.

2. METHODS

2.1 Patients and Study Design

Five patients (3 men and 2 women) with a mean (standard error of the mean [SEM]) age of 58 (12) years (range 38-73 years) and a mean (SEM) duration of disease of 16 (6) years (range 8-31 years) were considered for STN neurosurgery between September 1999, and April 2000 (Table 3). Selection criteria included a clinically diagnosed severe idiopathic Parkinson's disease (Hoehn & Yahr score of 4 and 5) significantly responsive to levodopa therapy (more than 50% improvement in motor disability after an acute levodopa challenge test), and presenting with disabling motor fluctuations and dyskinesias despite optimal antiparkinsonian management. Prior response to dopamine agonists and their tolerability were further warranted for patients' enrollment into the proposed protocol. Written consents were obtained from all recruited patients.

Excluded patients were older than 75 years, with Parkinson –like syndromes, cognitive impairment, active psychiatric disorders, and MR imaging evidence of other neurological diseases.

Table 3. Baseline patients characteristics.

Case	*Age(y)/ sex*	*Disease Duration (y)*	*H&Y* (off/on)*	*UPDRS III§ (off/on)*	*UPDRS IV (A/B)¤*	*LEDD¶ (mg)*
1	*38/M*	*31*	*5/3*	*76/15*	*5/6*	*3150*
2	*49/M*	*10*	*4/2.5*	*72/12*	*6/5*	*1200*
3	*56/F*	*15*	*5/1.5*	*68/12*	*10/5*	*1900*
4	*73/M*	*8*	*4/2.5*	*42/18*	*3/5*	*850*
5	*72/F*	*15*	*5/3*	*78/16*	*10/7*	*100*
Mean (SEM)	*58 (7)*	*16 (4)*	*4.6 (0.2)/ 2.5 (0.3)*	*67 (6.5) / 15 (1.2)*	*7(1.4)/ 6(0.4)*	*1440 (516)*

** Hoehn & Yahr score (range 0-5)*
§ Unified Parkinson's Disease motor score (range 0- 108)
¤ Unified Parkinson's Disease Rating Score for complications of therapy: Part A (Dyskinesias, range 0-13), Part B (Clinical fluctuations, range 0-7)
¶ Levodopa equivalent daily dose (LEDD) = levodopa dose +10 x bromocriptine or apomorphine dose + 20 x ropinirole dose + 100 x pergolide or lisuride or pramipexole dose.

The surgical procedure was mainly based on STN localization prior to surgery and intraoperative electrophysiological recording and exploratory stimulation. Implanted electrodes (Medtronic, Minneapolis, MN, USA) have four contacts numbered from 0 (distal) to 3 (proximal) over a length of 7.5 mm, through which current can be separately applied to the most effective STN sites. All patients were bilaterally operated during the same surgical session under local anesthesia; this was followed by the connection of the twelve electrodes to programmable pulse generators (Itrel II, or Kinetra, Medtronic, USA) implanted in the subclavicular areas via tunneled subcutaneous extension cables. The latter procedure was eventually done under general anesthesia.

2.2 Postsurgical Management

2.2.1 Determination of Electrical Settings

Optimal stimulation contacts and parameters (maximal antiparkinsonian effect and side effects threshold) were determined ten days after electrodes implantation in the off and on-drug conditions by the same observer after an overnight without antiparkinsonian medication, and then, after drug administration, using previously settled protocol. [125,132] Stimulation parameters could be further adjusted to the presenting clinical pattern, as needed.

2.2.2 Establishment of Pharmacologic Treatment

In the postoperative phase, patients were allocated to resume their pre-surgical dopaminergic therapy based on dopamine agonist. During the following three months study interim, patients were mainly maintained on dopamine agonists (pergolide). Pergolide dose was titrated for optimization and stabilization of the clinical status of individual patients, with an upper ceiling of 4mg per day. Patients who could not be maintained on sole pergolide therapy were rescued with levodopa + DDI. Domperidone was used to control nausea, vomiting, or dizziness. No concurrent antiparkinsonian agents were allowed to be administered throughout the study period, nor their new introduction into therapy. Any other interfering drugs were not also permitted to be used during this therapeutic period.

2.3 Clinical Assessment

Patients underwent a levodopa challenge within the two months before surgery using a supra-threshold levodopa dose (*i.e.* 50-mg more than the usual preoperative morning dose). This test was performed in the morning after a complete antiparkinsonian drug withdrawal for more than 12 hours. We scored patients at baseline and during the maximal motor improvement (usually after one hour of levodopa intake [153]) using the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS-III – see appendix).

After surgery, safety, tolerability and efficacy of the adopted therapeutic regimen were weekly assessed using UPDRS-III, and the Hoehn and Yahr staging scale (H&Y). Responders were defined as having at least a 30 % reduction in UPDRS-III score and an improvement in H&Y staging (stage 0-5, stage 5 being the most severe form) between baseline and last visit. A fixed dose of dopamine agonist was maintained for at least the last two weeks before determining the final measure of efficacy, 12 weeks after surgery in the on-stimulation and off- and on-drug conditions. Tolerability was evaluated using UPDRS part IV subscore (complications of therapy), by recording any reported adverse effects and measuring vital signs at each follow-up visits. The study was conducted in an open manner, and patients were prospectively followed for twelve weeks after surgery at the Parkinson's and Movements disorders center - Notre-Dame des Secours Hospital, Byblos-Lebanon. Figure 7 shows the evaluation protocol followed during the study period during which dopamine agonist therapy was adopted after bilateral STN HFS.

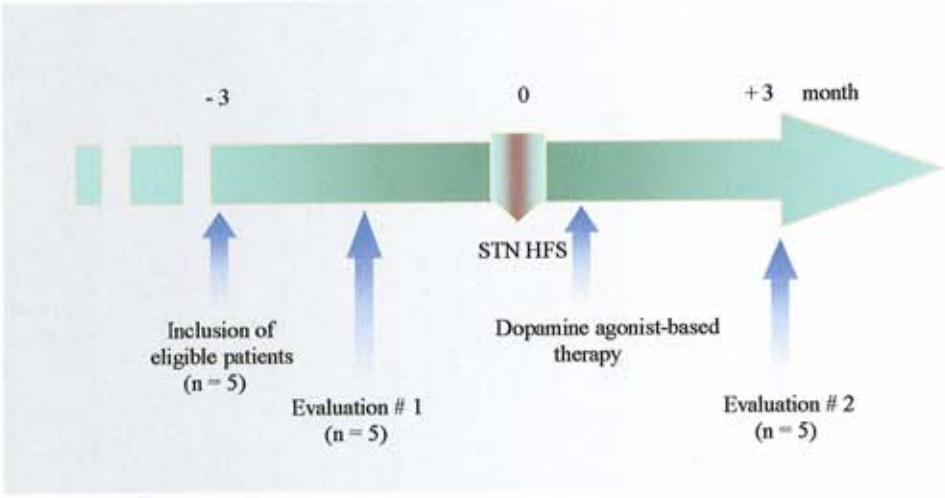


Figure 7. Study protocol flowchart.

2.4 Endpoints

The primary endpoint was the maintenance of STN patients on a dopamine agonist while eliminating or minimizing the need for levodopa therapy.

The secondary endpoint measures the clinical response of STN operated patients to dopamine agonist therapy, and the incidence of motor complications and adverse events 12 weeks after surgery.

2.5 Statistical Analysis

Results and doses were expressed as means with standard error of the mean (SEM). Data analysis was mainly performed on motor scores before and after surgery (stimulation on) in the off and on-drug conditions, as well as on levodopa and dopamine agonists dosage modulations. Outcomes were compared using the Wilcoxon signed rank paired statistical test. The significance threshold used for all analysis was set to $p < 0.05$.

3. RESULTS

The five patients enrolled in the study were able to reach the primary endpoint.

3.1 Efficacy of STN HFS and the proposed dopaminergic treatment

Before surgery, a supraliminal dose of levodopa improved motor disability by 78 % when compared to baseline subscore ($p = 0.043$). Twelve weeks after surgery, chronic STN stimulation alone was capable of achieving an 82 % reduction from baseline UPDRS motor score ($p = 0.043$), an approximately similar outcome to pre-surgical on-levodopa challenge ($p = 0.068$). The combination of STN stimulation and the assigned treatment permitted an 88.7% improvement from the baseline mean motor score ($p = 0.043$), a significantly greater achievement than that obtained either with STN stimulation alone ($p = 0.039$) or, preoperatively obtained after levodopa test ($p = 0.042$). (Figure 8)

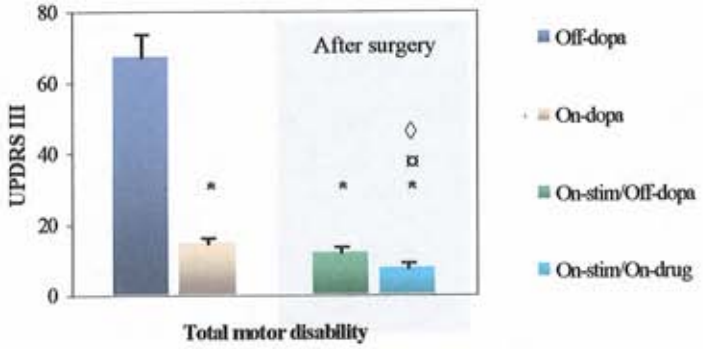


Figure 8. Effects of levodopa and the proposed treatment on the parkinsonian motor disability score (UPDRS III, range 0 -108) before, and 3 months after surgery. Values represent mean ± SEM.
* $p = 0.043$, when compared to baseline value; ¤ $p = 0.039$ when compared to sole STN HFS effect;
◊ $p = 0.042$, when compared to preoperative levodopa effect.

3.2 Tolerability of the Therapeutic Regimen

The postoperative stage has been characterized by an 82.14 % ($p = 0.042$) and 82.35% ($p = 0.043$) decrease in the rate and severity of motor fluctuations and dyskinesias, respectively, when compared to the presurgical condition (Figure 9). Their prevalence was nevertheless innocuous, never exacerbating the overall motor condition. No major side effects have been reported during the postoperative follow-up period that required patient's withdrawal from the study. However, patient 3 experienced a transient confusion and urinary incontinence and patient 5 developed a hematoma far from the surgical field. Domperidone was used to control nausea in the five patients. No clinically significant abnormalities in vital signs have been noted in any of our patients.

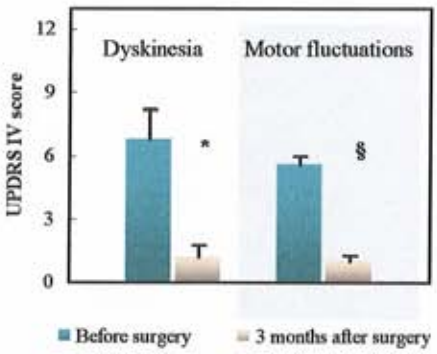


Figure 9. Effect of STN HFS and postoperative pharmacological therapy on motor complications. UPDRS IV-A (Dyskinesias) score range 0 – 13 (* $p = 0.043$, when compared to presurgical values); UPDRS IV-B (Motor fluctuations) score range 0 –7 (§ $p = 0.042$, when compared to presurgical values). Values represent mean ± SEM.

3.3 Treatment Modulation

Three of our patients were maintained on dopamine agonist monotherapy for 12 weeks after surgery. Two patients required the addition of levodopa. STN stimulation allowed a 77 % reduction of the levodopa-equivalent daily dose when compared to the preoperative level ($p = 0.08$). After surgery, levodopa therapy was stopped, while maintaining our patients on a constant pergolide dose insofar as possible. Pergolide dose was slowly titrated (often in increments of 0.25 mg every 3 days) in response to patient's condition. The mean (SEM) daily dose of levodopa was lowered from of 1265 (514) to 130 (97) mg per day, or 90 % from baseline level ($p < 0.01$), while the average (SEM) daily dose of pergolide equivalence was increased from 1.750 (0.67) mg to 2.05 (0.56) mg per day, or approximately 15% from preoperative level ($p = 0.5$). (Figure 10).

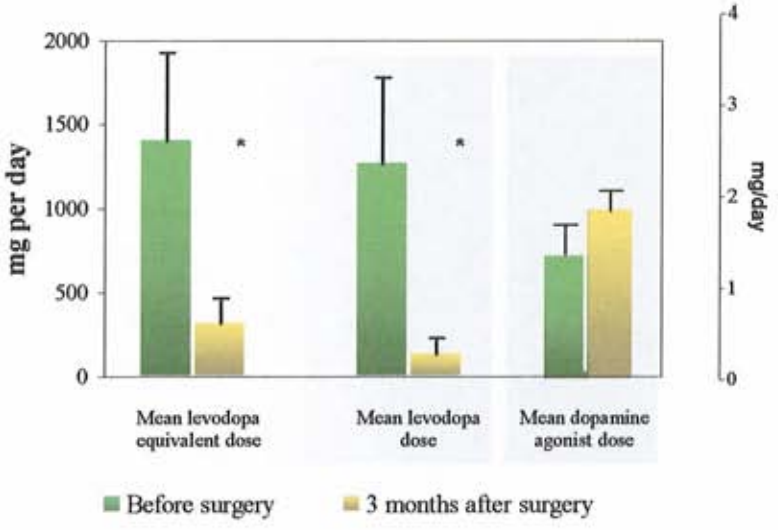


Figure 10. Detected variations in the pharmacological treatment 3 months after surgery. Values represent mean ± SEM. * $p < 0.01$.

4. DISCUSSION

Chronic bilateral stimulation of subthalamic nuclei was capable of controlling the general motor condition and attenuate implicated disabilities in these advanced PD cases. In agreement with previous results, [131,132,144] preoperative levodopa effect was highly predictive of the postoperative on-stimulation condition. Such positive outcome revealed that STN HFS positive effect could be complemented by adjunctive dopamine receptor stimulation for optimal stabilization and control of patients' condition. Concomitant levodopa intake provided further clinical improvement in motor disability. Indeed, this latter assumption was further reflected in our patients' response to dopamine agonist (with or without levodopa) therapeutic effect throughout the study period.

Our therapeutic approach mainly based on pergolide, a D_1/D_2 agonist, provided a considerable improvement in the overall parkinsonian condition, and a clinical control usually reported when used in early stages of the disease. [92]

In the postoperative phase, no major adverse events have been reported. The adopted therapeutic approach was well tolerated due to the successful slow titration regimen associated with domperidone intake. Experienced adverse effects were mild and comparable to those observed in other studies investigating the utility of pergolide in early and advanced disease stages. [92,150,152,156] Recently, a number of studies exploring STN HFS efficacy revealed an approximate 80% decrease in LID and a 90% reduction in the incidence rate of motor fluctuations. [132,145] This was thought to be partially attributed to the decrease in levodopa-equivalent dose and/or chronic STN stimulation effect on dyskinesia threshold. The congruency of our results with these latter findings reflects not only the efficacy of the neurosurgical procedure but also the implication of our postsurgical therapeutic approach on the clinical outcome.

Our series of operated patients responded well to a significantly reduced levodopa-equivalent dose that was superior to all previously reported findings. The maximum decrease in LEDD was 70%. [132] Similarly, our results showed a sustained benefit with a dramatically low mean levodopa dose. Patients were effectively and mainly controlled on a daily mean pergolide dose that was slightly higher than preoperative adjunctive mean dopamine agonist daily intake; This can be due to the dependence on dopamine agonist, as sole/main dopaminergic replacement therapy to control residual motor disabilities. Ensuing decrease in motor fluctuations and dyskinesia rates are, hence, partially attributed to the decrease in levodopa intake and the basic reliance on dopamine agonist usage.

Our results reflected the effectiveness of the therapeutic approach mainly based on dopamine agonists in controlling parkinsonian symptoms in PD patients subjected to STN HFS. Previous studies have already focused on the need for dopamine replacement therapy in most of these patients, while in a small percentage of them, no further treatment was needed. [131,132,145] The need for continuous dopaminergic stimulation resides from the permanent striatal dopamine deficiency in those advanced PD cases, responsible for the homeostatic control of basal ganglia output neurons.

While levodopa remained the mainstay antiparkinsonian treatment, dopamine agonist therapy was traditionally limited to early disease stages or later introduced when complex motor behavior emerges. Interestingly, the positive therapeutic benefit of our therapeutic approach mainly based on pergolide represents a major challenge in understanding the influence of chronic STN HFS on PD pathological condition. Levodopa therapy is known to induce pre- and postsynaptic alterations in dopamine receptors thought to be at the origin of motor complications experienced after its

chronic use. [53, 157-159] Indeed, while Blanchet et al. [158] have revealed the ability of pulsatile levodopa stimulation to induce a progressive sensitization and upregulation of putaminal D_1 receptors correlated with chorea of increasing intensity, Bordet et al. [159] revealed a heightened and long-lasting D_3 receptors expression in the denervated striatum.

Dopamine agonists are known to be long acting direct dopamine receptor stimulators, bypassing the degenerative condition of nigrostriatal terminals and the potential disturbances in mediator release. Therefore we speculate that dopamine receptors are more readily and fully accessible to exogenous direct acting dopamine agonists, rather than to levodopa, especially in chronically treated PD patients. In 70 to 100 % of patients with STN HFS there is a need for antiparkinsonian treatment after surgery.[131, 132,148] The advantages engendered by the use of dopamine agonists early in the treatment PD incite the establishment of an innovative postoperative pharmacological approach based on the use of dopamine agonist monotherapy after surgery. The aim is to reduce levodopa needs and avoid pulsatile dopaminergic insult reducing the risks of recurrence of motor fluctuations and levodopa-induced dyskinesias (LIDs).

On the other hand, current neurophysiological studies have demonstrated the paramount role of the subthalamic nucleus in conditioning the activity of nigral pars compacta (SNPC) neurons. [161,162] These *in vitro* studies demonstrated that the electrophysiological condition of SNPC neurons is mainly under the control of GABAergic afferents from pars reticulata (SNPR) neurons, particularly in advanced PD cases. Given the presumed STN HFS potential in limiting the hyperactivity of nigral and pallidal output gateways, we can postulate an indirect role of subthalamic

HFS to trigger dopamine synthesis and release from highly active residual pars compacta neurons. Nevertheless, the severe reduction in structural neuronal integrity in advanced PD precludes, in most of these cases, a tonic supra-threshold dopaminergic stimulation of striatal hypersensitive dopamine receptors. This resulted in a lower but continuous need for a concurrent dopaminergic therapy for the majority of PD patients after surgery.

Therefore, subthalamic DBS might have been contributing to the overall benefit either via inducing dopamine release, as discussed previously, boosting dopamine agonist effect, and /or via dysinhibition of thalamocortical pathway.

The latter assumption came in agreement with multiple previous findings favoring STN HFS as a potential mean to hamper the chaotic electrophysiological condition of basal ganglia gateways. [131,147] The ensuing dysinhibition of the thalamocortical circuitry restores the cortical glutamatergic input to nigral and striatal cells, and the subsequent neuronal activation. A further induction of striatal D_1 and D_2 receptors by the administration of pergolide can potentiate the glutamatergic excitatory effect from the cortex, via cAMP-protein kinase A and calcium-calmodulin-dependent kinase II pathways, respectively, favoring an enhanced control over GPi and SNPR nuclei. [46,163] Despite the ambiguity of the underlying mechanism, the expansion in the use of dopamine agonist after surgery would permit some delay in resuming levodopa therapy, or minimize its need. This will eventually decrease and delay the incidence of motor disability mostly associated with chronic levodopa intake, especially that a little is still known about STN HFS impact on PD pharmacodynamic and neuropathologic conditions. By virtue of their long half-life and their potential to assure a continuous stimulation of dopamine receptors, dopamine agonists represent an alternative therapeutic option to anticipate or smooth out emerging motor swings

and off-period dystonia. Ancillary sensory, autonomic, cognitive and psychiatric fluctuations associated with "on/off" fluctuations would additionally be attenuated with the use of continuous dopaminergic stimulation. [164] The use of pergolide by our patients could thus be considered preventive as well as a therapeutic measure. Overall, the results of the current study do not reflect but a mere evidence of the potential values of dopamine agonist therapy after STN HFS. With our small series of patients, short follow-up period, and the absence of a parallel comparison with a levodopa-based treatment, we cannot claim the definite efficacy of our therapeutic approach, nor its superiority to other regimens. This study was nevertheless designed to be the pilot in setting forth the need for a larger, double-blind, randomized and well controlled clinical trial investigating, in a comparative context, the differential value of levodopa and dopamine agonists after STN surgery. This can ultimately set valuable clues to the establishment of the finest therapeutic management of the post subthalamic stimulation era.

CONCLUSION

Despite the lack of firm evidence revealing the genuine etiopathogenesis of PD, the antiparkinsonian arsenal includes now a wider spectrum of pharmacological agents and surgical techniques, which can control motor disability but not cure or prevent the progression of the disease.

Levodopa therapy remains the most potent symptomatic treatment of PD, but after several years motor complications (dyskinesias and motor fluctuations) arise. The use of dopamine agonists, as early monotherapy or add-on therapy, has shown to be effective in reducing and delaying treatment complications. However, despite optimal pharmacological management, these complications increase leading to severe disability and loss of normal motor function. Our clinical study revealed that STN HFS is an adaptable, safe, and effective stereotactic procedure with a reproducible effect on PD patients; it permitted to control the entire constellation of parkinsionian motor symptoms. We suggest that dopamine agonists can be potentially used in the management of residual motor disability before adding levodopa until a general guideline gets established.

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APPENDIX

Unified Parkinson's Disease Rating Scale*

(UPDRS)

I – Mentation, Behavior and Mood

1. Intellectual Impairment

0 = None
1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder
0 = None.
1 = Vivid dreams.
2 = "Benign" hallucinations with insight retained.
3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
4 = Persistent hallucinations, delusions, or forrid psychosis. Not able to care for self.

3. Depression
0 = Not present
1 = Periods of sadness or guilt greater than normal, never sustained to days or weeks.
2 = Sustained depression (1 week or more).
3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative
0 = Normal.
1 = Less assertive than usual; more passive.
2 = Loss of initiative or disinterest in elective (non-routine) activities.
3 = Loss of initiative or disinterest in day to day (routine) activities.
4 = Withdrawn, complete loss of motivation.

II. Activities of Daily Living [For both 'on' and 'off']

5. Speech

0 = Normal.
1 = Mildly affected. Not difficulty being understood.
2 = Moderately affected. Sometimes asked to repeat statements.
3 = Severely affected. Frequently asked to repeat statements.
4 = Unintelligible most of the time.

6. Salivation
0 = Normal.
1 = Slight but definitive excess of saliva in mouth; may have night-time drooling.
2 = Moderately excessive saliva; may have minimal drooling.
3 = marked excess of saliva with some drooling.
4 = marked drooling, requires constant tissue or handkerchief.

7. Swallowing
0 = Normal.
1 = Rarely choking.
2 = Occasional choking.
3 = Requires soft food.
4 = Requires NG tube or gastrostomy feeding.

8. Handwriting
0 = Normal.
1 = Slightly slow or small.
2 = Moderately slow or small; all words are legible.
3 = Severely affected; not all words are legible.

9. Cutting food and handling utensils
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can cut most foods. Although clumsy and slow; some help needed.
3 = Food must be cut by someone, but can still feed slowly.
4 = Needs to be fed.

10. Dressing
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Occasional assistance with buttoning, getting arms in sleeves.
3 = Considerable help required, but can do some things alone.
4 = Helpless.

11. Hygiene
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Needs help to shower or bathe; or very slow in hygienic care.
3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4 = Foley catheter-or-other mechanical aids.

12. Turning in bed and adjusting bed clothes
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can turn alone or adjust sheets, but with great difficulty.
3 = Can initiate, but not turn or adjust sheets alone.
4 = Helpless.

13. Falling [unrelated to freezing]
0 = None.
1 = Rare falling.
2 = Occasional falls, less than once per day.
3 = Falls an average of once daily.
4 = Falls more from freezing.

14. Freezing when walking.
0 = Normal.
1 = Rare freezing when walking, may have start-hesitation.
2 = occasional freezing when walking.
3 = Frequent freezing. Occasional falls from freezing.
4 = Frequent falls from freezing.

15. Walking.
0 = Normal.
1 = Mild difficulty. May not swing arms or may tend to drag leg.
2 = Moderate difficulty, but requires little or no assistance.
3 = Severe disturbance of walking, requiring assistance.
4 = Can not walk at all, even with assistance.

16. Tremor [Symptomatic complaint of tremor in any part of body]
0 = Absent.
1 = Slight and infrequently present.
2 = Moderate; bothersome to patient.
3 = Severe, interferes with many activities.
4 = Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism.
0 = None.
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching, not distressing.
3 = Frequently painful sensations.
4 = Excruciating pain.

III. Motor Examination

18. Speech
0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. Facial expression
0 = Normal.
1 = Minimal hypomimia, could be normal 'Poker face'.
2 = Slight but definitely abnormal diminution of facial expression.
3 = Moderate hypomimia; lips parted some of the time.
4 = masked or fixed facies with severe or complete loss of facial expression; lips parted ¼ inch or more.

20. Tremor at rest
0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplutide, but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

21. Action or Posture [Tremor of hands]
0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

22. Rigidity [judged on passive movement of major points with patient relaxed in sitting position; ignore cogwheeling]
0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

23. Finger Taps [Patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately]
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

24. Hand Movements [patient opens and closes hands in rapid succession with widest amplitude possible, each hand separately.]
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands [Pronation supination movements of hands, vertically or horizontally, with as large an amplitude as possible, each hand separately.]
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

26. Leg Agility [Patient taps heel on ground in rapid succession, picking up entire leg. Amplitude should be about 3 inches.]
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

27. Arising from Chair [Patient attempts to arise from a straight-back wood or metal chair with arms folded across chest.]
0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try rare than than one time, but can get up without help.
4 = Unable to arise without help.

28. Posture
0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaned to one side.
4 = Marked flexion with extreme abnormality of posture.

29. Gait
0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbances to gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability [Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared, and can have had some practice runs.]
0 = Normal.
1 = Retropulsion, but recovers unaided.

2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, trends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. Body Bradykinesias and Hypokinesia. [Combining slowness, hesistancy, decreased arms swing, small amplitude, and poverty of movement in general.]
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

IV. Complications of Therapy [in the past weeks.]

A. DYSKINESIAS
32. Duration: What proportion of the waking day are dyskinesias present? [Historical information.]
0 = None.
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

33. Disability: How disabling are the dyskinesias? [Historical information; may be modified by office examination.]
0 = Not disabling.
1 = Mildly disabling.
2 = Moderately disabling.
3 = Severely disabling.
4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias: How painful are the dyskinsias?
0 = No painful dyskinesias.
1 = Slight.
2 = Moderate.
3 = Severe.
4 = Marked.

35. Presence of Early Morning Dystonia [Historical information.]
0 = No.
1 = Yes.

B. CLINICAL FLUCTUATIONS
36. Are any 'off' periods predictable as to timing after a dose of medication?
0 = No.
1 = Yes.

37. Are any 'off' periods unpredictable as to timing after a dose of medication?
0 = No.
1 = Yes.

38. Do any of the 'off' periods come on suddenly, e.g., over a few seconds?
0 = No.
1 = Yes.

39. What proportion of the waking day is the patient 'off' on average?

0 = None.

1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

C. OTHER COMPLICATIONS

40. Does the patient have anorexia, nausea, or vomiting?
0 = No.
1 = Yes.

41. Does the patient have any sleep disturbances. e.g. insomnia or hypersomnolence?

0 = No.
1 = Yes.

42. Does the patient have symptomatic orthostasis? [Record the patient's blood pressure, height and weight on the scoring form.]
0 = No.
1 = Yes.

V. Modified Hoehn and Yahr Staging

Stage 0	No signs of disease.
Stage 1	Unilateral disease.
Stage 1.5	Unilateral plus axial involvement.
Stage 2	Bilateral disease, without impairment of balance.
Stage 2.5	Mild bilateral disease; with recovery on pull test.
Stage 3	Mild to moderate bilateral disease; some postural instability; physically independent.
Stage 4	Severe disability; still able to walk or stand unassisted.
Stage 5	Wheelchair bound or bedridden unless aided.

VI. Schwab and England Activities of Daily Living Scale [It's O.K. to select a number in between the definitions.]

100% Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.

90% Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.

80% Completely independent, in most chores. Takes twice as long. Conscious of difficulty and slowness.

70% Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.

60% Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.

50% More dependent. Help with half of chores, slower, etc. Difficulty with everything.

40% Very dependent. Can assist with all chores, but few alone.

30% With effort, now and then does a few chores alone or begins alone. Much help needed.

20% Nothing alone. Can b slight gelp with sone chores. Severe invalid.

10% Totally dependent. Helpless. Complete invalid.

0% Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bed-ridden.

* Fahn S, Elton R, Members of the UPDRS Development Committee. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. *Recent Developments in Parkinson's Disease*, Vol 2.Florham Park, NJ. Macmillan Health Care Information 1987, pp 153-163.