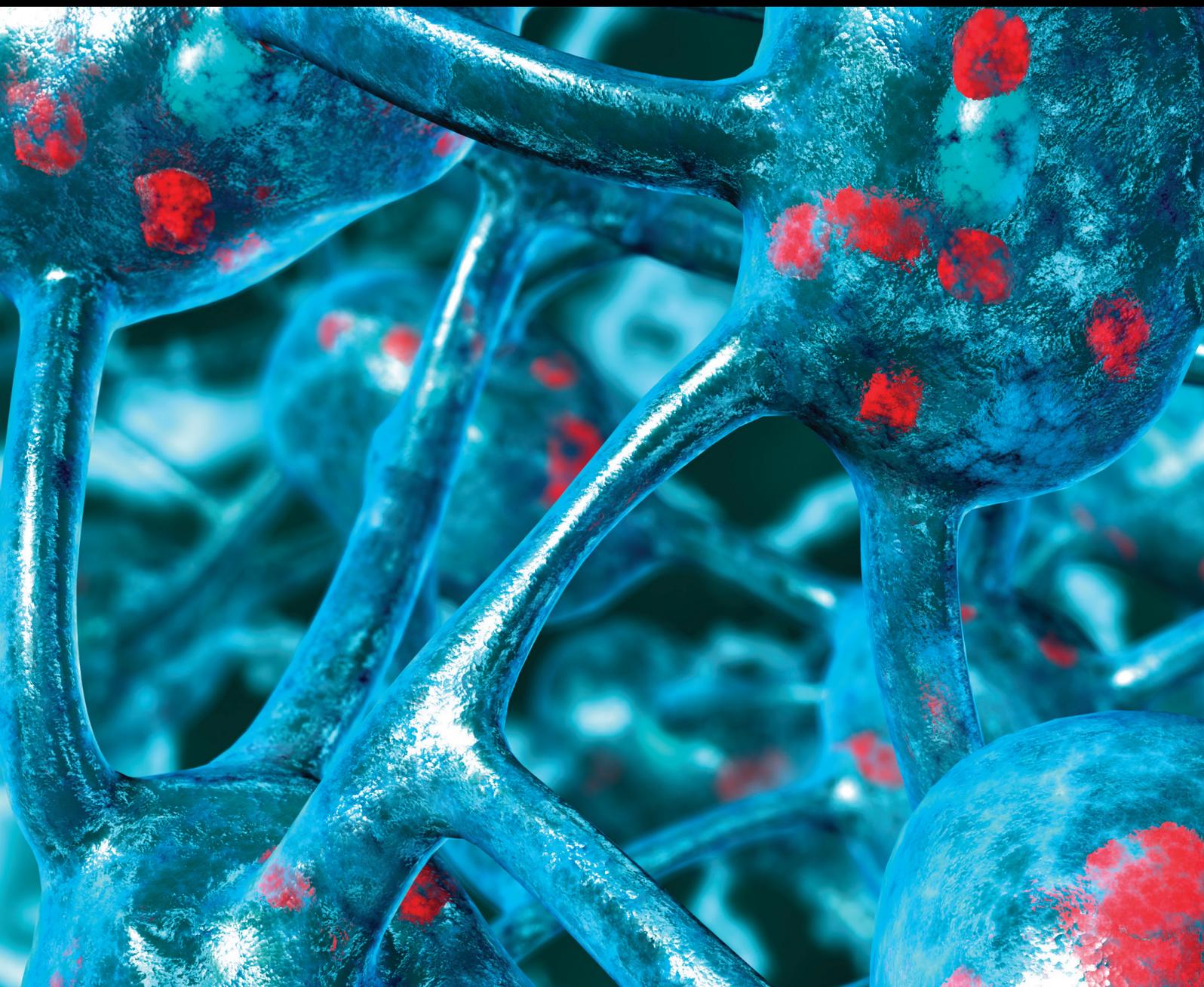


Parkinson's Disease

Parkinson's Disease: New Insights into Pathophysiology and Rehabilitative Approaches

Guest Editors: Vincenza Frisardi, Andrea Santamato, and Binith Cheeran





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Editorial

Parkinson's Disease: New Insights into Pathophysiology and Rehabilitative Approaches

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Parkinson's disease (PD) is a multifactorial neurodegenerative disorder, but up till now, its etiology remains largely unknown. Progressive impairment of voluntary motor control, which represents the primary clinical feature of the disease, is caused by a loss of midbrain substantia nigra dopamine (DA) neurons. PD prevalence increases steadily with age. Therefore, with the aging population, we will see an increase in social and health impact of this disease. Currently, the drugs available improve physical performances and lengthen life expectancy and autonomy in the activities of daily living by reducing adverse events; it follows that they improve the quality of life of patients. However, these drugs are symptomatic and not curative. When the patient reaches the maximum allowable therapeutic dosage of levodopa, we have to face great difficulties and impotence in disease's management.

Recently, the role of rehabilitation in the field of neurodegenerative diseases is becoming more and more important as it results from several studies. In this special issue, we wanted to focus our attention on the "holistic view" of the disease because we believe that only a multidisciplinary approach could help to face it in the best way. PD involves miscellaneous systems (physical, mental, and behavioral structures) affecting also the autonomy in self-care management. Furthermore, in this special issue we wanted to draw the attention to the importance of rehabilitation in PD.

An amount of epidemiological evidence stressed the importance of the relationships between genetic and environmental factors. L. Polito et al. summarize evidence on

gene-environment interplay in the development of PD focusing on susceptibility factors and causal genetic mutation. To the best of our knowledge, this review is the first attempt to analyze all those genetic factors that modify the impact of environmental exposure.

Brilliantly, F. Magrinelli et al. contributed to examining the neuropathology, neuropharmacology, and neurophysiology of motor dysfunction of PD, with particular attention to those clinical features that impair quality of life and functional ability of patients. Starting from anatomic basis of the main circuit involved in PD, subsequently they analyzed the pathophysiology of PD motor symptoms (bradykinesia and tremor rigidity) and signs (postural balance, gait impairment, fatigue, and pain).

Currently, pharmacological treatment of motor symptoms of PD depends mainly on the administration of dopaminergic drugs (levodopa and dopamine agonists) and other drugs involved in levodopa metabolism (monoamine oxidase-B inhibitors and catechol-O-methyltransferase inhibitors). Usually, in the late disease stages, PD patients treated by dopaminergic drugs display various complications, such as *on-off* fluctuations of Parkinsonian symptoms and dyskinesia. Unfortunately, most patients with advanced PD are unsatisfactorily controlled by the usual therapeutic approach. A. Daniele et al. examine other pharmacological targets regardless of the dopaminergic pathway. In particular, they focus on potential beneficial effects of zolpidem, a positive allosteric modulator of GABAA receptors, on the motor

symptoms of PD. In fact, some studies have previously suggested that there is a high density of zolpidem binding sites in the globus pallidus and in the substantia nigra, which are the output structures of the basal ganglia.

Two experimental works complete this brief special issue. The first is a case control study carried out by M. Tramontano et al. with the aim of investigating the efficacy of a blindfolded balance training in the improvement of gait parameters in people with PD compared to patients who underwent a standard physical therapy program.

The second is a prospective open-label feasibility study evaluating the impact of 8-week action observation training (video-therapy) for the treatment of postural instability and balance impairment in PD patients. Although in this latter study A. Santamato et al. did not find positive results, they underline one of the most important shortcomings in PD rehabilitation field. In fact, absence of standard procedures to improve balance and posture in PD subjects makes this area a virgin field to explore.

We hope that the contents of this special issue may help clinicians better understand the rationale of current pharmacological and rehabilitation strategies for PD and give viability to further studies that integrate current knowledge with innovations in the field of rehabilitation.

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Review Article

Pathophysiology of Motor Dysfunction in Parkinson's Disease as the Rationale for Drug Treatment and Rehabilitation

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Cardinal motor features of Parkinson's disease (PD) include bradykinesia, rest tremor, and rigidity, which appear in the early stages of the disease and largely depend on dopaminergic nigrostriatal denervation. Intermediate and advanced PD stages are characterized by motor fluctuations and dyskinesia, which depend on complex mechanisms secondary to severe nigrostriatal loss and to the problems related to oral levodopa absorption, and motor and nonmotor symptoms and signs that are secondary to marked dopaminergic loss and multisystem neurodegeneration with damage to nondopaminergic pathways. Nondopaminergic dysfunction results in motor problems, including posture, balance and gait disturbances, and fatigue, and nonmotor problems, encompassing depression, apathy, cognitive impairment, sleep disturbances, pain, and autonomic dysfunction. There are a number of symptomatic drugs for PD motor signs, but the pharmacological resources for nonmotor signs and symptoms are limited, and rehabilitation may contribute to their treatment. The present review will focus on classical notions and recent insights into the neuropathology, neuropharmacology, and neurophysiology of motor dysfunction of PD. These pieces of information represent the basis for the pharmacological, neurosurgical, and rehabilitative approaches to PD.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease (AD), with an overall prevalence of 300 per 100,000 [1] that rises from 41 in the 40–49 years' age range to 1903 in people older than age of 80 years [2].

PD has been traditionally considered as a pure movement disorder secondary to focal degeneration of dopaminergic neurons in the substantia nigra, but, in recent years, the clinical phenotype has been better illuminated, showing that PD is a multisystem neurodegenerative disorder with motor and nonmotor features (Table 1) [3]. Among motor symptoms and signs, the cardinal ones (bradykinesia, rest tremor, and rigidity) are mainly ascribed to the loss of dopaminergic neurons [4], but those involving posture, balance, and gait

are largely secondary to degeneration of nondopaminergic pathways and significantly contribute to impairment and disability in advanced PD patients [5]. Nonmotor features result from multiple neurotransmitter deficiencies in the central and peripheral nervous system [6] and include psychiatric (depression, apathy, hallucinations, and delusions) and autonomic (constipation, orthostatic hypotension, and urinary and genital disturbances) features, cognitive impairment (involvement of executive functions, memory, and visuospatial functions up to dementia) [7, 8], sleep disorders, olfactory dysfunction, and pain [9] that together contribute to worsening the quality of life (QoL) and patient's disability [6].

Multiple agents have been studied in randomized controlled trials (RCTs) designed to assess disease modification

TABLE 1: The glossary of the main motor and nonmotor symptoms and signs in Parkinson's disease.

Symptom or sign	Description
Cardinal motor symptoms and signs	
Bradykinesia	Slowness of voluntary movement and/or a movement that is ongoing. For the companion terms akinesia and hypokinesia, see below
Rest tremor	Asymmetric 4–6 Hz moderate amplitude tremor, which usually involves the thumb (<i>pill-rolling</i> tremor). It may involve other body parts, such as the forearm pronation/supination, the leg adduction/abduction, and the jaw. Head tremor is rarely seen in PD. For other PD tremor types, see the text
Rigidity	Increased muscle tone felt during examination by passive movement of the affected segment, involving both flexor and extensor muscles and not increased with higher mobilization speed (in contrast with spasticity)
Postural instability	Impaired postural adjustment due to decrease or loss of postural reflexes
Other motor symptoms and signs (early and advanced disease stages)	
Akinesia	Reduction, delay, or absence of either voluntary, spontaneous, or associated movement
Hypokinesia	Reduced movement amplitude, particularly with repetitive movements
Hypomimia	Reduced facial expression
Hypophonia	Reduced voice volume
Micrographia	Small handwriting that becomes progressively smaller and less readable
Festination	Involuntary gait acceleration with step shortening
Tachyphemia	Acceleration of speech segments
Sialorrhea	Drooling of saliva
Dysarthria	Slurred speech
Dysphagia	Difficulty in swallowing
On phase	A phase characterized by a beneficial effect of levodopa with release from the parkinsonian symptoms and signs
Off phase	A phase, in which the parkinsonian symptoms and signs take over, sometimes in the form of a crisis with severe bradykinesia, rigidity, and tremor. Nonmotor off features include pain, paresthesia, sweating, thoracic oppression, and anxiety symptoms
Freezing of gait	Difficulty in gait initiation (start hesitation) and paroxysmal unintentional episodes of motor block during walking
Postural instability	Impaired postural adjustment due to decrease or loss of postural reflexes
Akathisia	Feeling of inner restlessness and strong need to be in constant motion associated with the inability to sit or stay still
Camptocormia	Abnormal involuntary flexion of the trunk that appears when standing or walking and disappears in the supine position
Anterocollis	Marked neck flexion (>45%), disproportionate to trunk flexion
Pisa syndrome	Tonic lateral flexion of the trunk associated with slight rotation along the sagittal plane
Selected nonmotor symptoms and signs	
Hyposmia/anosmia	Reduction/loss of the sense of smell
Constipation	Infrequent and frequently incomplete bowel movements
Orthostatic hypotension	A decrease in systolic blood pressure of at least 20 mm Hg or a decrease in diastolic blood pressure of at least 10 mm Hg within three minutes of standing when compared with blood pressure from the sitting or supine position
Fatigue	Overwhelming sense of tiredness and feeling of exhaustion with difficulties in initiating and sustaining mental and physical tasks
Apathy	Lack of motivation characterized by diminished goal-oriented behavior and cognition and reduced emotional expression
Restless legs syndrome	Movement disorder characterized by compelling urge to move the legs, particularly when in bed and trying to sleep

For depression, cognitive problems, and pain, see the text. PD: Parkinson's disease.

or neuroprotection in PD, but all have failed [10], and medical treatment remains symptomatic [10]. Pharmacological therapy is based on levodopa and dopamine agonists and is very successful in the early stages of the disease, when dopaminergic symptoms and signs are predominant and long term motor complications still have not developed, but other treatment strategies are almost invariably necessary as time passes [3]. Long term levodopa-induced motor complications include motor fluctuations and dyskinesia and affect almost all PD patients at some point during the disease course, with relevant implications in global health status [11]. Despite various pharmacological approaches, as well as more invasive strategies including devices and functional neurosurgery, being available to manage such complications, many patients remain significantly disabled, and a fully satisfying management of motor complications is still an unmet need of PD therapy [11]. Nonmotor symptoms and signs are integral to PD at onset and throughout the disease course, but to date their treatment is largely unsatisfactory [9].

This review will summarize the evidence on the pathophysiology of PD motor symptoms and signs and give some insight into their neuropathological and neuropharmacological bases. These pieces of information may help the clinicians to better understand the rationale of current pharmacological and rehabilitation strategies for PD and encompass the large areas of uncertainty that should represent the focus for further studies.

2. The Functional Anatomy and Pathophysiology of the Basal Ganglia and the Role of the Cerebellum

The basal ganglia (BG) include the striatum, which comprises the caudate nucleus, putamen, and nucleus accumbens, the globus pallidus that is divided into an external segment (GPe) and an internal segment (GPi), the substantia nigra that can be divided into a pars compacta (SNc) and a pars reticulata (SNr), and the subthalamic nucleus (STN) [14]. The main input region of the BG is the striatum, which receives afferents from many regions of the cerebral cortex, including motor and premotor, cingulate, and prefrontal cortices, and the intralaminar nuclei of the thalamus [14–16]. The major output regions of the BG are the GPi and the SNr, which project to the thalamus modulating activity of cortical regions and to the brainstem [14–16]. The input and output regions are connected via either the direct or the indirect pathways, both of which arise from the matrix medium spiny neurons of the striatum (Figure 1), while the striosomal medium spiny neurons control dopaminergic projections from the SNc [14–17]. Corticostriatal projections, intrinsic BG circuits, and output pathways are functionally arranged according to the BG loop involved (Figure 2) [16, 17]. The main neurotransmitter of BG circuit is the inhibitory gamma-aminobutyric acid (GABA), while neurons of the STN use excitatory glutamate, and those of the SNc use dopamine [18]. Despite its oversimplification, the basic BG circuitry and the balance between the direct and indirect striatal pathways provide a simple heuristic model for PD cardinal signs and

dyskinesia [16, 17]. According to this model, the pathophysiological hallmark of PD hypokinetic signs is the prevalence of the indirect pathway over the direct one resulting in increased neuronal firing activity in the output nuclei of the BG and leading to excessive inhibition of thalamocortical and brainstem motor systems, interfering with normal speed of movement onset and execution (Figure 1) [14–16]. At variance, overactivity in the direct pathway and imbalance with the indirect one may cause reduced inhibitory BG output and result in reduced BG filtering and parallel facilitation of multiple movement fragments causing dyskinesia, including those induced by levodopa in advanced PD [16, 19]. This model and its prediction of increased STN and GPi activity in PD fit well with the efficacy of targeting and inhibiting these two nuclei with deep brain stimulation (DBS), which represents the gold standard treatment of motor fluctuations and dyskinesia in advanced PD [20]. Despite its merits, this model is blinded to a number of experimental and clinical data, including the following issues: (a) the large number of BG neurotransmitters, neuromodulators, and their receptors goes beyond GABA, glutamate, and dopamine [21], and the complex arrangement of medium spiny neurons in matrix and striosome [17] does not fit well with a simple direct-indirect pathway imbalance; (b) the model should go beyond the simple concept of firing rate and include firing pattern, synchronization, and coincidence to better understand BG circuitry functioning; (c) while the model can convincingly explain bradykinesia, it fails to completely account for the appearance of rigidity and tremor; (d) pallidotomy or GPi DBS does not cause hyperkinesia, as predicted by this model, but may paradoxically reduce PD hyperkinetic signs; (e) hypokinetic and hyperkinetic signs can coexist in PD patients and cannot be simply considered as two sides of the same coin; (f) BG surgery and DBS can be performed with little or no apparent deficits [16, 22]. Future updated models of BG functions should incorporate a more complex BG circuitry and include nonlinear dynamics to address these issues [16].

The BG circuitries play a key role in selecting a motor program and inhibiting undesired ones and in movement preparation and execution, but their functions go beyond the motor system and include crucial functions such as learning, planning, executive functions, and emotions [14]. According to their connections, BG loops are functionally subdivided into motor, oculomotor, associative, and limbic ones (Figure 2) [12, 13, 16]. The motor loop is organized somatotopically and according to specific tasks or parts of a motor sequence [12, 16]. Abnormally synchronized oscillatory activity in this loop correlates with motor deficit in PD, and its suppression by dopaminergic therapies, ablative surgery, or DBS might provide the basic mechanism for the amelioration of motor impairment [23]. The oculomotor circuit is involved in the control of saccadic and smooth pursuit eye movements, which are abnormal in most PD patients [24]. The main abnormality consists of saccade hypometria, although all types (predictive, anticipatory, and memory-guided) of saccade generation may be involved [24]. Dopaminergic therapy and DBS of the STN reduce saccade latencies in parallel with the improvement of hand bradykinesia [25]. The dysfunction of the limbic circuit contributes broadly to some

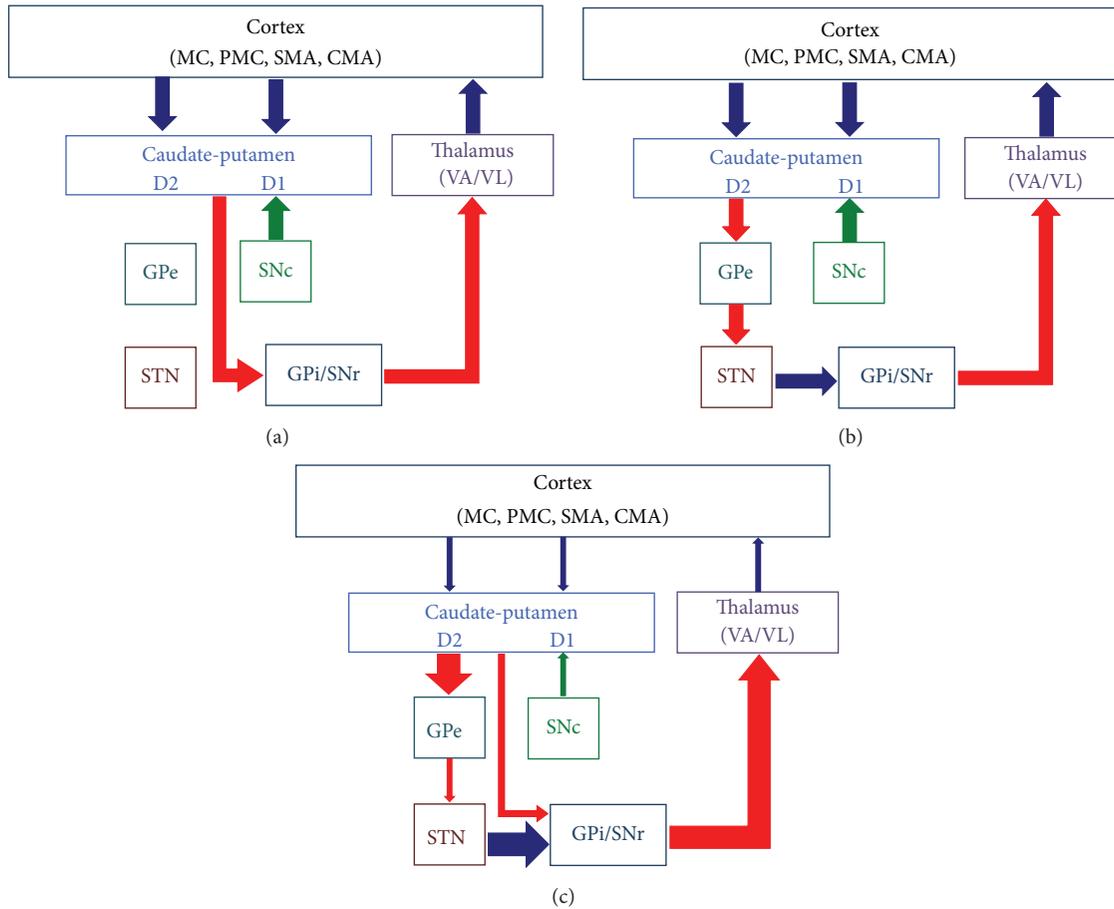


FIGURE 1: A simplified view of the functional anatomy of the basal ganglia (BG). The main input and output connections and the basic internal circuitry of the BG are shown. Here are represented the direct pathway (panel (a)), the indirect pathway (panel (b)), and the alteration of the balance between the direct and indirect pathways in Parkinson's disease (panel (c)). Blue arrows show the excitatory glutamatergic pathways, red arrows indicate the inhibitory GABAergic pathways, and green arrows mark the dopaminergic pathway. CMA: cingulate motor area; D1: dopamine D1 receptor; D2: dopamine D2 receptor; GPe: external segment of the globus pallidus; GPi: internal segment of the globus pallidus; MC: primary motor cortex; PMC: premotor cortex; SMA: supplementary motor area; SNc: substantia nigra pars compacta; SNr: substantia nigra pars reticulata; STN: subthalamic nucleus; VA/VL: ventral anterior/ventrolateral thalamic nuclei.

PD behavioral aspects, which include reward dysregulation phenomena, emotional blunting [26], and impulse control disorders secondary to dopaminergic treatment [27]. The associative loop takes part in prefrontal cognitive functions, and its impairment is responsible for cognitive inertia and executive dysfunction in PD [26].

The BG and the cerebellum modulate the activity of largely overlapping cerebral cortical areas through multisynaptic loops, which were traditionally assumed to be anatomically and functionally separate [28]. Recent studies showed that the dentate nucleus of the cerebellum projects to the striatum and to the GPe and that the STN has topographical projections to the cerebellar cortex via the pontine nuclei [29]. These reciprocal connections between the BG and the cerebellum, together with neuropathological changes in the cerebellum, account for the hypothesis that the cerebellum plays a role in the pathogenesis of PD symptoms and signs [28]. Functional MRI studies showed hyperactivation or strengthened connectivity in the cerebellum of

PD patients [30], but whether it represents a pathogenetic or compensatory change is still debated [31]. Converging pieces of evidence accumulated recently in favor of a role of the cerebellum in some PD symptoms and signs, including tremor [32], gait disturbances through its connections with the pedunculopontine nucleus (PPN) [33], dyskinesia [34], and nonmotor symptoms, suggesting that the cerebellum might represent a promising new target for neuromodulation [28].

3. The Neuropathology of PD

The classical pathologic substrate for PD is the accumulation of neuronal inclusions composed of α -synuclein and called Lewy bodies and neurites and neuronal loss [35]. Neuronal loss is most marked in the SNc [35], but Lewy bodies in PD extend well beyond this region [36]. Based on the distribution of α -synuclein pathology, a staging scheme for PD has been proposed [36]. According to this scheme, neuronal pathology

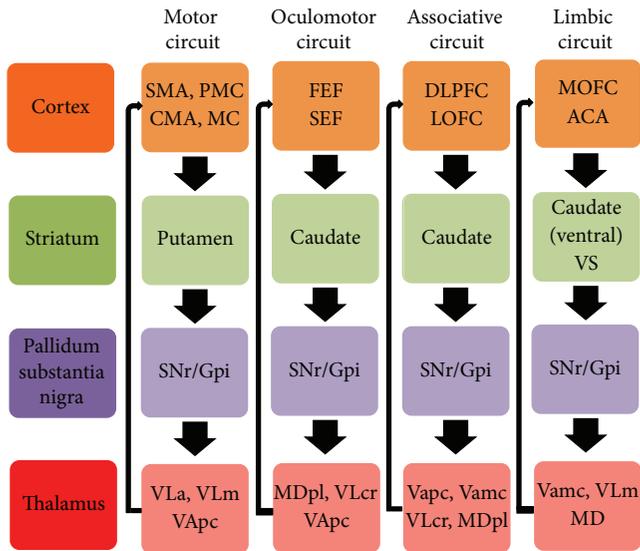


FIGURE 2: The parallel motor, oculomotor, associative, and limbic circuits of the basal ganglia. ACA: anterior cingulate area; CMA: cingulate motor area; DLPFC: dorsolateral prefrontal cortex; FEF: frontal eye fields; Gpi: internal segment of the globus pallidus; LOFC: lateral orbitofrontal cortex; MC: primary motor cortex; MD: mediodorsal nucleus of the thalamus; MDpl: mediodorsal nucleus of thalamus, pars lateralis; MOFC: medial orbitofrontal cortex; PMC: premotor cortex; SEF: supplementary eye field; SMA: supplementary motor area; SNr: substantia nigra pars reticulata; VAmc: ventral anterior nucleus of thalamus, pars magnocellularis; VApc: ventral anterior nucleus of thalamus, pars parvocellularis; VLa: anterior ventrolateral nucleus of the thalamus; VLcr: ventrolateral nucleus of thalamus, pars caudalis, rostral division; VLm: ventrolateral nucleus of thalamus, pars medialis; VS: ventral striatum [12, 13].

occurs early in the dorsal motor nucleus of the vagus and the olfactory bulbs, then spreads to the locus coeruleus and SNc when motor signs appear, later on extends to the basal forebrain, amygdala, and the medial temporal lobe structures, and finally affects the convexity cortical areas in final stages [36]. Although this staging scheme is attractive since it fits well with the occurrence of nonmotor symptoms and signs across the clinical course of PD, it has been debated because it is based on autopsy and not on longitudinal studies, and it does not always hold true in all the patients [37]. In addition to a number of brain areas, neuronal loss and α -synuclein deposition involve also the peripheral nervous system, suggesting that PD is a multiorgan disease process, not merely a disorder of the central nervous system [38].

It has become increasingly evident that PD is a heterogeneous disorder in terms of symptoms and signs and natural history, and, based on cluster analysis, two PD subtypes have been proposed, namely, tremor-dominant PD and postural instability and gait difficulty (PIGD) PD [39, 40]. Tremor-dominant PD occurs earlier (20–40 years); it is often genetic and has good prognosis with slow progression, good response to levodopa, and motor fluctuations [40]. At variance, PIGD PD occurs sporadically after the age of 60 years with predominant bradykinesia and rigidity and earlier

occurrence of depression and dementia [40]. Some studies suggested that the two PD subtypes show neuropathological differences, which include greater neuronal loss in the SNc, especially in its lateral portion, and the locus coeruleus, more severe dopamine loss in the ventral Gpi and a larger number of cortical Lewy bodies in PIGD PD, and more severe loss of neurons in the midbrain retrorubral A8 field in tremor-dominant PD [40]. Although these data suggest that PD subtypes have different neuropathology, they are based on small autopsy studies, with no available biological markers that can lend support to this hypothesis in vivo [40].

4. The Neuropharmacology of PD

The neuronal loss and α -synuclein deposition in the SNc cause the involvement of dopaminergic neurons, the neuropharmacological hallmark of PD, and the rationale for the treatment with levodopa and dopamine agonists [35]. PD symptoms and signs appear only after substantial (i.e., >70%) degeneration of the SNc neurons, documenting remarkable compensatory phenomena within the nigrostriatal system [41].

The neuropathological changes in other brain areas result in degeneration of nondopaminergic pathways, which contributes to motor and nonmotor PD features. Nondopaminergic neurotransmitters and neuromediators include cholinergic, adenosinergic, glutamatergic, GABAergic, noradrenergic, serotonergic, opioidergic, and histaminergic systems (Table 2) [21]. The relative contribution of each of these pathways to single motor and nonmotor symptoms and signs and motor complications in PD is only partially explored, but they may represent potential targets for new pharmaceutical interventions [21]. In recent years, many RCTs have been completed and are ongoing or planned to explore drugs to counterbalance the loss of these neurotransmitters (Table 2), and it has been hypothesized that multiple targeting may be a more efficacious strategy, especially if they act in a synergistic manner [21].

Loss of cholinergic neurons in the PPN and the nucleus basalis of Meynert may contribute to posture and gait signs and falls through failure in the direct control of spinal circuitries and the deficits in the attentional processes required for these tasks [42, 43] and to cognitive impairment [7, 43]. The large aspiny interneurons in the striatum contain also large quantities of acetylcholine, which interacts with muscarinic and nicotinic receptors [44]. Centrally acting cholinesterase inhibitors, such as donepezil and rivastigmine, which delay acetylcholine degradation and prolong its effect, are commonly used in AD- and PD-related dementia and appear to offer promising preliminary results for gait disturbances in PD (Table 2) [21].

Adenosine acts with the A_{2A} receptors, which are located in the dendritic spines of the medium spiny neurons of the striatum and counteract the inhibitory action of indirect dopaminergic D2 receptors with no effect on the excitatory D1 pathway [21]. Drugs that antagonize A_{2A} receptor activity in combination with levodopa have been found to reduce off time in PD patients with motor fluctuations and improve on time with dyskinesia without changing the amount of

TABLE 2: Nondopaminergic neurotransmitters involved in the pathogenesis of Parkinson's disease and pharmacological agents potentially active or tested to counteract their deficit.

Neurotransmitter	Site	Symptom/sign	Drug
Acetylcholine	PPN, nucleus basalis of Meynert, striatum	Posture and gait disturbances, FOG, cognitive problems	Cholinesterase inhibitors, nicotinic receptor agonists
Adenosine	Striatum	Motor fluctuations, dyskinesia	Adenosine A_{2A} receptor antagonists, caffeine
GABA	GPe, STN	Motor fluctuations, dyskinesia	GAD gene therapy
Glutamate	Striatum, STN	Dyskinesia, FOG	NMDA receptor antagonists, AMPA receptor antagonists, mGluNAMs
Histamine	Striatum	Dyskinesia	H_2 receptor antagonists
Noradrenaline	GPe, locus coeruleus	Balance and gait disturbances, FOG, dyskinesia	Methylphenidate, α_2 receptor antagonists
Serotonin	Dorsal raphe nucleus, striatum, GP, SN	Motor fluctuations, dyskinesia	5-HT $_{1A}$ receptor antagonists

5-HT $_{1A}$: serotonin receptor 1A; A_{2A} : adenosine receptor A2; AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; FOG: freezing of gait; GABA: gamma-aminobutyric acid; GAD: glutamic acid decarboxylase; GP: globus pallidus; GPe: external segment of the globus pallidus; mGluNAMs: metabotropic glutamate receptor negative allosteric modulators; NMDA: N-methyl-D-aspartate; PPN: pedunculopontine nucleus; SN: substantia nigra; STN: subthalamic nucleus.

troublesome peak-dose dyskinesia [45]. Caffeinated coffee consumption is inversely related to PD risk, suggesting a possible and largely debated neuroprotective effect of caffeine and/or effect on motor function [21]. Caffeine is a nonselective A_{2A} receptor antagonist that has been found to improve motor signs in PD in small trials [46], but larger RCTs are needed to confirm these preliminary findings and to establish whether they are sustained [21].

5. Pathophysiology of Bradykinesia in PD

The terms bradykinesia, hypokinesia, and akinesia collectively define a group of functional disturbance of voluntary movement prominently characterized by slowness [47]. Bradykinesia refers to slowness of movement that is ongoing, akinesia indicates failure of voluntary, spontaneous (e.g., in facial expression), or associated movement (e.g., arm swing during walking) to occur, and hypokinesia refers to movements that are smaller than desired, in particular with repetitive movements [47]. In addition to whole-body slowness, bradykinesia may impair the fine motor movements, which is usually demonstrated in PD patients during rapid alternating movements of fingers, hand, or feet as a progressive reduction of speed and motion amplitude [47]. Bradykinesia is represented cranially by loss of facial expression (hypomimia), decreased frequency of blinking, monotonic and hypophonic speech, and drooling due to decreased spontaneous swallowing. Other manifestations of bradykinesia are slowness in raising from a chair, loss of spontaneous gesturing, reduction of handwriting (micrographia), reduced arm swing when walking, and reduced gait amplitude and velocity [47]. Although both speed and movement amplitude are affected in PD, the former is usually disproportionately more affected in off state and less normalized by levodopa than the latter, suggesting that they may be associated with partially separate mechanisms [48].

The pathophysiology of bradykinesia is not completely understood, but among PD cardinal signs, it is the one that fits better with the classical model of the prevalence of the indirect pathway over the direct one in the BG (Figure 1) [14–16]. According to this model, failure of the BG output to reinforce the cortical mechanisms may involve the preparation of the movement or its execution [14–16, 47].

Deficits in movement preparation in PD patients have been documented by slower reaction times [49, 50] and slower increase in premovement cortical excitability [51], which together suggest abnormal retrieval of stored motor commands [47]. EEG studies showed premovement potential abnormalities [52], which were more marked in self-paced versus externally triggered movements [53] and are consistent with reduced activity in the supplementary motor area during movement programming [47]. EEG activity is physiologically represented by predominant alpha (10 Hz) and beta (20–30 Hz) range during motor inactivity and tonic position holding and when stopping a preplanned movement, while alpha and beta power is decreased ~1s before movement [54]. Beta activity has been hypothesized to represent an idle rhythm that favors the status quo over new movements [55]. Premovement EEG beta desynchronization is reduced in PD patients, and this abnormality is at least partially normalized by dopaminergic stimulation [56]. Local field potential recording in the BG indicates a coupling between cortical and STN and GPi beta rhythms off medication, while they are decoupled on medication [57]. Beta band power suppression to levodopa was demonstrated to correlate with improvement in bradykinesia and rigidity but not tremor, suggesting a specific pathogenetic significance [58]. In accordance with these pieces of evidence, closed loop STN DBS, where stimulation frequency is automatically adjusted online according to the current state of the underlying network activity, may offer advantages over current fixed frequency

(usually 130 Hz) DBS and its application could represent a therapeutic advancement in PD [59].

Deficits in movement execution include difficulties in producing maximal voluntary contraction [60] and abnormalities in the ballistic movement triphasic electromyographic pattern, which is composed of a first agonist muscle burst, followed by a second antagonist muscle burst and variably by a third agonist burst [47]. The size and duration of the first agonist burst in PD patients are reduced and suggest inappropriate scaling of the dynamic muscle force to the required movement parameters [61]. PD patients have additional difficulties represented by fatigue in complex or repetitive movements, and this can be clinically assessed when testing repetitive hand opening/closing or finger tapping [62]. It has also been suggested that PD patients have limited processing mechanisms that may interfere with their ability to run complex or simultaneous tasks [63].

Abnormalities of cortical excitability [64, 65], somatosensory function [66], and sensorimotor integration [67, 68] and changes in the pattern of activation in the motor and premotor cortices and the supplementary motor area [69, 70] may also contribute to deficits in movement execution in PD [47]. Whether these alterations represent true pathogenetic mechanisms of bradykinesia or compensatory changes is still unclear [64, 70, 71].

Secondary factors that may contribute to bradykinesia include muscle weakness [60], rigidity [72], rest and action tremor [73], and movement variability and bradyphrenia [47].

6. Pathophysiology of Tremor in PD

PD patients can show different tremor types [74, 75]. They include rest tremor, which stands among the PD cardinal signs, especially in the tremor-dominant subtype [4, 40], an action tremor named *reemergent tremor*, which reappears few seconds after the transition from rest to posture and has a frequency similar to that of rest tremor, essential tremor, dystonic tremor [74], and exaggerated physiological tremor [75]. We will focus on the pathophysiology of rest tremor, which is usually asymmetric with moderate amplitude, medium (4–6 Hz) frequency, and an agonist-antagonist alternate contraction pattern [76]. It typically involves the hand, manifesting as a pill-rolling movement, and less frequently the forearm as a pronation-supination, the leg as an adduction-abduction, the jaw, and/or head as a yes-yes or no-no motion [76]. Rest tremor is usually enhanced by motor or cognitive tasks and not influenced by weighting [76].

The pathophysiology of rest tremor is largely unknown, but there is good evidence that it differs from that of bradykinesia and rigidity [77]. Rest tremor can be more severe on the side opposite that of worse bradykinesia and the magnitude of tremor is not related to dopamine deficiency and does not respond readily to dopaminergic treatment [75]. Some reports suggest a role of dopaminergic loss in the midbrain retrorubral A8 field, which projects to the pallidum and is separate from the nigrostriatal pathways, in the genesis of rest tremor [32, 77]. The severity of rest tremor was found to correlate with a decrease in median raphe serotonin

receptor binding [78], suggesting that serotonergic rather than dopaminergic neuron loss might be more relevant to the pathogenesis of this symptom, but this point is controversial because serotonergic drugs do not usually improve tremor in PD [75].

Several hypotheses, which share the view of a central rather than peripheral origin, have been suggested to explain the pathophysiology of rest tremor [32]. Bursts that are correlated with tremor have been demonstrated in a number of cortical and subcortical areas, but the exact localization of the primary tremor pacemaker is still debated [32, 76]. Thalamocortical relay neurons have ion channel properties that support pacemaking at approximately rest tremor frequency and may be modulated through hyperpolarization by reducing excitatory drive or excitatory input from the cerebellum [79]. Other models suggest a role of the recurrent loop between GPe and the STN as the primary oscillator [80] and the STN-cortical oscillatory coupling [81]. The cerebellum seems to have a central role in PD tremor pathogenesis, because rest tremor disappears following lesions of the ventralis intermedius (VIM) thalamic nucleus, which receives cerebellar input, and cerebellar stimulation may alter the timing of peripheral tremor. An emergent model indicates abnormally synchronized BG-thalamocortical (BGTC) loop, a GPe-STN pacemaker, and the cerebellar dentate-thalamocortical (CTC) circuit as the main actors producing rest tremor [32, 77]. According to this hypothesis, the GPe-STN pacemaker and the BGTC loop trigger tremor episodes, and the CTC circuit maintains and modulates their amplitude [77]. This model is in accordance with the observation that stereotactic lesions in selected areas of the BGTC (STN, primary motor cortex, ventrolateral thalamic nucleus, and pallidum) or the CTC (VIM) may abolish rest tremor [77, 81].

7. Pathophysiology of Rigidity in PD

PD rigidity is characterized by increased muscle tone to palpation at rest, reduced distension to passive movement, increased resistance to stretching, and facilitation of the shortening reaction [82]. Rigidity is more marked in flexor than extensor muscles, may be enhanced by voluntary movement of other body parts, and is more remarkable during slow than fast stretching, and these features help differentiating PD rigidity from spasticity, which is worse during fast displacement [82, 83]. Cogwheel phenomenon is the result of coexisting rigidity and tremor [82].

The pathogenesis of PD rigidity has been hypothesized to include changes in the passive mechanical properties of joints, tendons, and muscles, the enhancement of stretch-evoked reflexes from segmental spinal or supraspinal activity, and abnormalities in peripheral sensory inputs that may influence the response to muscle stretch [83–86]. Studies on spinal reflexes indicate a shift of spinal cord motoneurons towards increased activity in response to peripheral stimulation [84, 85] and increased response to muscle stretch [83], with a possible contribution of transcortical long-latency stretch reflex [86]. How these changes are associated with dopamine deficiency and BG output abnormalities, which are

stipulated by the classical BG pathophysiological model, is still unclear [82].

8. Pathophysiology of Motor Fluctuations and Dyskinesia

After several years of smooth and stable response to oral levodopa treatment, PD patients invariably develop motor complications, which include motor fluctuations and dyskinesia [87, 88]. Motor fluctuations include wearing-off, delayed-on, partial-on, no-on, and on-off fluctuations (Table 3) [87]. Dyskinesia is choreic, ballistic, or dystonic involuntary movements and can be classified into peak-dose, diphasic, and square-wave dyskinesia (Table 3) [87]. Dystonia often accompanies motor fluctuations and dyskinesia and may appear in off and on phases (Table 3) [87].

The pathogenesis of motor complications is not completely understood, but central and peripheral mechanisms have been suggested to contribute to motor fluctuations and dyskinesia [88]. The main central mechanisms include (a) the progression of nigrostriatal degeneration, which results in the reduction of the capacity of storing dopamine in the presynaptic vesicles and releasing them physiologically, (b) enhanced conversion of levodopa to dopamine and aberrant release in the striatum as false neurotransmitter by serotonergic neurons, (c) alterations in dopaminergic receptors that undergo plastic changes, which include supersensitivity to dopamine because of the loss of nigrostriatal projections, desensitization, and downregulation because of the presence of nonphysiological high doses of dopamine, and (d) increased glutamatergic activity in the striatum [87, 88]. The peripheral mechanisms encompass (a) reduced gastric emptying that is related to PD autonomic dysfunction and (b) competition of levodopa, which is a neutral amino acid and requires a carrier to pass the gut-blood and blood-brain barriers, with other dietary amino acids after a protein-rich meal [87]. The cumulative exposure to levodopa treatment, which becomes necessary after a few years of PD disease because of the limited therapeutic effect of dopamine agonists, has been traditionally considered as a major player in the pathogenesis of motor fluctuations and dyskinesia, which are called levodopa-induced motor complications [87, 88]. A recent study on PD patients from a sub-Saharan African country, where access to medication is limited, suggests that motor complications are not associated with the duration of levodopa therapy but rather with longer disease duration and higher levodopa daily dose, arguing against the common practice to delay levodopa treatment in favor of dopamine agonists to delay the occurrence of motor complications [89].

Management strategies for motor complications and dyskinesia include various pharmacological combined approaches, such as fractionating levodopa by administering small multiple daily doses, reducing the interval between levodopa doses, adding controlled release, dispersible, and soluble levodopa formulations, adding or increasing dopamine agonists in particular controlled release and transdermal formulations, monoamine oxidase-B inhibitors or catechol-O-methyltransferase inhibitors, amantadine or

clozapine, botulinum toxin, subcutaneous apomorphine, levodopa/carbidopa intestinal gel, and DBS (Table 3) [87]. Other strategies include adjusting protein intake throughout the day, taking levodopa on an empty stomach, treating constipation, tapering drugs that may interfere with gastric emptying, and eradicating *Helicobacter pylori* (Table 3) [87].

9. Posture, Balance, and Gait Disturbances in PD and Their Pathophysiology

Posture, balance, and gait disturbances are common in PD and largely contribute to motor impairment, risk of falls, and worse QoL [90, 91]. PD patients commonly show the classic stooped appearance, with flexion of the hips and knees, and rounding of the shoulders, but an important subset of patients shows more severe postural deformities, including camptocormia, antecollis, Pisa syndrome, and scoliosis [91, 92]. The pathophysiology of axial postural abnormalities in PD is not well understood, and a number of central and peripheral causes have been proposed, including asymmetry of the BG outflow, rigidity, dystonia, abnormal processing of vestibular or proprioceptive afferents, abnormal spatial cognition, focal myopathy in the paraspinal muscles, spinal and soft tissue changes, and side effects of dopaminergic and nondopaminergic drugs [90, 92]. Because of the poor knowledge on the pathogenesis of postural abnormalities, their management is largely unsatisfactory, as they respond poorly to medication, brain surgery, or physiotherapy [92].

Gait and balance disorders, which occur during the course of PD, are a major problem and an unmet therapeutic target, in that dopaminergic drugs and DBS often fail to improve these signs and may worsen them in some cases [91]. Gait is the result of dynamic interactions between the activation of central movement programs and feedback mechanisms [93]. Animal studies demonstrated the presence of a spinal central pattern generator (CPG), which is controlled by supraspinal centers [93]. Recent studies point to a key role of the mesencephalic locomotor region (MLR), which is located in the reticular formation and is composed of the PPN and the cuneiform nucleus, for the control of gait and balance in humans [93, 94]. The MLR has reciprocal connections with the BG, receives inputs from the cerebellum and motor cortices, and has outputs to the descending reticulospinal pathway and the ascending thalamocortical pathway through the thalamic centromedian nucleus [91]. The spinal CPG and the MLR are under cortical control [93]. An indirect pathway from the frontal cortex via the BG to the MLR allows modulation of the gait pattern in response to external demands [95]. A direct pathway from the primary motor cortex to the spinal CPG can bypass the MLR during undisturbed locomotion [95]. Input from the cerebellum conveys both pathways in the MLR to control speed and gait pattern, according to proprioceptive, vestibular, and visual information [93, 95]. Given the complex anatomy underlying locomotion, gait and balance signs may be heterogeneous in PD patients [91]. In early PD, hypokinetic gait, which is characterized by reduced gait speed and amplitude with nearly normal cadence, is an expression of the bradykinesia

TABLE 3: Levodopa (LD)-induced motor fluctuations and dyskinesia, their pathophysiology, and treatment strategies.

Phenomenon	Description	Pathophysiology	Treatment strategies
Motor fluctuations			
Wearing-off	Predictable earlier end-of-dose deterioration and reemergence of PD motor/nonmotor symptoms/signs before the next scheduled oral LD dose	Loss of SNc dopaminergic neurons resulting in reduction in LD internalization and production, storage, and physiological release of DA	Assess compliance with current treatment. Reduce the interval between LD doses. Increase LD doses, particularly the first one in the morning or those in the afternoon. Use CR-LD. Add or increase DA agonists. Add COMT inhibitors and/or MAO-B inhibitors. Consider SA, LCIG, or DBS
Delayed-on	Increased latency between taking an oral dose of LD and experiencing clinical benefit from it	Delayed absorption of LD in the proximal jejunum or across BBB because of large amount of dietary neutral AAs that compete with LD active transport, erratic gastric emptying, anticholinergic or dopaminergic drugs, and food <i>per se</i>	Adjust protein intake by avoiding it in the first part of the day or spreading it throughout the day. Take LD on an empty stomach or with a small snack. Treat constipation and reduce or stop anticholinergic agents. Eradicate <i>Helicobacter pylori</i> . Add soluble oral LD preparations. Consider SA, LCIG, or DBS <i>See treatment strategies for delayed-on fluctuations</i>
Partial-on	Partial response to an oral dose of LD	Reduced absorption of LD. <i>See pathophysiology of delayed-on fluctuations</i>	<i>See treatment strategies for delayed-on fluctuations</i>
No-on	Occasionally no response of PD symptoms/signs to an oral dose of LD	<i>See pathophysiology of delayed-on fluctuations</i> . Markedly reduced or absent absorption of LD	<i>See treatment strategies for delayed-on fluctuations</i>
On-off	Sudden and unpredictable fluctuations between on and off phases (Table 1)	Possible pharmacodynamic neuroplastic changes in striatal medium spiny neurons and the BG	<i>See treatment strategies for wearing-off fluctuations</i>
Dyskinesia		Loss of SNc dopaminergic neurons resulting in reduction in LD internalization and leading to greater amount of DA production by serotonergic neurons. Neuroplastic changes in DA and GABA receptors and overactivity of glutamatergic NMDA receptors in the BG. Disinhibition of the MC and associated motor cortices	
Peak-dose dyskinesia	Involuntary movements at the time of the LD peak, which coincide with the best antiparkinsonian effect of LD		Fractionate LD doses (smaller amounts, more frequently). Switch CR-LD to regular LD. Add or increase long-acting DA agonists. Discontinue COMT or MAO-B inhibitors. Add amantadine or clozapine. Consider SA, LCIG, or DBS

TABLE 3: Continued.

Phenomenon	Description	Pathophysiology	Treatment strategies
Diphasic dyskinesia	Involuntary movements at the beginning and/or the end of LD effect	See <i>pathophysiology of peak-dose dyskinesia</i>	Reduce the interval between LD doses. Add or increase long-acting DA agonists. Add soluble or crushed oral LD. Consider SA, LCIG, or DBS
Square-wave dyskinesia	Involuntary movements throughout the entire duration of LD effect	See <i>pathophysiology of peak-dose dyskinesia</i>	See <i>treatment strategies for peak-dose and diphasic dyskinesia</i>
Dystonia	Sustained involuntary and painful muscle contraction during the off phase and/or on awakening	See <i>pathophysiology of wearing-off and delayed-on fluctuations</i> . Short half-life of oral LD for early morning dystonia	See <i>treatment strategies for motor fluctuations</i> . Minimize off time. Add bedtime CR-LD or overnight doses of regular LD for early morning dystonia. Botulinum toxin injection. Add muscle relaxant drugs or benzodiazepines. Consider DBS
Off phase dystonia, including early morning dystonia	Sustained involuntary muscle contraction during the on phase. It may often accompany peak-dose or diphasic dyskinesia	See <i>pathophysiology of peak-dose dyskinesia</i>	See <i>treatment strategies for peak-dose dyskinesias</i> . Botulinum toxin injection. Add muscle relaxant drugs or benzodiazepines. Consider DBS
On phase dystonia			

AA = aminoacid; BBB = blood-brain barrier; BG = basal ganglia; COMT = catechol-O-methyl transferase; CR = controlled release; DA = dopamine; DBS = deep brain stimulation; GABA = gamma-aminobutyric acid; LCIG = levodopa/carbidopa intestinal gel; LD = levodopa; MC = primary motor cortex; MAO-B = monoamine oxidase type B; NMDA; N-methyl-D-aspartate; PD = Parkinson's disease; SA = subcutaneous apomorphine.

and is related to a deficit in internal generation of adapted step length [96]. In line with this concept, hypokinetic gait may be ameliorated by dopaminergic treatment and external visual cues [91]. The characterization of gait problems is more complex in later PD stages, when changes in multiple neural systems may contribute to them [21, 91, 97]. In advanced PD patients, gait is clearly abnormal, but it is often difficult to distinguish between the specific contribution of sensory, motor, and cognitive (i.e., executive functions and attention) deficits and factors like fear, imbalance, muscle weakness, loss of basic locomotion rhythmicity, and misjudgment of hazard risk [97]. In later PD, different neurotransmitters have been hypothesized to contribute to gait disturbance, including noradrenalin and serotonin systems, but converging evidence points to a key role of cholinergic dysfunction in the PPN [21, 42, 43, 94]. According to this view, some reports showed improvement of PD gait disturbances to inhibitors of cholinesterase [21, 43]. Despite these results needing to be replicated in more robust studies, this pharmacological strategy should not be discarded [91]. Bilateral PPN low frequency DBS was suggested to effectively control gait and balance disorders in small samples of patients, but these preliminary data were not confirmed by two RCTs [98], suggesting that better criteria for selecting patients and for optimal targeting within the MLR are needed [91].

10. Pathophysiology of Freezing of Gait

Freezing of gait (FOG) is an episodic gait disturbance [97], which is characterized by difficulty in gait initiation (*start hesitation*) and paroxysmal unintentional episodes of motor block during walking [99]. A FOG episode can manifest with step size reduction (*shuffling gait*), knee trembling, or akinesia and is typically described as feeling the feet as *frozen* or *glued to the ground* [100]. FOG is often triggered or worsened by challenging situations or provocative environments, such as changing direction (*turning hesitation*), approaching narrow doorways (*tight quarter hesitation*) or destinations (*destination hesitation*), moving into crowded spaces, walking on a slippery surface, crossing thresholds or changes in floor, stepping into an elevator, or entering a revolving door [100]. Furthermore, freezing episodes can occur when patients are required to deal with simultaneous activities (*dual tasking*), like walking and talking [99, 101]. Emotional factors such as stress or anxiety may also contribute to triggering FOG episodes [100]. All the above circumstances require a dynamic adaptation of motor schema, because of an increased cognitive load [100, 101]. Different subtypes of FOG are defined according to clinical manifestations and response to external stimuli (e.g., visual or auditory cues) and to levodopa [100]. It has long been observed that freezing phenomena in PD patients are responsive to visual cues, such as stepping over a small obstacle (e.g., a foot or a laser on the cane/walker), or auditory cues, such as following a rhythm (e.g., counting, listening to a metronome or music) to step to the beat, and this clinical observation offers a rationale for some rehabilitation strategies for FOG [91]. FOG is common in advanced PD and is associated with increased risk of falls and reduced mobility and QoL [102].

The neuropharmacological bases of FOG are poorly understood [99, 100]. Despite being common in advanced PD patients, FOG may appear early in the disease course [100]. Moreover, the response of FOG to dopaminergic therapy and DBS may be poor, and this clinical phenomenon is not unique to PD [100]. These observations suggest that severe dopamine depletion alone could not explain FOG and critical brain regions for this phenomenon should differ from those involved in cardinal PD features [94, 100]. As for other gait disturbances in PD, cholinergic loss in the PPN, which stands at the crossroad between supraspinal and spinal gait centers, may play a role in FOG [93, 94]. In keeping with this hypothesis, bilateral DBS of the caudal PPN may improve FOG [103]. Cortical cholinergic loss and amyloid deposition [104] and gray matter atrophy in the inferior parietal lobe and angular gyrus [105] may also contribute to FOG pathophysiology.

There are several theories regarding the occurrence of FOG [100, 106]. Based on the association between its occurrence and some visual stimuli, such as passing through a narrow space, FOG has been suggested to depend on impaired visuospatial ability that interferes with online movement planning [106, 107]. Visuospatial tests may discriminate freezers from nonfreezers and their deficits are strongly related with FOG severity and metrics [108], but other studies contradicted the notion that the lack of visuospatial ability per se may be primarily responsible for FOG [107, 109].

Impaired coupling between postural control and step initiation has also been hypothesized to contribute to FOG, because of its strong correlation with postural instability [100]. While a single anticipatory postural correction that shifts weight off the stepping leg precedes a voluntary step in normal gait, PD patients with FOG show delayed step initiation associated with repetitive anticipatory postural adjustments, as if they cannot inhibit their postural preparation and release the stepping program [110].

The hypotheses on FOG pathophysiology have recently shifted towards a multisystem dysfunction, where cognition plays a significant role [101, 111]. Although gait has been long considered a low-level automated motor activity that requires minimal higher cortical functions, growing evidence suggests a role for cognition, especially attention and executive functions in gait control [99]. Different models, which incorporate cognition in the pathogenesis of FOG, have been recently proposed and some of them will be briefly reviewed [111].

According to the *interference model*, FOG is the consequence of concurrent cognitive overload during walking [112]. This model suggests that reduced neural reserve in the BG leads to communication breakdown between motor, associative, and limbic parallel circuits causing abnormal pallidal output and temporary interruption of gait pathways [112]. Because of reduced automaticity in PD, there is an overload of systems involved in performing voluntary actions, especially when patients are asked to perform a dual task [99, 101]. According to this hypothesis, during a virtual reality gait task where the cognitive load was manipulated, PD patients with FOG demonstrated functional decoupling between the BG and the cognitive control networks in association with the occurrence of paroxysmal motor arrests [113].

The *cognitive model* stipulates that impaired decision making because of executive dysfunction [114] leads to stronger automatic activation of incorrect responses and less efficient suppression of conflicting responses and results in delayed response selection and FOG [111]. Executive functions are an umbrella term for a set of abilities, which are involved in inhibition, switching, and updating, and flexibly control behavior towards goals [115, 116]. Among executive functions, difficulties in set shifting have stronger association with the presence of FOG [113]. The frontostriatal circuits are central for action selection and response inhibition, in signaling conflict and temporarily preventing premature action by raising the decision threshold, such that response selection is delayed until conflict is resolved [117]. A growing body of evidence suggests that cognitive impairment, in particular executive dysfunction, often coexists with posture and gait abnormalities, FOG, and risk of falls in PD, but their interplay appears to be complex [118] and may represent a promising basis for new rehabilitative approaches to treat gait disturbances in PD patients [99].

11. Fatigue and Pain in PD

Fatigue is defined as an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion, with difficulties in initiating and sustaining mental and physical tasks in the absence of motor or physical impairment and consisting of a mental and physical component [119, 120]. The pathophysiology of PD-related fatigue appears to be complex, in that it involves both motor and nonmotor mechanisms, which depend on the involvement of nondopaminergic and extrastriatal dopaminergic pathways [119].

PD patients often complain of pain, which may be associated or not with the presence of dystonia in the same body regions affected by pain [121]. Experimental evidence suggests the presence of abnormal processing of nociceptive afferents in pain pathways, independently of dystonia and motor disturbances in PD [122, 123].

Despite not representing motor disturbances, fatigue and pain may negatively influence motor performances in PD [120]. Some reports suggested that caffeine [46] and monoamine oxidases inhibitors alone or in combination with antidepressants [124] may improve fatigue in PD and that opioids might be effective for some subtypes of PD-related pain [125]. Despite these recent advancements, pain and fatigue are two symptoms that are underrecognized and with no established therapy in PD, and they may represent interesting targets for nonpharmacological treatments, such as aerobic exercise [126] or rehabilitation procedures.

12. Depression, Apathy, and Cognitive Problems in PD

Depression, apathy, and cognitive deficits are common in PD patients and may sometimes overlap and interact [127]. Despite the fact that they can have a negative effect on QoL and the functioning of PD patients, as well as reduced compliance to pharmacological and nonpharmacological treatment, they are often underrecognized and undertreated [127, 128].

Depression may affect 50–70% of PD patients, is a multifactorial condition, which depends upon degeneration of noradrenaline and serotonin neurons, and represents a reactive condition to PD [129]. Pharmacologic treatment with antidepressant medications, specifically the selective serotonin reuptake inhibitors, and cognitive behavioral interventions may significantly improve depression in PD patients [129].

Apathy is defined as lack of motivation characterized by diminished goal-oriented behavior and cognition and reduced emotional expression [26, 128]. Although apathy can occur as a symptom of depression, it may represent a separate phenomenon in PD [130]. While depression is a highly negative affective experience, apathy is characterized by complete affective flattening in the absence of sadness [26]. However, in the clinical setting, separating depression from apathy is often not a straightforward task [26, 128]. Up to 40% of PD patients suffer from apathy, which is more common in older men with more severe motor impairment, worse executive dysfunction, and a higher risk of developing dementia [130]. Apathy in PD is caused by a dysfunction or neuronal loss in a complex neural network, which is not limited to the limbic loop of the BG, but includes the mesocorticolimbic pathway, the caudate nucleus, the lateral prefrontal cortices, the inferior medial frontal gyrus, the cingulate cortex, the insula, the cuneus, and the temporoparietal region [131, 132]. The treatment of apathy in PD is currently controversial, but there is a good rationale for the use of dopaminergic drugs to improve the emotional and behavioral aspects and for cholinesterase inhibitors to treat the cognitive aspects of apathy [26, 133].

Cognitive deficits may affect every cognitive domain, including memory, language, attention, visuospatial abilities, and executive functions, with the latter showing the most profound impairment [134]. The spectrum of cognitive dysfunction in PD ranges from mild cognitive impairment (MCI) to dementia, with MCI representing a transitional state between normal cognition and dementia [7, 135]. The recent introduction of diagnostic criteria for PD-related MCI [135] is important for its early recognition and treatment [7].

13. Rehabilitation Procedures in PD and Their Pathophysiological Grounds

Despite optimal medical treatment and neurosurgical interventions, PD patients develop progressive disability [136]. The role of rehabilitation in PD is to maximize motor and cognitive functional abilities and minimize secondary complications in order to optimize independence, safety, and well-being, thus enhancing QoL [137]. Several rehabilitative approaches have been proposed in PD, including nonspecific physiotherapy (i.e., muscle strengthening and stretching, balance, and postural exercises) [138, 139], occupational therapy [140], treadmill and robotic training [141–145], dance and martial arts therapy [146], multidisciplinary approaches including speech and cognitive therapy [8, 147, 148], motor imagery and action observation therapy [137, 149], and virtual reality and telerehabilitation [150]. There is evidence that physiotherapy causes short-term, significant, and clinically

important benefit for walking speed, balance, and clinician-rated disability in PD [138], but it is insufficient to support or refute the superiority of an intervention over another because of the small number of patients examined by previous studies, the methodological flaws, and the variety of the approaches that have been proposed [137]. However, exercise is generally accepted as an intervention that could ameliorate motor and nonmotor PD symptoms and should be considered as the basic element of any rehabilitative treatment in PD patients [126, 137].

The principles of neuromechanics are a framework for understanding the patterns of neural activity that generate movements in healthy people and are important for the rehabilitation of patients with motor deficits [151]. Together with neural plasticity, they support the development of motor modules, which have been defined as coordinated patterns of muscle activity flexibly combined to produce functional motor behaviors [151]. The neuromechanical principles include motor abundance (i.e., for any given task, there are many functionally equivalent motor solutions), motor structure (i.e., motor modules reflect biomechanical task relevance), motor variability (i.e., motor module variations across individuals are high if the effect on motor output is low), individuality (i.e., individuals express different motor styles that depend on evolutionary, developmental, and learning processes), and multifunctionality (i.e., muscle activity can be combined in many ways to produce a wide range of different actions) [151].

BG loops have been hypothesized to contribute to choosing the desired motor output and selectively inhibiting competing motor programs [152] and to be involved in reward prediction and habit formation [153, 154]. In PD, the BG dysfunction is supposed to lead to inappropriate selection of motor modules [151, 152]. Upon these premises, PD rehabilitation procedures are aimed to improve the appropriate recruitment of motor modules through exercise and practice of complex tasks according to a goal-based learning approach, which involves planning and execution of composite and/or unfamiliar movements (e.g., backward walking) [137, 151].

Motor rehabilitation may be regarded as a process of motor relearning through practice and training [155]. The acquisition of motor skills is supposed to go through different phases (i.e., fast, slow, consolidation, reconsolidation, automatization, and retention), which differentially involve the corticostriatal and corticocerebellar pathways and depend upon online and offline triggered plastic changes in the brain [156]. PD patients show preserved ability in motor learning [155], but BG dysfunction may impair consolidation of learned material, and translation to the clinical setting may be critical [137]. Along this line, reduced experience-dependent neuroplasticity, which is largely influenced by intensity, repetition, specificity, difficulty, and complexity of practice, may represent a crucial issue in PD [137]. Motor cortical plasticity may be a compensatory change that contributes to delaying motor signs onset in the early phases of PD, but it deteriorates as the disease progresses [157].

Other largely unexplored mechanisms involved in PD rehabilitation include focusing on external cues to bypass the

dysfunctional BG activity and access the corticocerebellar pathways [158], enhancing cognitive engagement through problem solving, attentional demand and motivation [137], and aerobic training to increase cardiopulmonary function, oxygen consumption, and blood flow to the brain [159].

14. Conclusions and Future Perspectives

This brief review summarized the current hypotheses on the pathophysiology of motor dysfunction in PD. The neuropathological, neurochemical, and neurophysiological bases of PD motor symptoms offer the rationale for current pharmacological and nonpharmacological treatment of this condition but may also represent the bases for future strategies for managing this condition [21, 137]. Future studies aimed at a better understanding of PD pathophysiology will offer the premises for new pharmacological strategies [21], as well as new targets for DBS [59, 87, 98] and rehabilitation procedures [160], and to achieve a personalized medicine approach to PD based on biomarkers [161].

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

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Review Article

Can a Positive Allosteric Modulation of GABAergic Receptors Improve Motor Symptoms in Patients with Parkinson's Disease? The Potential Role of Zolpidem in the Treatment of Parkinson's Disease

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At present, patients with advanced Parkinson's disease (PD) are unsatisfactorily controlled by currently used anti-Parkinsonian dopaminergic drugs. Various studies suggest that therapeutic strategies based on nondopaminergic drugs might be helpful in PD. Zolpidem, an imidazopyridine widely used as sleep inducer, shows high affinity only for GABA_A receptors containing the α -1 subunit and facilitates GABAergic neurotransmission through a positive allosteric modulation of GABA_A receptors. Various observations, although preliminary, consistently suggest that in PD patients zolpidem may induce beneficial (and sometimes remarkable) effects on motor symptoms even after single doses and may also improve dyskinesias. Since a high density of zolpidem binding sites is in the two main output structures of the basal ganglia which are abnormally overactive in PD (internal globus pallidus, GPi, and substantia nigra pars reticulata, SNr), it was hypothesized that in PD patients zolpidem may induce through GABA_A receptors an inhibition of GPi and SNr (and, possibly, of the subthalamic nucleus also), resulting in an increased activity of motor cortical areas (such as supplementary motor area), which may give rise to improvement of motor symptoms of PD. Randomized clinical trials are needed in order to assess the efficacy, safety, and tolerability of zolpidem in treating motor symptoms of PD.

1. Introduction

Parkinson's disease (PD) is the most common neurodegenerative movement disorder, with a prevalence of 0.3% in the general population in industrialized countries and a prevalence of 4% in elderly people aged over 80 years [1]. The clinical manifestations of PD include motor symptoms (bradykinesia, rigidity, postural instability, and resting

tremor) and a variety of nonmotor symptoms, including cognitive impairment, behavioural symptoms [2], sleep disturbances, and olfactory and autonomic dysfunction.

At present, pharmacological treatment of motor symptoms of PD, mainly based on the administration of dopaminergic drugs (levodopa, dopamine agonists) and other drugs involved in levodopa metabolism (monoamine oxidase-B inhibitors, COMT inhibitors), may induce beneficial effects

on Parkinsonian motor symptoms only for some years after the onset of such symptoms and becomes usually less effective later in the disease course [3]. In late disease stages, various complications usually arise in PD patients treated by dopaminergic drugs, such as *on-off* fluctuations of Parkinsonian symptoms and dyskinesias (involuntary movements of the head, trunk, and upper or lower limbs). On the whole, at present, most patients with advanced PD are unsatisfactorily controlled by the currently most widely used anti-Parkinsonian drugs.

In the last fifteen years, the most significant advances in the treatment of PD were represented by neurosurgical procedures aimed at modulating the activity of specific brain structures, such as deep brain stimulation (DBS) of the internal globus pallidus (GPi) and DBS of the subthalamic nucleus (STN), which may induce remarkable beneficial effects in PD patients [4], even after more than 10 years from the neurosurgical intervention [5]. Preliminary studies suggest that neurosurgical procedures alternative to DBS, such as extradural stimulation of the motor cortex, are definitely less effective than DBS of the STN or GPi, although extradural stimulation of the motor cortex may induce slight beneficial effects on Parkinsonian motor symptoms, including axial motor symptoms which are usually poorly responsive to drug treatment [6, 7].

It is well established that neuropathological processes underlying PD involve not only dopaminergic systems, but also noradrenergic, serotonergic, glutamatergic, and cholinergic systems in several brain structures. So far, a number of nondopaminergic drugs have been available for the treatment of motor symptoms of PD [8], while other nondopaminergic drugs are still under investigation. Among anti-Parkinsonian drugs with pharmacological effects on nondopaminergic systems, adenosine A2A receptor antagonists, safinamide (an agent inhibiting both glutamate release and monoamine oxidase-B), and the antiepileptic agent zonisamide have been proposed as add-on drugs which may extend the duration of effects of levodopa. To reduce levodopa-induced dyskinesias, antiglutamatergic drugs, such as amantadine (a nonselective N-methyl D-aspartate antagonist) and antagonists of metabotropic glutamate receptor (mGluR₅), might be helpful in PD patients. As regards drugs with pharmacological effects on serotonergic and noradrenergic systems, 5-HT_{2A/2C} antagonists (such as the atypical antipsychotic clozapine) and α 2-adrenergic receptor antagonist (such as fipamezole) may reduce dyskinesias in PD patients. As to nondopaminergic drugs which can be used in PD patients for the treatment of tremor, various options can be considered, including anticholinergic drugs (muscarinic M4 cholinergic antagonists), β -adrenergic antagonists (such as propranolol), 5-HT_{2A} antagonists, and drugs with pharmacological effects on both serotonergic and cholinergic systems (such as clozapine and the antidepressant mirtazapine). It has been pointed out that while dopaminergic drugs still remain the most effective option to treat motor symptoms in PD, alternative therapeutic strategies based on the use of nondopaminergic drugs in PD are currently needed to improve symptoms that are (or become) poorly responsive to dopaminergic drugs [8].

2. Potential Beneficial Effects of Zolpidem, a Positive Allosteric Modulator of GABA_A Receptors, on the Motor Symptoms of PD

In the late 1980s, some opinion leaders in the field of movement disorders [9] had suggested that drugs that may specifically enhance GABAergic neurotransmission may be potentially helpful in the treatment of PD, but at that time there was scanty evidence supporting this intriguing hypothesis. In particular, a pilot study had suggested that GABA agonists such as progabide [10] might be helpful in the treatment of motor symptoms of patients with PD, in agreement with an experimental study in rats showing the effects of progabide [11] on motor function (turning behaviour) and with previous postmortem findings showing abnormalities in the GABAergic systems of the brain of patients with Parkinson's disease [12].

Zolpidem is an imidazopyridine drug with short half-life, which has been widely used for more than two decades for the treatment of insomnia. Both zolpidem and benzodiazepines (BZ) exert their pharmacological effects by facilitating GABAergic neurotransmission through a positive allosteric modulation of GABA_A receptors. GABA_A receptors, which are the major inhibitory neurotransmitter receptors in the brain, are heteropentamers and are classified according to their α subunits. In GABA_A receptors containing specific isoforms of α subunits (α 1, α 2, α 3, and α 5), there is a binding site for BZ and zolpidem in the α subunit [13]. BZ bind relatively unselectively to several subtypes of GABA_A receptors, namely, those containing the α 1, α 2, α 3, or α 5 subunits. Unlike BZ, zolpidem is an agonist with high affinity only for GABA_A receptors containing the α -1 subunit [14]. The interaction of zolpidem with the BZ binding site of GABA_A receptors (particularly, of GABA_A receptors containing the α -1 subunit, given the high affinity of zolpidem for such GABA_A receptor subtype) results in facilitation of GABAergic neurotransmission, particularly in neurons with GABA_A receptors containing the α -1 subunit. It has been recently suggested that, according to pharmacological data from both rodents and nonhuman primates, among drugs currently available for clinicians, zolpidem has a peculiar pharmacological profile, which differentiates zolpidem from BZ [15]. Some studies have previously suggested that there is a high density of zolpidem binding sites in the GPi and in the substantia nigra pars reticulata (SNr), which are the output structures of the basal ganglia [16, 17].

In the mid-1990s, Daniele and coworkers observed a 61-year-old woman affected by juvenile-onset PD in an advanced disease stage after a 25-year clinical history, who received at bedtime an oral immediate-release formulation of zolpidem for insomnia [18]. Surprisingly, 45 to 60 minutes after the assumption of the first 10 mg dose of zolpidem as sleep inducer, this patient showed no drowsiness but a remarkable improvement of Parkinsonian motor symptoms (akinesia, rigidity, and resting tremor). In this woman, the motor improvement induced by a single 10 mg dose of zolpidem immediate-release was comparable to the improvement observed after the administration of levodopa/carbidopa,

while no beneficial effect on her Parkinsonian motor symptoms was observed when she assumed other hypnotic drugs (triazolam and zopiclone). This patient with advanced PD assumed zolpidem chronically (10 mg four times daily) for more than 5 years, with no side effects and persistent beneficial effects on Parkinsonian motor symptoms over time.

Following such serendipitous observation, a pilot study (double-blind, placebo-controlled crossover) was carried out in ten patients with a clinical diagnosis of PD [18], with a mean disease duration of 9.2 years and a mean Hoehn and Yahr score of 2.9 years. Since in the first serendipitous observation even a single 10 mg dose of zolpidem showed beneficial effects on Parkinsonian motor symptoms about one hour after the drug administration, in such pilot study PD patients were given in randomized order a 10 mg fixed dose of immediate-release zolpidem and placebo in two different days, after withholding of all anti-Parkinsonian medication 12 hours before motor assessment. PD patients were assessed by means of the motor examination part (part III) of the Unified Parkinson's Disease Rating Scale (UPDRS-III) before (baseline) and one hour after the administration of zolpidem or placebo. In each individual PD patient, a positive response was defined as a decrease of more than 20% of the UPDRS-III score at baseline. In this pilot study, the administration of a single 10 mg fixed dose of immediate-release zolpidem, unlike placebo, induced in the overall group of ten PD patients a statistically significant improvement of Parkinsonian motor symptoms, with a 18% mean reduction of UPDRS-III scores from baseline. Six out of 10 PD patients could be defined as responders to a single 10 mg dose of zolpidem and showed on average a 30% improvement of motor symptoms, ranging from 21% to 59% in different individuals affected by PD. In PD patients who resulted in being responders to zolpidem, such improvement (which appeared 45–60 minutes after the administration of zolpidem and lasted about 2–4 hours) mainly involved facial expression, rigidity, akinesia/bradykinesia, posture, and gait. In this group of 10 PD patients, in those patients who presented resting tremor, the administration of a single 10 mg dose of zolpidem improved also resting tremor, although this finding was not mentioned among the results reported by Daniele and coworkers [18]. Interestingly, the 6 patients who resulted in being responders to zolpidem included 3 out of the 4 most severely affected PD patients and 3 out of the 6 less severely affected PD patients, suggesting the hypothesis that beneficial effects of a single 10 mg dose of immediate-release zolpidem on Parkinsonian motor symptoms may perhaps be more likely observed in PD patients with more severe motor symptoms. In this pilot study, the only adverse effect observed after the administration of a 10 mg single dose of immediate-release zolpidem was drowsiness, which occurred in 4 out of 10 PD patients and was severe in 2 patients, moderate in one patient, and mild in another patient. Interestingly, drowsiness was observed only in one out of the 4 most severely affected patients and 3 out of the 6 less severely affected patients, suggesting that after a single 10 mg dose of immediate-release zolpidem the occurrence of drowsiness may be less likely observed in PD patients with more severe motor symptoms. Despite the beneficial effects

on Parkinsonian motor symptoms in 6 out of 10 PD patients, a single 10 mg dose of zolpidem did not induce dyskinesias in any patient, even in 3 PD patients who had showed levodopa-induced dyskinesias.

In 2000, Růžička and coworkers [19] reported a 45-year-old woman with 12-year history of PD. Eight months after levodopa was started in 1992 and 5 years after disease onset, the patient developed choreic dyskinesias of the right hand. Later on, dyskinesias became generalized and were present most of the time. A number of treatment strategies (controlled-release levodopa, addition to levodopa of bromocriptine, terguride, and tiapride) failed to alleviate such dyskinesias. In 1994, she was given zolpidem for insomnia, and 30 minutes after 2.5 to 5 mg of zolpidem, her dyskinesias substantially diminished or disappeared for 2 hours, without any drowsiness. In 1997, when motor fluctuations developed, she also noticed an improvement of motor function, if the dose of zolpidem was taken in the “off” state. This PD patient increased the dosage of zolpidem up to 30 mg per day (divided into 6 doses of 5 mg), with a persistent antidyskinetic effect “on” levodopa and improved motricity (especially gait initiation) in the “off” state, without daytime somnolence. After more than 3 years of chronic treatment with zolpidem, the single doses of zolpidem had not been substantially increased. This observation suggested the potential benefits of the chronic administration of zolpidem not only on Parkinsonian motor symptoms, but also on dyskinesias in late stages of PD.

In 2004, at the 8th International Congress of Parkinson's Disease and Movement Disorders organized by the Movement Disorders Society, Tagaris and coworkers [20] presented preliminary data on some remarkable beneficial effects induced by the administration of zolpidem on motor symptoms of patients with advanced PD. As far as we are aware, such interesting data have been reported so far only as an abstract of such congress. In an initial study on a group of 14 PD patients receiving zolpidem for insomnia ([20]; Tagaris, personal communication, 2004), Tagaris and coworkers investigated a subgroup of 5 PD patients, who self-reported robust beneficial effects on Parkinsonian motor symptoms induced by the assumption of zolpidem for insomnia. In this first subgroup of 5 PD patients, who also showed frequent and severe dyskinesias, Parkinsonian motor symptoms were assessed by means of the UPDRS-III before and after the administration of single doses of levodopa and single 5 or 10 mg doses of immediate-release zolpidem. In this subgroup of 5 PD patients, zolpidem (unlike the BZ temazepam) induced a dramatic improvement of Parkinsonian motor symptoms, comparable to the improvement induced by levodopa. Accordingly, in this subgroup of 5 PD patients, zolpidem was administered chronically, in daily doses of 30 mg or more. One of such PD patients out of five showed a tendency to abuse zolpidem and assumed zolpidem almost every 2 hours. Interestingly, 2 out of 5 PD patients reported an improvement of levodopa-induced dyskinesias if levodopa was administered in association with zolpidem, while no patient reported dyskinesias after the administration of zolpidem. In a second study (Tagaris, personal communication, 2004 [20]), a single oral dose of

immediate-release zolpidem 5 mg or flunitrazepam 1 mg was administered to another group of 10 patients with advanced PD, who had never received zolpidem before. If no anti-Parkinsonian effect and no sleepiness were detected after the administration of a 5 mg single dose of zolpidem (as observed in 5 out of 10 PD patients), the single dose of zolpidem was then increased to 10 mg. Soon (30–45 minutes) after the administration of a single oral dose of zolpidem, a significant motor improvement (decrease of more than 20% in the baseline score of UPDRS) was observed in 7 out of 10 patients with advanced PD. In these patients, no improvement of Parkinsonian motor symptoms was observed after the administration of the BZ flunitrazepam. In this latter study, a slight somnolence was observed in 4 out of those 5 PD patients who were given a single 10 mg dose of zolpidem and in 2 out of those 5 PD patients who were given a single 5 mg dose of zolpidem, while sleepiness was observed only in 1 PD patient after a single 5 mg dose of zolpidem. These preliminary observations showed that single oral doses of zolpidem as well as chronic administration of zolpidem may improve Parkinsonian motor symptoms in patients with advanced PD, suggesting that the anti-Parkinsonian effects of zolpidem may perhaps be more pronounced in PD patients with dyskinesias.

The hypothesis that the administration of zolpidem is more likely to improve Parkinsonian motor symptoms in patients with advanced PD was supported by a clinical observation reported by Chen and coworkers [21] in a 53-year-old patient with advanced PD, who underwent unilateral pallidotomy, unilateral thalamotomy, and bilateral DBS of the STN. In this PD patient, the administration of a single 10 mg dose of zolpidem rapidly induced a remarkable amelioration of Parkinsonian motor symptoms (akinesia, dystonia, and dyskinesias), with a 27% improvement on the UPDRS-III scale and no significant somnolence with a 10 mg dose of zolpidem. After the administration of a lower dosage of zolpidem (5 mg), there was an amelioration of dystonia and dyskinesias, in the absence of a satisfactory improvement of other Parkinsonian motor symptoms. In this patient, zolpidem was chronically administered at a daily dosage of 25 mg (5 mg three times a day and 10 mg before sleeping). This observation suggests that, in patients with advanced PD, such as patients who underwent DBS of the STN and more invasive neurosurgical interventions (pallidotomy and thalamotomy), zolpidem may improve various Parkinsonian motor symptoms, including dystonia and dyskinesias, possibly at relatively lower doses.

In 2010, at the 14th International Congress of Parkinson's Disease and Movement Disorders organized by the Movement Disorders Society, Abaroa and coworkers [22] described three patients affected by PD with motor fluctuations and dyskinesias. The first patient was a 50-year-old man, with a 3-year disease duration, in stage 3 on the Hoehn and Yahr (HY) scale. He showed wearing off and dyskinesias, with foot dystonia and severe pain in lower limbs in off state. The second patient (a 76-year-old man, with a 12-year disease duration, in stage 3 on the HY scale) showed wearing off and severe off states with akinesia, foot and oromandibular

dystonia, and pain in lower limbs. The third patient (a 61-year-old woman, with an 8-year disease duration, in stage 3 on the HY scale) showed wearing off, dyskinesias, severe trunk, and cervical dystonia associated with pain in lower limbs in off state. All 3 patients were assessed by means of the UPDRS-III before and after the oral administration of a single 7.5 mg dose of zolpidem. About 15–20 minutes after the oral administration of such single dose of zolpidem, in all patients dystonia disappeared and, for about 1–2 hours, there was a remarkable improvement of pain, dysphagia, and other Parkinsonian motor symptoms assessed by UPDRS-III (with a reduction of 30% or more of UPDRS-III scores). None of the 3 PD patients showed drowsiness after the assumption of zolpidem. It was briefly mentioned [22] that in two PD patients the remarkable improvement of UPDRS-III scores obtained after the administration of a single dose of zolpidem was comparable to the improvement obtained with levodopa, while in a third patient the improvement of UPDRS-III scores obtained after the administration of a 7.5 mg dose of zolpidem was even greater than the motor improvement obtained with levodopa. This report suggests that zolpidem may improve Parkinsonian motor symptoms (including dystonia and dyskinesias) in patients with fluctuating PD, such as patients with mild to moderate bilateral disease who have complications associated with long-term levodopa treatment.

In 2012, Huang and coworkers [23] reported a 61-year-old housewife with PD and a 12-year disease duration, with rest tremor of right limbs as presenting symptom. The patient was referred to hospital in March 2009 because of both the shortening of beneficial effects of pharmacological treatment in the preceding 3 years and the appearance of on-phase dyskinesias in the preceding 2 years. In June 2009, she underwent bilateral DBS of STN. The day after the neurosurgical intervention, the patient started to show “fluctuating spells of mental confusion (inertia and confusion with incoherent speech and fearing of being killed),” which persisted over time. In July 2009, soon after the administration of zolpidem for insomnia, the patient showed for few hours an improvement of Parkinsonian motor symptoms (with approximately a 25% improvement on the UPDRS-III scale) and an amelioration of behavioural symptoms: “she could chat normally with her caregiver and walk with assistance after taking zolpidem.” In keeping with the behavioural improvement observed after the administration of zolpidem, the total score on the Neuropsychiatric Inventory (which was administered to assess her behavioural symptoms) decreased from 56 to 30. Accordingly, zolpidem was administered to the patient at a dosage of 10 mg three times per day. In this patient, positron emission tomography with ^{18}F -fluorodeoxyglucose showed a reduction of metabolism in the right frontal and parietal cortex and in caudate nucleus, which improved after the administration of zolpidem.

In recent years, neurophysiological studies aimed at registering cerebral electrical activity in PD showed that in patients with PD a pathological increase of beta activity (15–35 Hz) oscillations may occur in various brain structures, such as the STN and the cerebral cortex [24, 25]. A relationship between such pathologically increased beta

activity in PD patients and severity of Parkinsonian motor symptoms has been hypothesized, since a reduction of such pathologically increased beta activity may be observed in PD patients after improvement of Parkinsonian motor symptoms following either pharmacological treatment with levodopa [26] or DBS of the STN [27]. It has been also suggested that beta activity oscillations in the primary motor cortex may be modulated by GABAergic mechanisms and that drugs modulating GABA_A receptors such as diazepam may reduce the frequency of beta activity oscillations [28].

In a recent study, Hall and coworkers [29] investigated a group of 9 PD patients in early disease stages (with unilateral Parkinsonian motor symptoms only) and a group of 9 age-matched healthy controls. Participants of both groups underwent two magnetoencephalography (MEG) recording sessions, at baseline and after the administration of a single low (namely, sub-sedative) oral dose of zolpidem (0.05 mg/kg). At baseline, as shown in previous studies, PD patients showed an increase of beta power in the primary motor cortex (M1), which was greater in M1 area contralateral to the body side affected by Parkinsonian motor symptoms, as compared to M1 area ipsilateral to the body side affected by Parkinsonian motor symptoms. After the administration of a single low (individually adjusted, according to body weight) oral dose of zolpidem, all PD patients showed a remarkable and statistically significant improvement of Parkinsonian motor symptoms (with approximately a 50% mean reduction of total score on UPDRS-III), with a statistically significant amelioration of most items of UPDRS-III (resting and postural tremor, rigidity of upper and lower limb, finger tapping, hand movements, rapid alternating movements of hands, postural stability, and bradykinesia). Moreover, after the administration of a single low oral dose of zolpidem in PD patients, beta power was significantly reduced in contralateral M1 area, while it was significantly increased in ipsilateral M1 area, resulting in a hemispheric beta power ratio between the right and left M1 areas that approached parity. Furthermore, in PD patients there was highly significant correlation between the changes in hemispheric beta power ratio in M1 areas induced by zolpidem (significant reduction of beta power in contralateral M1 area and significant increase of beta power in ipsilateral M1 area, resulting in a hemispheric beta power ratio between the right and left M1 areas that approached parity) and the improvement induced by zolpidem on Parkinsonian motor symptoms as assessed by scores on UPDRS-III scale. These findings show that in PD patients the oral administration of zolpidem in low doses may result in an improvement of Parkinsonian motor symptoms, which is associated with both a reduction of beta power in contralateral M1 area and an increase of beta power in ipsilateral M1 area, thus rebalancing the dynamic range of M1 network oscillations between M1 areas of the two cerebral hemispheres [29]. From a clinical viewpoint, this study suggests that low doses of zolpidem may improve Parkinsonian motor symptoms also in PD patients in early disease stages. It has been hypothesized that zolpidem may markedly reduce the synchronous power of pathological oscillations in brain structures in which a pathologically increased beta power can be detected, namely,

that zolpidem may desynchronize such pathological activity, with subsequent improvement of motor function [30].

In conclusion, the limited evidence available so far suggests that, after the administration of single oral doses mostly ranging between 2.5 mg and 10 mg, a response (motor improvement) to immediate-release formulations of zolpidem might be more likely in PD patients with the following clinical features: (a) patients with moderate to severe PD [18], including patients with advanced PD [18, 20, 21, 23]; (b) PD patients with dyskinesias [19–22] and motor fluctuations [19, 22]. Such preliminary evidence, however, does not rule out the possibility that even patients with mild PD may respond to zolpidem, as it has been shown that PD patients in early disease stages [22, 29] may show an improvement of Parkinsonian motor symptoms after the administration of low (0.05 mg/kg) single oral doses of zolpidem (e.g., a 3.5 mg dose for a patient who weighs 70 kg).

3. Possible Mechanisms Underlying the Potential Beneficial Effects of Zolpidem on Parkinsonian Motor Symptoms

It is well established that dopaminergic depletion resulting from neurodegenerative processes affecting dopaminergic neurons in the SN pars compacta gives rise in PD patients to overactivity of the two main inhibitory output structures of the basal ganglia, namely, the GPi and the SNr. The overactivity of such two inhibitory output GABAergic structures in the basal ganglia gives rise to decreased activity in specific thalamic nuclei and, in turn, in reduced activity of motor cortical areas (such as supplementary motor area), which may result in motor symptoms of PD (Figure 1(b)).

In order to explain the quite surprising potential beneficial effects on Parkinsonian motor symptoms even of single doses of the hypnotic drug zolpidem observed in their pilot study, Daniele and coworkers [18] proposed a hypothesis about the possible mechanisms underlying these effects. Such hypothesis is based on the fact that zolpidem, unlike benzodiazepines, is an agonist with high affinity for GABA_A receptors containing the α -1 subunit [14], previously named GABA_A-BZ₁ receptors, and therefore facilitates GABAergic neurotransmission in brain structures which preferentially contain GABA_A receptors with the α -1 subunit. Since some studies [16, 17] had suggested that there is a high density of zolpidem binding sites in the GPi and in the SNr (the two main output structures of the basal ganglia, which are abnormally overactive in PD), it was hypothesized that in PD patients zolpidem may induce through GABA_A receptors a selective inhibition of such two overactive and inhibitory GABAergic structures (the GPi and the SNr), resulting in turn in an increased activity of motor cortical areas (such as supplementary motor area), which may underlie the possible improvement of Parkinsonian motor symptoms which can be observed after the administration of zolpidem (Figure 1(c)) in PD [18] and other Parkinsonian syndromes [31]. According to this hypothesis, it was also speculated that the administration of zolpidem could provide a pharmacological equivalent of posteroventral pallidotomy [18].

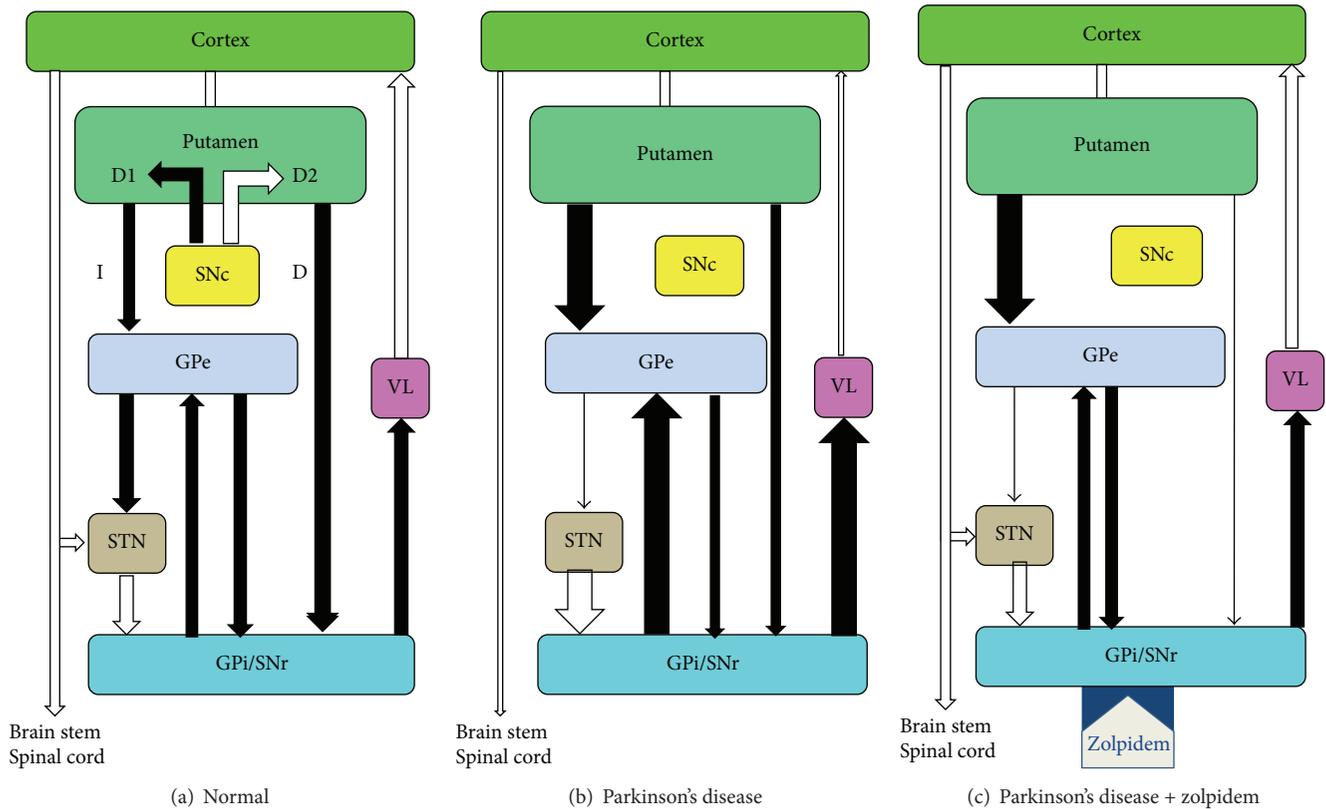


FIGURE 1: Schematic representations of the activity of the cortical-basal ganglia loops, showing the direct (D) and indirect (I) circuits in normal subjects (a), patients with Parkinson's disease/Parkinsonism (b), and patients with Parkinson's disease treated with zolpidem (c). In PD [18], zolpidem may induce, through GABA_A receptors containing the $\alpha 1$ subunit, a selective inhibition of the GPi and the SNr (the two main inhibitory GABAergic output structures of the basal ganglia), which are overactive in PD (b) and show binding sites for zolpidem (c). The inhibition of the GPi and the SNr directly induced by zolpidem may result in an increased activity of some motor cortical areas (such as supplementary motor area), which may underlie the possible improvement of Parkinsonian motor symptoms which can be observed after the administration of zolpidem. Although binding sites for zolpidem in the STN are not displayed in (c), the STN was found to have binding sites for zolpidem [36] and might be reasonably considered an additional target for zolpidem in PD patients. In PD, zolpidem might inhibit the STN as well, giving rise to decreased excitatory inputs from the STN to the GPi and SNr, resulting in a further mechanism leading to a decreased activity of the GPi and SNr, indirectly induced by zolpidem through its inhibition of the STN. White arrows = excitatory connections; black arrows = inhibitory connections.

This hypothesis has been subsequently supported by experimental studies in rats [32, 33] and has been quoted in several publications as a plausible explanation for the possible anti-Parkinsonian effects of zolpidem in patients with PD and other Parkinsonian syndromes [19–22, 31, 34, 35].

Chen and coworkers [32] investigated the *in vitro* and *in vivo* effects of zolpidem on the globus pallidus (GP) in rats. In their experimental study on *in vitro* slices of the GP in rats, a single 100 nM dose of zolpidem enhanced the action of GABA on postsynaptic GABA_A receptors and prolonged the duration of inhibitory postsynaptic currents recorded from neurons of the GP. Moreover, in a study aimed at investigating the effects of zolpidem *in vivo* on the GP in rats [32], when a single dose of zolpidem was acutely microinjected into the GP unilaterally, a change in motor behaviour, namely, a robust ipsilateral rotation (turning behaviour), was observed in the behaving rats. Chen and coworkers [32] suggested that this motor effect of zolpidem *in vivo* was due to the inhibition of the activity of neurons of the GP induced by zolpidem. All

such effects of zolpidem, *in vitro* and *in vivo*, were sensitive to the benzodiazepine antagonist flumazenil. These findings on the *in vitro* and *in vivo* effects of zolpidem on the GP in rats provided experimental support to the hypothesis of a GP-mediated mechanism of the anti-Parkinson effects of zolpidem in PD and suggested the need of further investigations aimed at assessing the potential beneficial effects of zolpidem in the treatment of movement disorders originating from dysfunction of the basal ganglia.

Zhang and coworkers [33] investigated *in vitro* and *in vivo* the effects of zolpidem on the SNr in rats. In *in vitro* slices of the SNr, superfusion of zolpidem at 100 nM/L induced a GABAergic inhibition of the SNr by activating postsynaptic GABA_A receptors and prolonged the duration of inhibitory postsynaptic currents recorded from neurons of SNr. In an experimental study on the effects of zolpidem *in vivo* on the SNr, it was observed that a unilateral microinjection of zolpidem into the SNr caused a change in motor behaviour, namely, a robust contralateral rotation in the behaving rats.

All such effects of zolpidem, *in vitro* and *in vivo*, were sensitive to the BZ antagonist flumazenil. These findings on the *in vitro* and *in vivo* effects of zolpidem on the SNr provided experimental evidence about a possible SNr-mediated mechanism of the anti-Parkinson effects of zolpidem in PD and further supported the idea of a potential role of zolpidem in the treatment of movement disorders arising from dysfunction of the basal ganglia.

In conclusion, the two studies mentioned above [32, 33] provided an experimental support to the hypothesis of Daniele and coworkers [18], who suggested that the potential beneficial effects of zolpidem on the motor symptoms of PD patients may fundamentally arise from a selective pharmacological inhibition, induced by zolpidem through GABA_A receptors in GPi and SNr (Figure 1(c)), of such overactive inhibitory structures (GPi and SNr), resulting in an increased activity of specific thalamic nuclei and, in turn, in an increased activity of specific motor cortical areas (such as supplementary motor area), which may give rise to an improvement of Parkinsonian motor symptoms.

Further data about the possible mechanisms which may underlie the potential anti-Parkinsonian effects of zolpidem were provided by an additional experimental study in rats [36], suggesting that zolpidem may induce beneficial effects on the motor symptoms of patients with PD also by inhibiting at least another subcortical nucleus overactive in PD (besides GPi and SNr), namely, the STN. Chen and coworkers [36] carried out an *in vitro* and *in vivo* study on the effects of zolpidem on the STN, a brain structure which also shows a high density of zolpidem binding sites [17] and plays a key role in the indirect pathway of the basal ganglia circuits. In the *in vitro* study [36], whole-cell patch clamp recordings were used to investigate the modulation of zolpidem on GABA_A receptor-mediated inhibitory synaptic currents in the STN. Zolpidem at a 100 nM dose significantly prolonged the decay time and rise time of miniature inhibitory postsynaptic currents in the STN, with no effect on the amplitude and frequency. At a high concentration of 1 μ M, zolpidem significantly increased the decay time, rise time, amplitude, and frequency of miniature inhibitory postsynaptic currents in the STN. The BZ antagonist flumazenil could completely block the effects induced by zolpidem, confirming that the effects of zolpidem are mediated by the BZ recognition site. In an *in vivo* study [36], a unilateral microinjection of zolpidem into the STN induced a significant contralateral rotation in the behaving rats. These results about the *in vitro* and *in vivo* effects of zolpidem on the STN provided experimental support to the hypothesis of a possible STN-mediated mechanism of the anti-Parkinson effects of zolpidem in PD and were in keeping with previous suggestions about a potential role of zolpidem in the treatment of movement disorders associated with a dysfunction of the basal ganglia. According to these latter findings, we might hypothesize that the administration of zolpidem, to some extent and perhaps in a subset of PD patients, could maybe provide a pharmacological equivalent also of neurosurgical procedures aimed at inhibiting the overactivity of the STN in patients with PD, such as DBS of the STN.

In conclusion, current available evidence suggests that zolpidem may induce a selective inhibition not only of the two output structures of the basal ganglia (GPi and SNr) which are overactive in PD [18], but also of an additional overactive structure in the basal ganglia pathways such as the STN, which might be reasonably considered an additional target for zolpidem, although it is not reported in Figure 1(c) as a target structure for zolpidem. Accordingly, zolpidem may induce a selective inhibition of various overactive structures in PD (GPi, SNr, and STN), which may be analogous to the functional inactivation of the STN or the GPi induced by DBS.

However, it is not possible to rule out the possibility that further brain structures containing GABA_A receptors, including specific neuron populations of some areas of the cerebral cortex, might be involved in the potential beneficial effects of zolpidem in improving Parkinsonian motor symptoms.

In a recent study on a mouse model of PD [37], it was shown that dopamine depletion induced by the neurotoxin MPTP may give rise (through D1 and D2 receptors) to marked changes in synaptic dynamics of pyramidal neurons in M1, which receive direct dopaminergic projections from the ventral tegmental area and the substantia nigra pars compacta. In such MPTP-treated mice, the synaptic remodeling in M1, induced through D1 and D2 receptors (with D1 receptor signaling linked to dendritic spine elimination and D2 receptor signaling linked to dendritic spine formation), gives rise to a net loss of stable dendritic spines in pyramidal cortical neurons of layer V and results in abnormal structural and functional plasticity in the motor cortex. Likewise, it was hypothesized that in patients with PD an abnormal synaptic plasticity in the motor cortex may contribute to the development of motor impairment (including impairment of motor learning) and that treatment strategies aimed at modifying such abnormal synaptic plasticity in the motor cortex may have beneficial effects in PD patients [37].

Recently, an experimental study in rats [38] using an *in vitro* brain slice model of neuronal oscillatory activity and a kinetic model of GABA_A receptor dynamics showed that zolpidem in low concentrations may reduce beta power in M1 cortical area, possibly through its action on inhibitory interneurons of the cortical area M1. Likewise, it has been also hypothesized [38] that in patients with PD low doses of zolpidem, through its possible effects on fast spiking inhibitory interneurons in M1 cortical area, may induce an increased tonic inhibition of such cortical interneurons in M1, which may give rise to an improvement of Parkinsonian motor symptoms.

4. Possible Mechanisms Underlying the Individual Variability of the Potential Effects of Zolpidem in Patients with PD

Current clinical evidence, although limited, suggests that, in those PD patients who show an improvement of Parkinsonian motor symptoms after the administration of zolpidem, the optimal dose of zolpidem may remarkably vary in different

individuals. Similarly, the dosage of zolpidem which may induce sedation or drowsiness seems also to markedly vary in different PD patients, since some PD patients do not experience drowsiness even with relatively higher doses of zolpidem, while other PD patients do easily experience drowsiness after taking relatively low doses of zolpidem. On the whole, provided that there is apparently some individual variability of the effects of zolpidem in different patients affected by PD, the scanty available evidence suggests that in PD patients in more advanced disease stages (and presenting with more severe Parkinsonian motor symptoms) a single dose of zolpidem of about 10 mg (the standard dose for insomnia) is more likely to induce an improvement of Parkinsonian motor symptoms, in comparison with PD patients in early stages and presenting with mild Parkinsonian motor symptoms [18–22]. Likewise, PD patients in more advanced disease stages and presenting with more severe Parkinsonian motor symptoms seem on average to better tolerate doses of about 7.5 or 10 mg of zolpidem (namely, they show less frequently sedation or drowsiness after the assumption of such doses of zolpidem), as compared with PD patients in early stages and presenting with mild Parkinsonian motor symptoms [18–22].

It is not easy to understand why, at least in a subset of PD patients, zolpidem does not induce drowsiness at dosages which usually induce sleep in normal subjects and why there is a remarkable individual variability in the occurrence of an improvement of Parkinsonian motor symptoms after the administration of zolpidem. In the attempt to give a possible answer to such intriguing questions, it is helpful to take into account some prompts deriving from few experimental studies.

In animal models of Parkinsonism, after lesions of the substantia nigra pars compacta (SNc) or lesion of striatal nuclei, an increase of the density of GABA_A receptors containing the binding sites for BZ (previously named GABA_A-BZ receptors) may occur in specific structures within the basal ganglia. In cynomolgus monkeys with experimental Parkinsonism induced by the injection of MPTP, an increased density of GABA_A-BZ receptors was observed in the GPi [39]. After unilateral 6-hydroxydopamine lesions of the medial forebrain bundle in the rat, an increased number of GABA and BZ binding sites were detected in the SNr and in the entopeduncular nucleus, which is the rodent counterpart of the GPi [40]. Moreover, it has been suggested that in PD the underactivity of GABAergic neurons of the putamen and caudate projecting through the direct pathway to GPi and SNr may result in compensatory upregulation of GABA_A receptors [39] in deafferented brain structures, namely, the GPi and SNr (Figure 2(b)).

In normal subjects, homeostatic mechanisms in the STN [41] may regulate the balance between excitatory glutamatergic projections from the motor cortex to the STN and inhibitory projections from GPe to the STN (Figure 1(a)), while in PD patients such balance may be disrupted, resulting in an overactivity of the STN (Figure 1(b)). Recently, an experimental study [41] showed that in a model of PD in mice the overactivity of glutamatergic projections from the motor cortex to the STN may give rise not only to a pathologically

increased activation of postsynaptic NMDA receptors in the STN (resulting in a pathological overactivity of the STN), but also to an increased expression of GABA_A receptors in the membrane of STN neurons.

On the basis of the experimental studies mentioned above [39–41], we can hypothesize that in PD the decreased GABAergic inhibition exerted by the external globus pallidus (GPe) through the indirect pathway on the glutamatergic neurons of the STN and the GABAergic neurons of the GPi and SNr may result in compensatory upregulation of GABA_A receptors in various deafferented brain structures, namely, the STN, GPi, and SNr (Figure 2(b)).

On the basis of such experimental studies [39–41], we might also speculate that, as compared to PD patients who after assuming zolpidem do not improve their motor symptoms or do experience drowsiness, in patients with PD who after the administration of zolpidem show an improvement of Parkinsonian motor symptoms and do not show remarkable drowsiness, a more marked upregulation of GABA_A receptors may occur in some critical structures overactive in PD (GPi, SNr, and STN). Accordingly, it might be hypothesized that in the subset of patients who resulted in being responders to zolpidem with a hypothetical more marked upregulation of GABA_A receptors in such overactive structures (GPi, SNr, and STN), zolpidem might bind to a relatively greater extent to these specific subcortical structures (GPi, SNr, and STN), at variance with other PD patients or normal subjects in whom zolpidem might preferentially bind to other brain structures (different from GPi, SNr, and STN) involved in sleep induction, thus inducing drowsiness. In the subset of PD patients responders to zolpidem, we might hypothesize that the relatively greater binding of zolpidem (Figure 1(c)) to such specific subcortical overactive structures in PD (GPi, SNr, and STN) may finally give rise to an increased inhibition of the two inhibitory output GABAergic structures of the basal ganglia (GPi and SNr), resulting in increased activity of specific thalamic nuclei and of specific cortical areas (such as the supplementary motor area). According to our hypothesis, such increased activity of specific cortical areas resulting from a more marked upregulation of GABA_A receptors in critical subcortical structures overactive in PD (GPi, SNr, and STN) might account for both the beneficial effects of zolpidem on Parkinsonian motor symptoms and the absence (or minimal degree) of drowsiness observed in a subset of PD patients (mostly with a good response to zolpidem), as compared to other PD patients who are nonresponders to zolpidem or show drowsiness even after low doses of this drug.

Accordingly, we might also speculate that, as compared to PD patients in early stages presenting with mild Parkinsonian motor symptoms, PD patients in more advanced disease stages and presenting with severe Parkinsonian motor symptoms might on average tolerate higher dosages of zolpidem, possibly because in advanced PD there might be a greater deafferentation of critical subcortical structures overactive in PD (GPi, SNr, and STN), in whom a more marked upregulation of GABA_A receptors may occur.

PD patients [18]. After the assumption of such single dose of zolpidem, this patient showed for some hours a remarkable improvement of several motor symptoms of PSP (akinesia, rigidity, voluntary eye movements, and dysarthria), in the absence of drowsiness. Following such observation, a pilot study (with a double-blind, placebo-controlled, crossover design) was carried out in 10 patients with a clinical diagnosis of probable PSP [31], who received in four separate trials in randomized order two single oral doses of zolpidem (5 and 10 mg), a single dose of levodopa (250 mg) plus carbidopa (25 mg), and placebo. After withholding of all anti-Parkinsonian medication 12 hours before motor assessment, PSP patients were examined by means of the UPDRS-III scale before (baseline) and one hour after the administration of the active drug or placebo. A positive response in each individual patient was defined as a decrease of more than 20% of the UPDRS-III score at baseline. In this pilot study, the administration of a single 5 mg dose of immediate-release zolpidem, unlike placebo, induced a slight but significant improvement of motor symptoms of PSP as assessed by UPDRS-III scale (namely, a 6.5% mean reduction of UPDRS-III scores from baseline). After the administration of zolpidem, two out of 10 PSP patients showed a decrease of more than 20% of the UPDRS-III score at baseline and an improvement of voluntary saccadic eye movements was observed in 4 out of 10 patients. In PSP patients responding to zolpidem, the motor improvement appeared 40–60 minutes after the administration of zolpidem, lasted about 2 hours, and mainly involved rigidity, akinesia/bradykinesia, and voluntary saccadic eye movements. In this pilot study, the only adverse effects observed after the administration of immediate-release zolpidem were drowsiness and increased postural instability, which were more marked after a single 10 mg dose of zolpidem. Subsequent observations with immediate-release and controlled-released formulations of zolpidem [63–66] confirmed that in patients with PSP the administration of zolpidem (both in single doses and chronically) may induce remarkable beneficial effects on most motor symptoms of PSP (akinesia, rigidity, voluntary eye movements, dysarthria, and dysphagia), which in some patients became more evident after the administration of controlled-released formulations of zolpidem, with a possible delay of some weeks between the start of treatment with controlled-released zolpidem and the appearance of an improvement of motor symptoms of PSP.

In 2001, Farver and Khan [34] described a 34-year-old man affected by schizoaffective disorder and antipsychotic-induced Parkinsonism with tremors of the hands for numerous years, unresponsive to various medications (benztropine, biperiden, amantadine, and propranolol). Zolpidem was administered to this patient (10 mg four times daily) and the tremor significantly decreased. Moreover, after one month of chronic treatment with zolpidem, the patient showed a dramatic improvement of Parkinsonian motor symptoms, with a score decrease from 29 at baseline to 9 on the motor examination part of the UPDRS (UPDRS-III). After a 4-month period of chronic treatment of the Parkinsonian motor symptoms of this patient with zolpidem (at a dosage of 10 mg q.i.d.), he showed a worsening of psychotic symptoms (delusions, hallucinations). Accordingly, clozapine was

started and zolpidem was discontinued, due to excessive sedation induced by the administration of clozapine together with zolpidem. After the discontinuation of chronic treatment with zolpidem, tremor reemerged in this patient. In the attempt to improve again his Parkinsonian motor symptoms, chronic treatment with zolpidem was reinitiated at a lower dosage (5 mg q.i.d.), with stabilization of Parkinsonian motor symptoms over a 2-year period. This report suggests the potential benefits of the chronic administration of zolpidem in patients affected by Parkinsonism induced by neuroleptics.

In 2006, at the 10th International Congress of Parkinson's Disease and Movement Disorders organized by the Movement Disorders Society, Kawashima and coworkers [69] reported a 70-year-old woman with a diagnosis of Parkinsonism, presenting with resting tremor, bradykinesia, and rigidity. This patient was treated with levodopa/carbidopa, with unsatisfactory results, and underwent cardiac ¹²³I-metaiodobenzylguanidine scintigraphy, which showed decreased uptake. Over the subsequent two years, Parkinsonian motor symptoms gradually progressed and at the age of 72 years she could not speak, eat, and walk. Fifteen minutes after the administration of a single 5 mg dose of zolpidem for insomnia, her rigidity and akinesia dramatically improved for about four hours and she could speak clearly, eat foods, and take several steps with bilateral assistance. After the administration of a single 5 mg dose of zolpidem, the total score obtained on the motor examination part of the UPDRS (UPDRS-III) decreased from 78 at baseline to 56. The authors suggested that, in a subgroup of patients with Parkinsonism with poor response to levodopa, the administration of zolpidem (even in low doses) may induce remarkable beneficial effects on Parkinsonian motor symptoms.

X-Linked Dystonia Parkinsonism (XDP), known otherwise as Lubag, is an X-Linked neurological syndrome afflicting male adults in the Philippines [68], clinically characterised by dystonia and Parkinsonism, poorly responsive to pharmacological treatment. XDP is associated with mutations in two genes, the */DYT3/* gene and the */TAF1/* (TATA binding protein-associated factor-1) gene. Dystonia usually starts focally in the lower limbs or oromandibular region and may then spread to become generalized, while Parkinsonism usually presents in later in the disease course, usually in combination with dystonia. It has been reported that the administration of a single 10 mg oral dose of zolpidem in three patients affected by XDP [67] induced after 15–45 minutes in all three patients a dramatic improvement of dystonia (100%, 32%, and 31% improvement on the Burke-Fahn-Marsden dystonia score, resp.) and a dramatic improvement of Parkinsonism (bradykinesia and rigidity) in 2 out of 3 patients (with 40%, 34%, and 0% improvement on the UPDRS-III scale, resp.). All three patients affected by XDP were treated chronically with zolpidem [67]. Patient 1, with a slow titration of the daily dose of zolpidem and with caffeine intake, adapted to sedation induced by zolpidem and was treated chronically with very high daily dosages of zolpidem (10 mg every 2 hours). On follow-up, one year after starting the chronic treatment with zolpidem, in patient 1, efficacy on motor symptoms of XDP was still maintained. Patient 2 did not tolerate daily doses of zolpidem higher

than 20 mg but showed beneficial effects on motor symptoms of XDP after chronic treatment with a 20 mg daily dose of zolpidem (10 mg b.i.d.). Six months after starting the chronic treatment with zolpidem, patient 2 developed diarrhea and discontinued zolpidem, with subsequent disappearance of diarrhea. In patient 3, a chronic treatment with zolpidem had to be discontinued after 2 months, only due to financial straits of this patient. Since patient 3 was unemployed, a benefactor gave him 120 tablets of zolpidem, which he stretched out by taking only one 10 mg tablet b.i.d. In this patient, the administration of zolpidem 10 mg b.i.d. induced beneficial effects with no side effects, but he ran out of zolpidem tablets after 2 months of chronic treatment with zolpidem. In a review paper on XDP [68], it has been pointed out that zolpidem was the only drug showing remarkable beneficial effects on disabling motor symptoms of patients affected by XDP.

As to the mechanisms underlying the clinical improvement observed after the administration of zolpidem in various neurological disorders other than movement disorders (including Parkinson's disease and Parkinsonian syndromes), although such mechanisms are still unclear, it seems plausible to us that they might be related to the selective action of zolpidem on GABA_A receptors containing the $\alpha 1$ subunit, resulting in enhanced activity of specific GABAergic circuits across various brain structures. This general hypothesis is supported by a recent experimental study on ischaemic stroke in mice, suggesting that zolpidem may improve recovery after stroke in mice by enhancing phasic GABAergic inhibition during the repair phase of stroke [70], which can be associated with an increased number of $\alpha 1$ receptor subunit-containing GABAergic synapses in the peri-infarct cerebral cortex.

Currently available evidence [71–73] suggests that in patients with brain damage due to stroke or associated with various pathologies resulting in disorders of consciousness the likelihood of beneficial effects of zolpidem seems to be remarkably lower, unfortunately, as compared with the likelihood of a motor improvement in PD patients. In our view, in order to give a possible explanation for such relatively low likelihood of beneficial effects of zolpidem in patients affected by stroke or disorders of consciousness, we might hypothesize that in such neurological conditions the distribution of damage across different brain structures is much less predictable than in patients with PD, in whom the likelihood of beneficial effects of zolpidem seems accordingly to be relatively higher, consistently with the hypothesis of a selective action of zolpidem on GABA_A receptors of various subcortical structures (GPI, SNr, and STN), which are overactive in PD. In other words, in stroke or disorders of consciousness a poorly predictable distribution of damage across different brain structures results in high individual variability in the patterns of brain damage across different patients. Accordingly, only in a (possibly relatively small) subset of patients with stroke or disorders of consciousness, a positive allosteric modulation of GABA_A receptors induced by the administration of zolpidem may give rise to a positive allosteric modulation of GABAergic synapses in

specific neuronal networks, which may result in a clinical improvement in such subset of patients. This hypothesis might account for those observations reporting that the proportion of brain-damaged patients with disorders of consciousness who improve after the administration of zolpidem might be relatively low in placebo-controlled and open-label trials carried out on a relatively higher number of subjects [71–73].

6. Concluding Remarks and Perspectives

Various studies and observations, although still preliminary and sometimes published only in abstract form, consistently suggest that zolpidem may induce beneficial (and often clinically remarkable) effects in the treatment of motor symptoms associated with a variety of movement disorders [35], including PD and other Parkinsonian syndromes.

As to PD, a potential role of zolpidem in the treatment of this disabling disorder is suggested by the following considerations: (a) a number of clinical observations provided some clear-cut, although preliminary, evidence that the oral administration of zolpidem may remarkably improve most motor symptoms of PD, even after a single dose of zolpidem, as may be observed only with the most powerful anti-Parkinsonian drugs (levodopa and apomorphine); (b) in patients with PD, unlike most anti-Parkinsonian drugs, zolpidem may also have antidyskinetic effects, which may be very helpful in patients with advanced PD, who experience dyskinesias and other symptoms associated with long-term levodopa treatment; (c) in patients with advanced PD, who become usually poorly responsive to current options of pharmacological treatment and in whom alternative pharmacological approaches are more urgently needed, the beneficial effects of zolpidem on Parkinsonian motor symptoms seem to be more remarkable and a lower incidence of side effects of zolpidem (such as drowsiness) may be observed with the standard 10 mg dose of zolpidem used for insomnia.

It remains to be ascertained whether in PD patients the possible beneficial effect of zolpidem on Parkinsonian motor symptoms may decrease after a certain period of treatment with zolpidem, possibly due to disease progression or due to the possible development of tolerance after the chronic administration of zolpidem. The scanty evidence available so far suggests that, at least in some individual PD patients, the chronic administration of zolpidem might have persistent beneficial effects for several months [21] or even for years, namely, more than 3 years [19] or up to 5 years [18]. Interestingly, in some PD patients the doses of zolpidem had not been substantially increased over more than 3 years of chronic administration [19] or had not been increased at all up to 5 years of chronic administration of zolpidem [18]. Long-term clinical trials are needed to clarify whether in PD patients the possible beneficial effects of zolpidem on Parkinsonian motor symptoms may decrease after a certain period of chronic treatment with zolpidem and to clarify whether specific clinical or pathophysiological features of PD patients might predict the occurrence over time of a decrease of beneficial effects of zolpidem on Parkinsonian motor symptoms.

The safety of a long-term treatment with zolpidem in patients with PD has been recently questioned by two recent retrospective observational studies, which analyzed a large Taiwan National Health Insurance database [74, 75]. These studies suggested that the overall incidence of PD was significantly greater among a group of subjects with a history of assumption of zolpidem for more than 3 months as sleep-inducer, as compared to a group of subjects without a history of assumption of zolpidem [74, 75]. In the first study [74], the group of subjects who received zolpidem had a higher cumulative rate of PD than the group of subjects who did not receive zolpidem during a 5-year follow-up period, while in the second study [75] after 5 years of observation the incidence of PD did not differ between the two groups. Such two studies, which according to their authors have various limitations, suggested the hypothesis that the assumption of zolpidem over more than 3 months may increase the risk for PD. Interestingly, some experimental studies had suggested that zolpidem may have neuroprotective effects, including *in vitro* and *in vivo* antioxidant activity [76–78] and protective effects against hypoxic stress [78]. It has been pointed out [79] that no plausible mechanism was proposed for the hypothetical relationship between the prolonged assumption of zolpidem and an increased risk for PD. An alternative and perhaps more parsimonious explanation for the findings of such two retrospective studies has been recently proposed by Andrade [79], who suggested that subjects with persistent sleep disturbances (and therefore assuming zolpidem for more than 3 months) are more likely to develop PD later, since it has been established that in patients who develop PD sleep disorders may antedate the onset of motor symptoms by several years [80]. According to this latter view, persistent sleep disturbances and the subsequent prolonged use of zolpidem may have some predictive value, as persistent sleep disturbances (requiring a prolonged use of zolpidem) in a subgroup of subjects may simply represent very early nonmotor symptoms of PD. Although according to this perspective the prolonged assumption of zolpidem per se would not play any significant role as a risk factor for PD, further epidemiological studies are needed in order to draw reliable conclusions about this potential safety issue related to a long-term treatment with zolpidem.

In conclusion, a number of questions and issues need to be faced at present. Controlled randomized clinical trials are certainly needed in order to confirm the efficacy of zolpidem in treating (possibly most) motor symptoms of PD patients, to investigate the safety and tolerability of zolpidem in PD patients, to find the most appropriate daily dose range of zolpidem that can be administered to PD patients (ideally, following an individualized and slow titration, in order to find the optimal daily dosage of zolpidem in each patient), to understand which are the best strategies to minimize the possible occurrence of daytime drowsiness as adverse effect of zolpidem, to check whether in patients treated with zolpidem plus levodopa (or other dopaminergic agents) it is possible to reduce the daily dosage of levodopa (or of other dopaminergic agents), and to identify potential features in individual PD patients (according to clinical symptoms or according to possible neurophysiological or neuroimaging

markers) that might ideally predict a good chronic response to zolpidem in PD patients.

Competing Interests

The authors declare that they have no competing interests.

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Research Article

Blindfolded Balance Training in Patients with Parkinson's Disease: A Sensory-Motor Strategy to Improve the Gait

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Aim. Recent evidence suggested that the use of treadmill training may improve gait parameters. Visual deprivation could engage alternative sensory strategies to control dynamic equilibrium and stabilize gait based on vestibulospinal reflexes (VSR). We aimed to investigate the efficacy of a blindfolded balance training (BBT) in the improvement of stride phase percentage reliable gait parameters in patients with Parkinson's Disease (PD) compared to patients treated with standard physical therapy (PT). *Methods.* Thirty PD patients were randomized in two groups of 15 patients, one group treated with BBT during two weeks and another group treated with standard PT during eight weeks. We evaluated gait parameters before and after BBT and PT interventions, in terms of double stance, swing, and stance phase percentage. *Results.* BBT induced an improvement of double stance phase as revealed (decreased percentage of double stance phase during the gait cycle) in comparison to PT. The other gait parameters swing and stance phase did not differ between the two groups. *Discussion.* These results support the introduction of complementary rehabilitative strategies based on sensory-motor stimulation in the traditional PD patient's rehabilitation. Further studies are needed to investigate the neurophysiological circuits and mechanism underlying clinical and motor modifications.

1. Introduction

Difficulty in walking is a pathognomonic sign of Parkinson's Disease (PD). Gait disorders, balance impairment, falls, and fall-related injuries are also present in PD patients [1]. Indeed, patients with PD demonstrate impaired ability to walk [2, 3] and to change direction [4]. PD patients' gait is characterized by small shuffling steps, stooped posture, and reduced arm swing. As disease progresses, these features worsen, treatment efficacy wanes, and gait impairment becomes increasingly disabling [5]. The management of PD has been traditionally based on pharmacological and surgical therapy; even with optimal medical management, PD patients experience deterioration in body function, daily activities, and participation [6]. Therefore, rehabilitation therapies represent an adjuvant to pharmacological and neurosurgical treatment [7]. The target of the traditional motor rehabilitation program

was muscle stretching, motor coordination, balance, and gait trainer [8]. Recent evidence suggested that the use of treadmill training may improve gait parameters, such as gait speed and stride length [9]. Moreover, the study of kinematic alteration of the gait through gait analysis system showed specific altered spatiotemporal parameters in PD patients [10].

The gait cycle consists in three important phases of step: stance, swing, and double stance of both sides of body. These can be observed by different point of view: time, space, and jerk, but the more commune and coherent method is the normalization of step cycle in percentage (phase stride percentage) [11]. In particular, motor rehabilitation program reduced temporal variables in the stance phase and increased the swing phase; only the single support phase was decreased, while the double stance phase was not significantly changed

after traditional rehabilitation program [12]. Transitioning from double stance to single stance is challenging to maintain postural stability, as one has to shift weight from a relatively stable position during double stance to a smaller base of support during single stance [13]. The relationship between altered gait and postural instability is very close in PD patients and despite optimal medication therapy, significant gait impairment remains even in very early disease [1, 14]. The impairment of sensory integration has been suggested to influence balance control in Parkinson's Disease [15]. Recent studies [16, 17] supported the role of visual deprivation as a potential driver in using alternative sensory strategies to control dynamic equilibrium and stabilize gait. Furthermore, as reported by De Nunzio et al. [18], PD patients showed central deficit in reorganizing sensory information for postural control which induces a delay in balancing strategy adaptation. These sensory processing impairments could be enhanced in PD by means of dedicated strategies during PT programs. In particular, rehabilitative training based on the enhancement of sensorial input could be essential to improve balance and gait in PD patient [19]. These assumptions indicated that more attention should be given to adopting rehabilitation strategies which improve postural responses by means of sensorial integration afferences. However, several questions remain unanswered, particularly regarding training methods as well as intensity and duration and specific exercises need to improve gait and balance control in PD. Here we introduced specific dynamic exercises performed with visual deprivation in order to stimulate reweighting of sensory information in the context of dynamic activity [20, 21]. March on foam would make inputs less reliable, so with eyes closed the subject would have to rely more on the vestibular system to maintain balance [22]. We hypothesized that rehabilitation therapy based on sensory-motor stimulation could contribute to acquisition of compensative strategies to improve gait, given the important role that the visual and proprioceptive deprivation has in sensory substitution [23]. This study aimed to investigate the efficacy of a blindfolded balance training (BBT) in the improvement of gait parameters in people with PD compared to patients who underwent physical therapy program.

2. Patients and Methods

Forty-four hospitalized patients with Parkinson's Disease (PD) according to the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria were enrolled in the study. Local ethical committee approved the project and written informed consents were obtained from all subjects (Prog. 297/11). Patients with (i) systemic or metabolic diseases, (ii) uncertain or unclear history of responsiveness to L-dopa treatment, (iii) presence of brain lesions or marked cortical and subcortical atrophy on brain CT and MRI scans, or (iv) dementia diagnosed by a clinical examination or a Mini-Mental State Examination score <26 [24] are excluded. The patients underwent preliminary gait analysis. Thirty subjects have been selected and were randomized with the support of Research Randomizer Software [25] in 2 groups (PT and BBT groups); each group consisted of 15 subjects.

All patients were being treated exclusively with Levodopa therapy (mean: $719 \text{ mg} \pm 356$); the pharmacological treatment was stable for at least 2 weeks before the start of the study and was not modified. Clinical data of PD patients are reported in Table 1.

2.1. Outcome Measures. Gait analysis was performed using the equipment and procedures developed at the motion laboratory of IRCCS Fondazione Santa Lucia, Rome, Italy. It included an optoelectronic system (SMART system, BTS, Padova, Italy) to measure the three coordinates of 23 retro-reflective markers. The technical procedure is described elsewhere [12]. The Unified Parkinson's Disease Rating Scale Part III (UPDRS) [26] and gait analysis recording were carried out twice: at the beginning and at the end of rehabilitation programs (PT and BBT). All testing was carried out 2 h after the first morning's drug administration (in ON clinical status). PT group patients are tested before and after traditional rehabilitation program. BBT group patients are tested before and after blindfolded balance training program.

2.2. Gait Analysis. To position the markers correctly, we used an extended "Davis" protocol [27]. Extending the marker configuration of the "Davis" model, 23 spherical (10 mm in diameter) markers (axial: C7, T12, and S1; right and left: acromion, olecranon, ulnar styloid, anterior superior iliac spine, thigh, external femoral condyle, calf, external malleolus, second metatarsal head, and heel) were attached to the body with double sided tape. For the calves and thighs only, markers were attached to iron rods positioned approximately 7–10 cm away from the skin. PD subjects were blind as to when gait analysis recording would take place. The following instructions were given: "Walk as you normally do," as reported by Jiang and Norman [28]. Gait measurements were obtained for six straight-line walking trials [11]. Patients received no additional instructions during recording and needed no physical support. The gait acquisition process involved three steps: (1) gait capture with video cameras, (2) transformation (using tracker software) of 2D acquired data into a 3D model by applying the "Davis" model, and (3) stride analysis using the extended "Davis" protocol. To perform the analysis we used "SMART" (BTS, Padova, Italy) version 1.10.427.0 software. The following variables were studied: stance, swing, and double stance percentages with respect to the stride phase [29]. The variables studied were evaluated considering (for each PD patient) the more affected body side (MABS) resulting from the clinical exam.

2.3. Interventions

2.3.1. Physical Therapy (PT). Therapists with experience in PD rehabilitation treated the patients individually for eight consecutive weeks; 45 min treatment sessions were held in the morning and in the afternoon five times a week. In summary, each PD patient performed 80 sessions of physical therapy (40 in the morning and 40 in afternoon). In the morning, the exercises included active and assisted limbs mobilization, four limbs coordination exercises, balance training on instable platform, gait training, and muscles stretching [30]. In

TABLE 1: Clinical and demographic characteristics of Parkinson's Disease patients.

	PD patients	MABS	Age	Years of disease	UPDRS III Pre	UPDRS III Post
BBT	15	7 R 8 L	70.1 ± 8.5	7.9 ± 5.0	27.3 ± 11.4	17.8 ± 4.8
PT	15	7 R 8 L	69.0 ± 10.3	8.8 ± 6.6	31.2 ± 10.8	19 ± 10.54

PT: physical therapy; BBT: blindfolded balance training; UPDRS: Unified Parkinson's Disease Rating Scale Part III before rehabilitation treatment; MABS: more affected body side; R: right; L: left.

the afternoon, the patients underwent a group therapy to promote control of strength, movement velocity, and motor coordination; in particular patients sitting in circle were requested to throw a ball of different size and weight to any person, increasing velocity [30].

2.3.2. Blindfolded Balance Training (BBT). Therapists with experience in PD rehabilitation treated the patients individually; for a period of two consecutive weeks 45 min treatment sessions were held in the morning in substitution of individual motor rehabilitation program and 45 min group therapy sessions were held in the afternoon five times a week. In summary, each PD patient performed 40 sessions of BBT (20 in the morning and 20 in afternoon). In the afternoon the patients of BBT group received the same treatment of PT group (control of strength, movement velocity, and motor coordination).

The BBT consisted of balance and walking exercises aimed at stimulating dynamic postural control and improving balance reactions. The main activity of the balance exercises was to march in place on a foam cushion blindfolded and walk blindfolded on a treadmill with speed increasing from 1 km/h to 3 km/h with supervision.

2.3.3. March in Place. Each patient was asked to get on a foam cushion of 10 cm in height and then was blindfolded. Immediately after that he was asked to stretch his arms forward with 90° of shoulder flexion, with his hands up against the wall as a reference point. Once the position was perceived, the patient was invited not to move away ~5 cm from the wall, losing touch of hands. When the patient was in the correct position he/she was given the following instruction: "march in this position with arms extended forward for one minute." At the end of the first minute of march, remaining blindfolded, the patient made 90° clockwise turn and repeated the exercise of marching in place for another minute. The same procedure was carried out at 180° and 270° for a total of 4 minutes. When patients made the mistake of changing direction, the physiotherapist helped them to keep the right position using verbal cues (e.g., you are turning left or right and you are going forward).

2.3.4. Treadmill Training. As preparation for training, all subjects underwent a 1-minute walk on treadmill with open eyes using preferred walking speed. Immediately after preparation, patients were blindfolded and were asked to

walk on treadmill without support of hands for 4 minutes. When patients made the mistake of changing direction, the physiotherapist helped them to keep the right position using verbal cues (e.g., you are turning left or right). The initial speed of the treadmill was set at 1 km/h and was increased by 0.5 km/h every minute, up to reaching a speed of 3 km/h for a total operating time of 4 minutes.

2.4. Statistical Analysis. One-way analyses of variance (ANOVAs) with GROUP (BBT versus PT) as between-subjects main factor were performed on baseline temporal gait parameters (stance phase, swing phase, and double stance phase). Mann-Whitney test was performed to compare UPDRS score between groups (BBT versus PT). Separate repeated-measures analysis of variance (ANOVA) was performed for the swing, stance, and double stance percentages with respect to the stride phase with GROUP (BBT versus PPT) as between-subjects main factor and TIME (before versus after) as within-subjects main factor. When a statistically significant effect was observed, Bonferroni's tests were used for post hoc analyses. For all statistical analyses, a p value of <0.05 was considered to be significant. Mauchly's test examined sphericity. The Greenhouse-Geisser correction was used for nonspherical data.

3. Results

We found no difference across groups (BBT versus PT) for baseline temporal gait parameters: stance phase ($F(1,28) = 0.87, p = 0.35$), swing phase ($F(1,28) = 0.73, p = 0.39$), and double stance phase ($F(1,28) = 0.15, p = 0.69$). We found no differences between groups' UPDRS scores ($p = 0.88$). BBT group has registered an improvement of double stance phase measured but with a decreased percentage in PT group, as revealed by ANOVA analysis which showed an effect of time main factor ($F(1,28) = 12.416, p < 0.01$) as well as GROUP \times TIME interaction ($F(1,28) = 9.55, p < 0.01$) (Figures 1 and 4). Post hoc analysis showed that the double stance phase's percentage was significantly reduced following BBT but not PT as measured after gait analysis ($p < 0.05$). Repeated-measures ANOVA performed on the stance phase's percentage showed a main effect of TIME ($F(1,28) = 18.02, p < 0.001$) but no effect for GROUP main factor ($F(1,28) = 2.3, p = 0.13$) and for TIME \times GROUP interaction ($F(1,28) = 1.25, p = 0.27$). Repeated-measures ANOVA performed on the swing phase's percentage showed a main effect of TIME

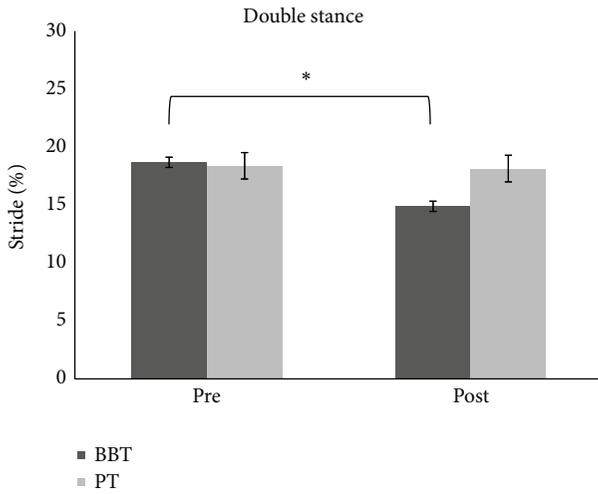


FIGURE 1: The graph shows the effects of BBT and PT (dark grey and light grey, resp.) on percentage of double stance phase with respect to entire stride phase. Error bars indicate the standard error. * $p < 0.05$. PT: physical therapy; BBT: blindfolded balance training.

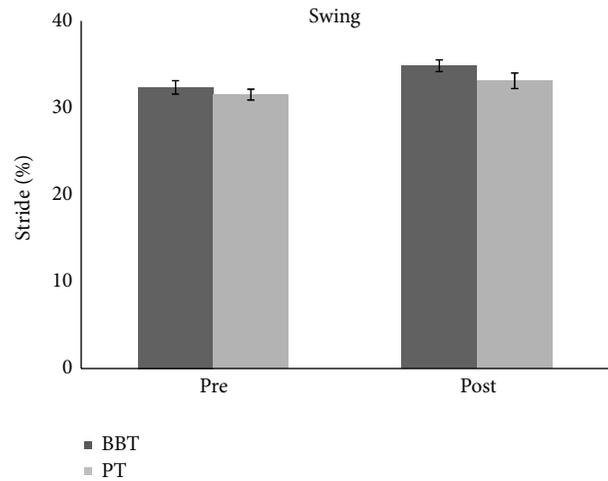


FIGURE 3: The graph shows the effects of BBT and PT (dark grey and light grey, resp.) on percentage of swing phase with respect to entire stride phase. Error bars indicate the standard error. PT: physical therapy; BBT: blindfolded balance training.

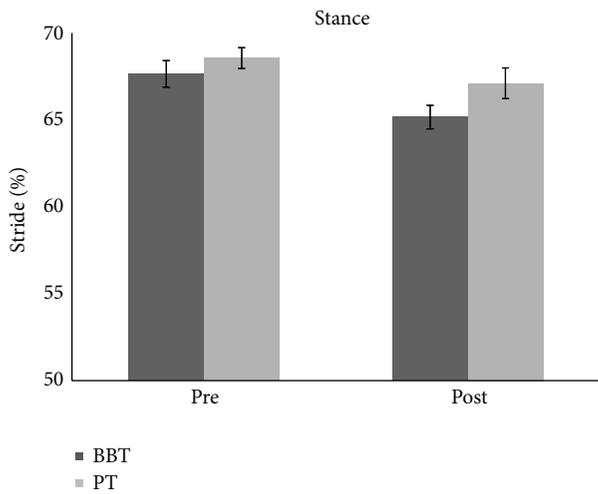


FIGURE 2: The graph shows the effects of BBT and PT (dark grey and light grey, resp.) on percentage of stance phase with respect to entire stride phase. Error bars indicate the standard error. PT: physical therapy; BBT: blindfolded balance training.

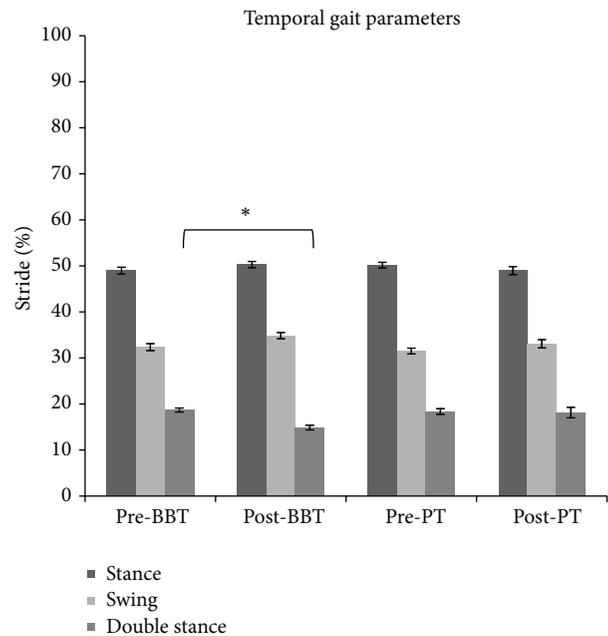


FIGURE 4: The graph shows the effects of BBT and PT on percentage of stance, swing, and double stance phases (dark grey, light grey, and grey, resp.) with respect to entire stride phase. Error bars indicate the standard error. * $p < 0.05$. PT: physical therapy; BBT: blindfolded balance training.

($F(1,28) = 18.85, p < 0.001$) but no effect for GROUP main factor ($F(1,28) = 1.86, p = 0.18$) and for TIME \times GROUP interaction ($F(1,28) = 0.93, p = 0.34$) showing that there was a significant modulation of stance (Figures 2 and 4) and swing (Figures 3 and 4) phases' percentage in both groups following therapy but it was not specific for any type of therapy.

4. Discussion

This study aimed to verify the modifications of stride phase's percentage after BBT. Our results are consistent with previous finding [12] showing an increase of percentage of stance phase and decrease of swing phase's percentage in PD patients treated with physical therapy. However, we found reduction

of double stance phase in PD patients treated with BBT but not with traditional rehabilitation [30]. The double stance phase's decrease is likely due to an improvement of postural stability, reflecting the patients' ability to transfer their weight correctly in preparation for stepping [13]. The double stance phase is expression of good balance control and requires the integration of sensory information from visual, somatosensory, and vestibular sources. This ability to integrate somatosensory information resulted affected in PD

patients. This deficit could be compensated by the vestibular system [31–33]. Here we introduced specific dynamic exercises performed with visual deprivation coupled with gait surface changes. The treadmill induces a body acceleration that is mediated by the visual system, but to maintain the balance in visual deprivation condition the response to this acceleration should be compensated by vestibular-spinal tract. Moreover, the vestibular-spinal tract is thought to play a significant role during the execution of voluntary forward steps [34] in the double stance phase [35]. In fact vestibular information is weighted more heavily during double support than at any other time of the gait cycle [35, 36]. We hypothesize that the vestibular-spinal stimulation would contribute to the subsequent correct facilitation of Anticipatory Postural Adjustment (APA), that is, acquired motor reflexes that are necessary to perform voluntary movements. In other words, the vestibular system can primarily induce modulation of antigravitary muscles and balance reactions [21] which in turn can be learned and used by feed-forward mechanisms prior to voluntary movements.

In conclusion, our results support the hypothesis that visual deprivation and proprioceptive perturbation could be compensated using other sensory strategies as vestibular system and that this approach may be useful to improve gait in PD patients. Our findings support the introduction of complementary rehabilitative strategies based on sensory-motor stimulation in the traditional PD patient's rehabilitation program helping to achieve better functional outcomes in shorter time. Further studies are needed to verify the long term efficacy of BBT and to investigate the neurophysiological circuits and mechanism.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Genetic Profile, Environmental Exposure, and Their Interaction in Parkinson's Disease

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The discovery of causative mutations for Parkinson's disease (PD) as well as their functional characterization in cellular and animal models has provided crucial insight into the pathogenesis of this disorder. Today, we know that PD pathogenesis involves multiple related processes including mitochondrial dysfunction, oxidative and nitrate stress, microglial activation and inflammation, and aggregation of α -synuclein and impaired autophagy. However, with the exception of a few families with Mendelian inheritance, the cause of PD in most individuals is yet unknown and the identified genetic susceptibility factors have only small effect size. Epidemiologic studies have found increased risk of PD associated with exposure to environmental toxicants such as pesticides, organic solvents, metals, and air pollutants, while reduced risk of PD associated with smoking cigarettes and coffee consumption. The role of environmental exposure, as well as the contribution of single genetic risk factors, is still controversial. In most of PD cases, disease onset is probably triggered by a complex interplay of many genetic and nongenetic factors, each of which conveys a minor increase in the risk of disease. This review summarizes the current knowledge on causal mutation for PD, susceptibility factors increasing disease risk, and the genetic factors that modify the impact of environmental exposure.

1. Introduction

Nineteen years ago, the discovery of the first genetic mutation responsible for Parkinson's disease (PD), p.A53T in the α -synuclein (*SNCA*) gene [1], provided the initial insights into the molecular genetics of PD. This finding was followed by data showing that α -synuclein is the major component of Lewy bodies (LB), a hallmark lesion in PD and other α -synucleinopathies [2]. Since then, an intensive search for other genetic causes for PD was launched and other mutated genes were reported to cause autosomal dominant or recessive forms of PD. Although monogenic forms are rare and altogether represent less than 10% of all PD cases [3], their functional characterization in cellular and animal models provided valuable insights into PD etiologic mechanisms. Recent advances of fundamental processes involved in neuronal death, particularly in the substantia nigra pars compacta, converge on abnormal endocytosis and endosome trafficking [4]. Starting from these dysfunctional mechanisms, multiple related processes, including mitochondrial

dysfunction, oxidative and nitrosative stress, microglial activation and inflammation, and aggregation of α -synuclein and impaired autophagy, derive [5]. Besides rare causative mutations, several genetic susceptibility loci were discovered but with small to modest effect sizes [6].

Exploring the contribution of environmental exposure markedly advanced our understanding of the mechanisms involved in the development of PD. Initial evidence came from findings that subjects exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) developed PD-like symptoms [7]. Since then, environmental exposure to pesticides [8, 9], polychlorinated biphenyls [10], organic solvents [11], metals [12], and air pollutants [13] has been proposed to increase risk for PD. However, results concerning the contribution of environmental factors in PD are still inconsistent.

Altogether, although genes are likely to play a role, the vast majority of PD cases cannot be ascribed exclusively to genetic factors. PD is probably caused by a complex interplay of many genetic variants interacting with many nongenetic risk factors.

Here, we briefly review research on the genetic and environmental causes of PD. We also summarize evidence on gene-environment interplay in the development of PD with an emphasis on positive findings. Anyway, negative studies will be cited. Furthermore, positive results from human association studies should be interpreted with caution as most of these studies are based on a relatively small number of exposed subjects. Certainly, more large-scale human association studies aimed at identifying gene-environment interactions in the development of PD may prove to be fruitful.

2. Monogenic Forms of PD

Mutations in two genes (*SNCA* and *LRRK2*) cause autosomal dominant forms of PD with peculiar features. Mutations in the *SNCA* gene are rare and highly penetrant and generally cause early onset autosomal dominant inherited forms of PD [3]. Besides the above mentioned p.A53T mutation in the *SNCA* gene, other point mutations in the same gene (p.A30P [14], p.E46K [15], p.H50Q [16], and p.G51D [17]), as well as duplications and triplications of the locus containing the *SNCA* gene [18], were identified to cause PD. Brain pathology in *SNCA* mutation carriers is characterized by diffuse LB pathology and Lewy neurites (LNs) [19]. Clinical features of *SNCA* mutation carriers range from classical symptoms (bradykinesia, muscle rigidity, resting tremor, and postural instability), and good response to levodopa therapy, to more atypical phenotypes resembling other synucleinopathies (Lewy body dementia or multiple system atrophy) [20].

Mutations in the leucine-rich repeat kinase 2 (*LRRK2*) gene are less rare and have incomplete and age-dependent penetrance. They generally cause late onset autosomal dominant inherited forms of PD. Although almost 80 gene variants have been identified in this large gene in PD patients, only seven of these (p.N1437H, p.R1441C, p.R1441G, p.R1441H, p.Y1699C, p.G2019S, and p.I2020T) can be considered as definitely disease causing mutations [21]. LB pathology is also the dominant pathology in most cases of *LRRK2*-related PD along with, more rarely, tau or TDP-43 pathology [22]. However, in some cases, LB pathology is not observed. Clinical features resemble classical motor symptoms and good response to levodopa therapy. *LRRK2* p.G2019S is the most common known cause of autosomal dominant PD, accounting for 1–40% of sporadic or dominantly inherited PD, depending on the population examined. The worldwide frequency of *LRRK2* p.G2019S was 1% of patients with sporadic PD [23]. The highest prevalence rates were registered for Ashkenazi Jewish [24] and North African Arab [25] populations, where *LRRK2* p.G2019S accounts for approximately 20% and 40% of PD cases, respectively.

Recently, mutations in three novel genes, that is, the vacuolar protein sorting 35 homolog (*VPS35*), eukaryotic translation initiation factor 4 gamma 1 (*EIF4G1*), and dnaJ homolog subfamily C member 13 (*DNAJC13*), were proposed to cause late onset autosomal dominant inheritance and need further replication to be confirmed [26–28].

Loss-of-function mutations in Parkin (*PARK2*, *PRKN*), PTEN-induced putative kinase 1 (*PINK1*), and Daisuke-Junko-1 (*DJ-1*) cause rare forms of autosomal recessive Parkinsonism with early onset and slow progression [29–31]. Recessively inherited forms of atypical Parkinsonism with juvenile onset are caused by mutations in the ATPase type 13A2 (*ATP13A2*), phospholipase A2 group VI (*PLA2G6*), and F-box only protein 7 (*FBXO7*) genes [32–34].

3. Genetic Variants Associated with PD

It has been estimated that about 90% of PD patients have no family history [35]. With the exception of a few families with Mendelian inheritance, PD etiology is most likely caused by the combination of several genetic and environmental factors [36]. Candidate gene association studies as well as genome-wide association studies (GWAS) have identified polymorphisms in a number of genes that were significantly related to the development of PD. Some of these were consistently replicated while, for the others, the true significance remains to be examined [6].

Candidate gene association studies focused on selected genes that were genetically, clinically, or functionally related to PD. Great effort has been spent in the last 20–30 years in this research field. This kind of approach was in many cases unsuccessful with some notable exceptions [20]. Several studies explored disease risk associated with allelic variants of genes already linked to monogenic PD or to other neurological diseases. For example, p.G2385R in the *LRRK2* gene is common among Chinese and Japanese populations and approximately doubles the risk for PD [37], while the REP1 microsatellite marker of the *SNCA* promoter region was consistently associated with a 1.4-fold increased risk of PD [38]. Additionally, the H1 haplotype of microtubule-associated protein tau (*MAPT*) gene has been identified as a risk factor for idiopathic PD [39]. Clinical observations led to the identifications that some gene variants, known to cause other diseases, were associated with higher risk for PD. Some examples are variants in the glucocerebrosidase (*GBA*) [40], the sphingomyelin phosphodiesterase 1 (*SMPD1*) [41], and the GTP cyclohydrolase 1 (*GCHI*) [42] genes, responsible for Gaucher's disease, Niemann-Pick A disease, and dopa-responsive dystonia (DRD), respectively.

Several GWAS have been performed to investigate the influence of common genetic variations in PD. The first GWAS confirmed the causal genes *SNCA*, *LRKK2*, and *MAPT* as risk genes also for idiopathic PD [43, 44]. Subsequent GWAS and meta-analyses revealed additional risk genes. Recently, meta-analysis pooling data from 15 PD GWAS, including 13,708 patients and 95,282 control individuals, identified 28 independent single nucleotide polymorphisms (SNPs) as susceptibility variants for PD across 24 different loci [6]. Although the effect of each individual locus was small, risk profile analysis showed substantial cumulative susceptibility in a comparison of the highest and lowest quintiles of genetic risk [6], suggesting that the risk for PD increases with the number of susceptibility alleles carried by a single subject.

4. Environment Factors Related to PD

Exploring the contribution of environmental exposure markedly advanced our understanding of the mechanisms involved in the development of PD. Since the initial evidence regarding 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [7], a number of studies have reported the association between exposure toxicants and increasing risk of developing PD. Among these, pesticides (e.g., rotenone, paraquat, dichlorodiphenyltrichloroethane, dieldrin, and organophosphates) have been largely studied [8, 9]. A recent meta-analysis of 46 studies from around the world found a summary risk ratio of 1.62 (95% CI [1.40–1.88]) for pesticide exposure (ever versus never) [9]. In particular, in a recent case-control study examining the risk of developing PD based on exposure to 31 specific pesticides, 2 were found to increase risk: paraquat (OR = 2.5; 95% CI, 1.4–4.7) and rotenone (OR = 2.5; 95% CI, 1.3–4.7) [45]. Besides pesticides, other toxicants were proposed to increase risk for PD, such as polychlorinated biphenyls [10], solvents [11], metals [12], and air pollutants [13].

In contrast, possible protective factors include cigarette smoking and coffee and tea consumption [46]. Risk in ever-smokers is half of that in never-smokers, and there is a clear dose-response relationship. Caffeine and coffee consumption were also consistently associated with reduced risk of PD; the magnitude of the reduced risk is similar to that of smoking, and a dose-response relationship is evident [47].

Overall, results of epidemiological studies, concerning the contribution of environmental toxicants in PD, are sometimes inconsistent. Identifying subpopulations at different genetic-based risk is one way to improve the study design. In this regard, the next two sections will be focused on the relevance of genetic polymorphisms in toxicokinetics and toxicodynamics in PD. Several interesting findings will be reported although sometimes not replicated, as mentioned in the relevant section within the paper. Positive findings related to the joint gene-environment contribution to PD susceptibility are also summarized in Table 1.

5. The Role of Genetic Variants in the Kinetics of Environmental Factors

Recently, epidemiologic studies have begun to consider the joint effects of toxicant exposure and polymorphisms in genes that affect the toxicants' absorption, metabolism, and excretion.

5.1. Absorption. P-glycoprotein (P-gp) is an efflux transporter encoded by the *ABCB1* (also known as *MDR1*) gene that protects the brain against neurotoxicants [66]. Certain *ABCB1* genetic variants, known to alter the function of this transporter, have been suggested to influence the risk to develop PD in conjunction with exposure to toxicants [48–50, 67]. A case-control study, in 599 European PD patients and controls, detected no relevant association between three *ABCB1* variants and PD, while it found that the distribution of c.3435C>T differed significantly between PD patients exposed to pesticides compared to those nonexposed (OR = 4.74, 95%

CI [1.01–22.31]) [48]. Another case-control study, among 207 PD cases and 482 matched controls, addressed the association between PD and 2 polymorphisms in *ABCB1* (c.2677G>[A/T], c.3435C>T), as well as the interaction between *ABCB1* and pesticides. Participants were classified as never users, user for gardening, and professional users of pesticides. This study found that *ABCB1* polymorphisms were not associated with PD. Among PD cases only, an association between carrying 2 variant c.2677G>[A,T] alleles and organochlorine exposure was found (OR = 5.4, 95% CI [1.1–27.5]) [49]. More recently, another study lent support to previous findings. In a population-based case-control study, including 350 cases and 724 controls, homozygote carriers of *ABCB1* c.2677G>[A/T] or/and c.3435C>T risk alleles, exposed specifically to organophosphorus pesticides, had from 2 to 3.7 times higher risk to develop PD versus noncarriers (OR = 2.1, 95% CI [1.3–3.2] for homozygotes of 1 risk allele; OR = 3.7, 95% CI [2.0–7.0] for homozygotes of both risk alleles) [50]. In contrast to all these reports mainly relating to participants of European ancestry, a Japanese hospital-based case-control study found no interaction between pesticide exposure and *ABCB1* rs1045642 [68]. Reason for this inconsistency could be that, unlike previous cited studies, authors examined interactions for rs1045642 using a dominant genetic model or might be explained by ethnic differences.

5.2. Metabolism. Paraoxonases and cytochromes P450 constitute two major classes of xenobiotic-metabolizing enzymes involved in the detoxification of pesticide chemicals.

One study investigated a functional polymorphism of the Paraoxonase I (*PON1*) gene (c.260T>A, p.L55M) on 351 incident PD cases and 363 controls taking into account residential exposure to organophosphates (OP). This study found that carriers of the “slower” metabolizer genotype (AA), exposed to OP (diazinon, chlorpyrifos), exhibited a greater than 2-fold increase in PD risk compared with persons who had the wild-type or heterozygous genotype and no exposure [51]. More recently, the same group extended its previous finding showing that several *PON1* variants may act together to modify PD risk for ambient OP pesticide exposure. Carriers of both *PON1* p.L55M and *PON1* p.Q192R slow metabolizer variants were more susceptible to pesticide exposure (e.g., for chlorpyrifos-exposed carriers of the MM-QQ diplotypes, OR = 3.28, 95% CI [1.02–10.58]) compared to those unexposed with a LL-RR diplotype [69]. Recently, a population-based case-control study suggested that household pesticide use increases the odds of developing PD especially for products that contain OP. Furthermore, exposed participants' carriers of *PON1* p.Q192R QQ variant were at higher risk than noncarriers who were rarely exposed or unexposed (OR = 2.62, 95% CI [1.4–4.8]) [52]. Lack of interaction was also reported in studies of the early 2000s [70, 71].

CYP2D6 is one of the CYP superfamilies of enzymes, which metabolizes several xenobiotics in the liver, including OP pesticides, the herbicide atrazine, and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The activity of CYP2D6 is largely determined by genetic variability and common sequence variants exist in human populations that lead to

TABLE 1: Environmental genetic significant interactions in Parkinson's disease.

Exposure	Gene	Risk variant ^{&}	Design for interaction	PD	CT	Interaction (p)	Joint effect OR [95% CI] or (SE)	REF
Pesticides	<i>ABCB1</i>	rs1045642 C>T, p.Ile1145Ile	Case-only	415	—	—	4.74 [1.01–22.31]	[48]
Organochlorines	<i>ABCB1</i>	rs2032582 G>[A,T], p.Ser893Ala/Thr	Case-only	207	—	—	5.4 [1.1–27.5] [*]	[49]
Organophosphorus	<i>ABCB1</i>	rs1045642 C>T, p.Ile1145Ile rs2032582 G>[A,T], p.Ser893Ala/Thr	Case-control	350	724	NA	1 allele 2.1 [1.3–3.2] [*] Both alleles 3.7 [2.0–7.0] [*]	[50]
Diazinon	<i>PONI</i>	rs854560 T>A, p.Leu55Met (SM)	Case-control	351	363	NA	2.2 [1.1–4.5]	[51]
Chlorpyrifos	<i>PONI</i>	rs854560 T>A, p.Leu55Met (SM)	Case-control	357	807	NA	2.6 [1.3–5.4]	[52]
Organophosphates	<i>CYP2D6</i>	rs3892097 G>A, null allele (PM)	Case-control	190	419	0.02	4.74 [1.29–17.45]	[53]
Pesticides	<i>CYP2D6</i>	rs3892097 G>A, null allele (PM)	Case-control	393	389	0.05	8.41 [1.01–69.76]	[54]
Caffeine	<i>CYP1A2</i>	rs762551 C>A rs2470890 C>T, p.Asn516Asn	Case-control	925	1249	0.05 0.04	0.33 [0.16–0.68] [§] 0.43 [0.27–0.69] [§]	[55]
Paraquat	<i>GSTT1</i>	Null allele	Case-control	87	343	0.027	11.1 [3.0–44.6]	[56]
Solvents	<i>GSTM1</i>	Null allele	Case-only	959	—	—	2.34 [1.08–4.62]	[57]
Smoking	<i>GSTP1</i>	<i>GSTP1</i> * C haplotype	Case-only	400	—	—	2 [1.11–3.60]	[58]
Pesticides	<i>SLC6A3</i>	5' A clade and 3' VNTR 9-repeats	Case-control	178 men	239 men	0.02	5.66 [1.73–18.53] [*]	[59]
Paraquat, maneb	<i>SLC6A3</i>	5' A clade and 3' VNTR 9-repeats	Case-control	324	334	<0.001	4.53 [1.70–12.09]	[60]
Smoking	<i>MAO-B</i>	rs1799836 A>G	Case-control	82	118	NA	0.24 [0.10–0.55] [§]	[61]
Pesticides	<i>MfnSOD</i>	rs4880 T>C p.Val16Ala	Case-control	153	155	<0.001	2.49 [1.18–5.26]	[62]
	<i>NQO1</i>	rs1800566 C>T p.Prol53Ser	Case-control	156	174	0.034	2.42 [1.16–4.76]	[63]
	<i>NOS1</i>	rs12829185 T>C rs10774910 T>C rs2682826 A>G	Case-control	156	174	0.026 0.028	3.12 [1.71–5.71] [§] 4.15 [1.85–9.34] [§] 3.52 [1.78–6.95] [§]	[63]
Smoking	<i>NOS2A</i>	rs2314810 G>C rs2248814 A>G	Case-control	179	204	0.024 0.021	0.56 [0.34–0.92] [§] 0.23 [0.09–0.59] [§]	[63]
Caffeine	<i>GRIN2A</i>	rs1060826 T>C	GWAS + replications	2472	2848	0.013	0.17 [0.06–0.49] [§]	[64]
Caffeine	<i>GRIN2A</i>	rs4998386 C>T rs4998386 C>T	Case-control	193	377	3 × 10 ⁻⁵ <0.001	0.41 (0.05) 0.38 [0.20–0.70]	[65]

[&]http://www.ncbi.nlm.nih.gov/projects/SNP/; ^{*} environmental exposure stratum, and [§] risk allele stratum. PD, Parkinson's disease patients; CT, unaffected subjects; OR, odds ratio; CI, confidence interval; REF, reference article; NA, not available; SM, slow metabolizer; PM, poor metabolizer.

poor metabolizer (PM) phenotypes [72]. These variants have been extensively studied as genetic risk factors for PD with inconsistent results. Two independent studies regarded gene-environment interactions and suggested that CYP2D6 poor metabolizers (PM), who were exposed to pesticides, exhibited an increased risk for PD both compared with unexposed subjects and pesticide-exposed CYP2D6 extensive metabolizers (EMs) [53, 54]. More recently, another study confirmed these findings [73]. Negative results were also reported [55].

Caffeine that was proposed to be a protective factor for PD is primarily metabolized by cytochrome P450 1A2 (CYP1A2). A study, investigating three CYP1A2 polymorphisms, found that the coffee-PD association was the strongest among subjects homozygous for either variant allele c.-164A>C (p for interaction = 0.05) or c.1545T>C (p for interaction = 0.04) (i.e., slow metabolizers of caffeine) [56].

5.3. Excretion. The role of glutathione S-transferases M1 (GSTM1), T1 (GSTT1), and P1 (GSTP1), involved in the detoxification of many xenobiotics, was explored. A recent study found that paraquat exposure, a herbicide structurally similar to MPP+, had little association with PD in individuals carrying two active copies of the GSTT1 gene (OR = 1.5, 95% CI [0.6–3.6]), while markedly increasing PD risk in those with homozygous GSTT1 gene deletions (OR = 11.1, 95% CI [3.0–44.6]) [74]. Another study proposed that herbicide exposure may be an effect modifier of the relation between GSTP1 polymorphisms and age at onset in familial PD. Exposure to herbicides was classified as absent, residential, or occupational exposure. Seven SNPs in the GSTP1 gene were genotyped. The strongest result regarded the rs762803–rs1799811 haplotype that was associated with an approximately 8-year-earlier onset in the occupationally exposed group and a 2.8-year-later onset in the nonexposed group [57]. Another evidence regarded a case-control study of 959 prevalent cases of Parkinsonism (767 with PD) and 1,989 controls across five European centers, where the average annual intensity of exposure to solvents, pesticides, and metals was estimated. This study found possible interaction effects between GSTM1 null genotype and solvent exposure in PD patients only. GSTM1 null subjects heavily exposed to solvents appeared to be at increased risk of PD [55].

Cigarette smoking is thought to reduce risk of PD, and emerging evidence suggests that genetic factors may modulate smoking's effect. One study, with a case-only design in four hundred PD cases, assessed interactions between GST gene polymorphisms and smoking in relation to PD and found that GSTP1**C* haplotypes were overrepresented among PD cases who ever smoked (OR = 2.00, 95% CI [1.11–3.60]). Noteworthy, the statistical significance of the interaction between smoking and the GSTP1 p.A114V VV carrier status increased with increasing smoking dose ($p = 0.02$ for trend). These data suggest that one or more GSTP1 polymorphisms may interact with cigarette smoking to influence the risk for PD [58].

6. The Role of Genetic Variants in the Dynamics of Environmental Factors

The dopamine transporter gene (*SLC6A3*) is a candidate gene for PD on the basis of its critical role in dopaminergic neurotransmission. A couple of studies suggested that *SLC6A3* genetic variability and pesticide exposure interact to increase PD risk [59, 60]. The first study explored 5' A clade and 3' VNTR 9-repeat allele risk variants in the *SLC6A3* and occupational pesticide exposure. This study found that, among pesticide-exposed subjects, the odds ratio for having two or more risk alleles was 5.66 (95% CI: 1.73–18.53), while in nonexposed subjects it was 1.17 (0.62–2.23) [59]. The second study explored again the 5' and 3' regions of *SLC6A3* and determined residential exposure to agricultural maneb and paraquat applications. This study found that high exposure to paraquat and maneb in carriers of one susceptibility allele was associated with a 3-fold increased PD risk (OR = 2.99, 95% CI [0.88–10.2]), while it was associated with a 4-fold increased risk in carriers of two or more alleles (OR = 4.53, 95% CI [1.70–12.1]) [60]. In line with epidemiological findings, a molecular study reported that paraquat, when converted to the monovalent cation PQ(+) by either a reducing agent or NADPH oxidase on microglia, is transported by DAT and is accumulated in dopaminergic neurons, where it induces oxidative stress and cytotoxicity [75].

Another interesting target to study is monoamine oxidase B (MAO-B) since this enzyme breaks down dopamine. MAO-B inhibitors are used to treat the symptoms of PD since they prolong the action of dopamine in the brain. The A/G polymorphism in intron 13 of the MAO-B gene has been associated with variability of the MAO-B enzyme activity. In a population-based case-control study, a reversal of the association of cigarette smoking with PD in relation to this polymorphism was found. A reduced PD risk related to pack-years of smoking was detected for persons with the G allele, whereas an opposite effect was found among persons with the A allele [61]. Another study, on 186 incident idiopathic PD cases and 296 matched controls, confirmed this result only in men. Indeed, gender-specific interactions between smoking and genetic polymorphisms of MAO-B intron 13 A/G polymorphism were found to influence PD risk (OR = 0.27, 95% CI [0.13–0.58] for ever-smokers versus never-smokers in men (genotype G), and OR = 1.26, 95% CI [0.60–2.63] for men of genotype A (interaction $\chi^2 = 8.14$, $p = 0.004$)). No association was found for women [76].

Several case-control studies and genome-wide association studies have examined the relationships between single nucleotide polymorphisms (SNPs) in the SNCA gene and Parkinson's disease (PD) and have provided inconsistent results. Evidence for biological interactions between SNCA SNPs rs356219 and rs356220 and smoking that affect sporadic PD was presented [77].

ATP13A2 belongs to the P-type superfamily of ATPases that transport inorganic cations and other substrates across cell membranes. As already mentioned, mutations in the ATPase type 13A2 (*ATP13A2*) gene are cause of recessively inherited forms of atypical Parkinsonism. Recently, it has been proposed that *ATP13A2* variations may be a risk marker

for neurotoxic effects of manganese (Mn) in humans. Mn intoxication can lead to a disorder known as manganism characterized by severe neurological deficits that often resemble the involuntary extrapyramidal symptoms associated with Parkinson's disease and may evolve to more Parkinson-like syndrome [78]. A study, settled in Val Camonica (Italy), a geographic area with higher prevalence of individuals affected by Parkinsonism, probably related to increased exposure to Mn in the air, soil, and water, examined individual susceptibility for Mn neurotoxicity. It examined whether polymorphism in genes regulating Mn metabolism and toxicity could modify neurophysiological effects of Mn exposure. It found that *ATP13A2* polymorphisms rs4920608 and rs2871776 significantly modified the effects of Mn exposure on impaired motor coordination in the elderly (p for interaction = 0.029, $p = 0.041$, resp.) [79].

Oxidative and nitrosative stress plays an important role in the degeneration of dopaminergic neurons in PD. Key antioxidant enzymes such as NAD(P)H:quinone oxidoreductase (NQO1) and manganese superoxide dismutase (MnSOD) are polymorphic. Individual vulnerability to oxidative stress due to genotypic polymorphisms and exposure to environmental xenobiotics has been considered to promote the development of PD. In a study from southwestern region of Taiwan, it was investigated whether functional variants of *MnSOD* and *NQO1* genes interacted with occupational pesticide exposure to increase PD risk. A total of 153 patients with idiopathic PD and 155 healthy controls were genotyped for *MnSOD* (rs4880) and *NQO1* (rs1800566) genetic variants. This study found significant differences in frequencies of both genotypes of *MnSOD* and *NQO1* polymorphisms between PD patients and the control subjects only among subjects who had been exposed to pesticide (OR = 2.49, 95% CI [1.18–5.26] for *MnSOD* C allele; OR = 2.42, 95% CI [1.16–4.76] for *NQO1* T allele). Moreover, among those exposed to pesticide, the combined *MnSOD* and *NQO1* variant genotype was significantly associated with a 4.09-fold increased risk of PD (OR = 4.09, 95% CI [1.34–10.64]) [62].

Nitric oxide synthase (NOS) may create excess nitric oxide that contributes to neurodegeneration in PD. A study, examining gene-environment interactions involving both pesticides and protective factors (cigarette smoking, caffeine, and nonsteroidal anti-inflammatory drugs), found significant interactions between pesticides exposure and the *NOS1* SNPs rs12829185, rs1047735, and rs2682826 in determining the risk of PD (range of $p = 0.012$ – 0.034). Interactions between *NOS2A* SNPs rs231480, rs2248814, and rs1060826 and smoking were also found (range of $p = 0.013$ – 0.024) [63]. A recent study, in 357 incident PD cases and 495 population controls, investigated 8 *NOS* SNPs and interactions with both household and ambient agricultural OP pesticide exposures. The OR for frequent household OP use combined with the presence of *NOS1* rs2682826 C/T CT+TT genotype was 2.84 (95% CI [1.49, 5.40], interaction p value 0.04), while combined with *NOS1* rs3741480 T/C CT+CC genotype it was 1.90 (95% CI [1.06–3.41], interaction p value 0.02). Similar results were seen for ambient OP exposure (*NOS1* rs1047735 C/T OR = 5.42, 95% CI [2.54–11.52], interaction p value 0.04; *NOS1* rs816353 G/T OR = 4.24, 95% CI

[2.30–7.83], interaction p value 0.03; *NOS1* rs3741480 T/C OR = 3.78, 95% CI [2.04–6.99], interaction p value 0.01) [80].

Epidemiological, clinical, and animal studies provided a comprehensive picture of the anti-Parkinsonian potential of caffeine. A recent genome-wide association and interaction study (GWAIS) identified *GRIN2A*, which encodes an NMDA-glutamate-receptor subunit involved in brain's excitatory neurotransmission, as a PD genetic modifier in inverse association with caffeine intake ($p_{\text{interaction}} = 3 \times 10^{-5}$) [64]. This result was questioned by another group that performed a reanalysis of the same data by examining the association between coffee and rs4998386 separately in cases and controls. This group found a strong positive association in controls between rs4998386-T and heavy coffee drinking (OR = 1.48, 95% CI [1.23–1.78]). On the contrary, among PD cases, heavy coffee drinking tended to be less frequent in carriers of the rs4998386-T allele, but this association was not statistically significant (OR = 0.82, 95% CI [0.65–1.03]). Therefore, it appeared that the interaction between rs4998386 and coffee consumption was in part explained by a positive association between the rs4998386-T allele and coffee consumption among controls, but not among PD cases [81]. An independent study replicated the reported association of a single nucleotide polymorphism, *GRIN2A* rs4998386, and its interaction with caffeine intake with PD in patient-control study in an ethnically homogenous population in southeastern Sweden in 193 sporadic PD patients and 377 controls. There was also a strong significance in joint effects of gene and caffeine on PD risk (TC heavy caffeine versus CC light caffeine: OR = 0.38, 95% CI [0.20–0.70], $p = 0.002$) and gene-caffeine interaction (OR = 0.998, 95% CI [0.991–0.999], $p < 0.001$) [65].

7. Conclusion

The discovery of causative mutations for PD as well as their functional characterization in cellular and animal models has provided crucial insight into the pathogenesis of this disorder. Candidate gene association studies as well as genome-wide association studies (GWAS) have identified polymorphisms in a number of genes that significantly correlate with the development of PD. Some of these were consistently replicated while for others the true significance remains to be examined. Recent advances have revealed that certain interactions modify the risk of PD. However, few studies have examined gene-environment interactions, probably because of some limitations such as the need of large sample size and difficulties in estimating exposures, particularly for toxicants. In the future, it will be crucial to consider genetic and environmental exposure cooccurrence for PD prevention and personalized medicine to treat this disease.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Postural and Balance Disorders in Patients with Parkinson's Disease: A Prospective Open-Label Feasibility Study with Two Months of Action Observation Treatment

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Action observation treatment has been proposed as therapeutic option in rehabilitation of patients affected by Parkinson's disease (PD) to improve freezing of gait episodes. The purpose of this prospective open-label feasibility study was to evaluate the impact of 8-week action observation training (video-therapy) for the treatment of postural instability and balance impairment in PD patients. Fifteen PD patients aged under 80 years with scores of 1 to 3 on the Hoehn and Yahr staging and without evidence of freezing of gait were recruited. They underwent 24 sessions of video-therapy training based on carefully watching video clips on motor tasks linked to balance, subsequently performing the same observed movements. No statistically significant differences were observed in the identified outcome measures with the Berg Balance Scale and the Activities-Specific Balance Confidence Scale after two months of follow-up. In the present study, a short course of action observation treatment seems to be not effective in reducing balance impairments and postural instability in patients affected by mild to moderate PD. Further studies with larger samples, longer follow-up period, and standardized protocols of action observation treatment are needed to investigate the effects of this rehabilitation technique in the management of postural and balance disorders of PD patients.

1. Introduction

Postural instability is one of the cardinal manifestations of Parkinson's disease (PD) and becomes a clinical concern in the middle-later stages, usually occurring after the onset of other clinical features [1]. Patients with PD have decreased stability during both static and dynamic motor tasks and

the risk of falling represents a serious and disabling issue that affects daily life and personal autonomy and generally may not respond to dopaminergic treatment. Up to 40% of PD patients with postural instability have multiple falls that predispose to injury, including wrist and hip fractures and the need for medical care [2, 3]. In addition, social isolation occurs because of the fear of walking. The pathophysiology

for postural instability is still uncertain; however, factors such as the impairment or loss of postural reflexes, disturbance in central sensory processing, inflexibility of postural reflexes, postural deformities, interactions of akinesia, bradykinesia, rigidity, and freezing of gait can contribute to imbalance in PD [4, 5].

The current mainstay of managing postural instability remains conventional physiotherapy (stretching, aerobic training, relaxation and muscle activation, and treadmill walking), although new strategies have emerged and may be used in rehabilitative settings in conjunction with pharmacological treatment. Based on the evidence of the involvement of the mirror neuron system (MNS) in the process of motor learning, a role of action observation treatment (AOT) in the field of neurorehabilitation in PD patients has been assumed. Observation of action performed by others may activate in an observer the same neural network as when he/she actually performs the same action [6]. These observations suggest that there is a common thread between observation and execution of movement through internalization of temporal sequences by the observer and activation of the same cortical motor areas. This assumption represents the neurophysiological rationale for AOT in patients suffering from neurological diseases. AOT (via video) has also been successfully incorporated into clinical stroke rehabilitation programmes, significantly improving motor function, more than physical therapy alone [7, 8], as well as in postsurgical orthopedic patients [9]. The subsequent repetitive execution of the observed actions transmitted via video, generally concerning daily life movements, is the way in which the activation of MNS can be stimulated. Promising results obtained by recent studies showed the improvement of freezing of gait episodes and then quality of life in PD patients undergoing video-therapy sessions [10]. To date, to the best of our knowledge, no study has assessed the role of AOT in the treatment of postural instability. In particular, our attention has been given to the assessment of postural instability and balance disorders, as measured by functional scales, but excluding patients with freezing of gait, which apparently is the only variable that seems to have changed in previous studies. Therefore, the purpose of the present prospective open-label feasibility study was to evaluate the effectiveness of AOT in improving postural and balance disorders and secondly to assess whether AOT could have a positive impact on self-confidence in activities of daily life and risk of falls.

2. Methods

The present study is a prospective open-label feasibility study conducted according to the World Medical Association's 2008 Declaration of Helsinki and the guidelines for Good Clinical Practice. This study was approved by the Institutional Review Board of the University of Foggia, Foggia, Italy. Consecutive outpatients with a clinical diagnosis of idiopathic PD according to UK Brain Bank diagnostic criteria [11], attending the Department of Physical Medicine and Rehabilitation, University of Foggia, Italy, from January 2014 to March 2015, were invited to participate and were screened for study eligibility. The patients included in the present

study had the following: age of < 80 years, time from PD diagnosis of ≤ 10 years, diagnosis of idiopathic PD made by a senior neurologist, Hoehn & Yahr (H&Y) stage ≤ 3 [12], Functional Ambulation Category (FAC) ≥ 4 [13], stable medication regime for the month prior to and for 2 months of the study period, and any type of rehabilitation in three months prior to and during the study protocol. Exclusion criteria were as follows: vascular and iatrogenic parkinsonism; vestibular dysfunction, cardiovascular, and musculoskeletal problems that might affect balance; Pisa Syndrome; severe visual disturbance; cognitive impairment that could have limited the adherence to treatment, in particular patients with a Minimal State Examination (MMSE) score < 24 [14]; severe dyskinesias or "on-off" fluctuations; and therapies involving cueing strategies or other exercise activities. Subjects with freezing of gait, identified using Freezing of Gait Questionnaire (FOG-Q) item 3 [15], were also excluded from the study. Furthermore, they were asked to make rapid 360° narrow turns from standstill, on the spot and in both directions as a further test to objectively unmask freezing of gait [16]. A total of 15 participants (9 females, 6 males) fulfilling inclusion criteria were enrolled and, after a complete description of the protocol, provided informed written consent to participate in the study.

2.1. Procedures. Participants underwent an 8-week rehabilitation programme for 3 times a week, and the treatment was conducted under the supervision of an experienced physiotherapist. Each therapy session took place in a bright and not furnished room to avoid elements that could have an impact on the attention of the patients. The total number of training sessions per subject was 24. Patients were sitting in a comfortable chair and monitor screen (25 inches) was placed 100 cm distance in front of them. They were instructed to carefully watch the videos projected concerning motor tasks and motor sequences linked to balance. The movements were recorded from the front, side, and rear to ensure that patient understood the correct execution in the three dimensions. Two different series of four videos have been shown in the first month of treatment and in the last month. This choice was motivated by the need to both perform motor actions increasingly complex and obtain a greater adherence by the patients. The duration of each video was 1.50'; then, it was repeated two more times with the last one in slow motion (2'), so that the total duration of the action seen was 5 minutes. At the end of each video, patients were requested to perform the observed action for other 5 minutes, with the therapist that constantly encouraged them to perform to their full potential. Every session of AOT and individual rehabilitation lasted 40 minutes. Table 1 shows the contents of the videos shown for AOT. During the study, participants were instructed to take their Parkinson's disease medications regularly and were trained during the ON phase, within 2 hours of the last dose.

2.2. Primary Outcomes Measures. Patients were evaluated at baseline (t_0) and after the end of rehabilitative treatment protocol lasting 8 weeks (t_1) by the same investigator. A battery of clinical tests, including primary and secondary outcome

TABLE 1: Videos for Action observation treatment (AOT) shown to the Parkinson's disease patients in the present open-label feasibility prospective study.

First 4-week AOT program	Last 4-week AOT program
<i>Unsupported Sitting on The Table with Upper Limbs Abducted to 90°.</i> The abduction movement is performed slowly by the actor, remaining for a few seconds with the shoulders abducted to 45° and subsequently completing the articular excursion up to 90°. The position is held for 90 seconds	<i>Unsupported Standing with One Foot for at Least 5 Seconds and Then Reverse.</i> The actor shifts his weight first on one foot and then on the other. The foot is kept away from the floor variably from patient to patient, at least 5 seconds. Where necessary, he may lean on the wall with the contralateral hand
<i>Picking Something off the Floor.</i> In the first part of the video, the actor is standing as close as possible to the object; then, bending one knee on the floor surface, he picks it up. After collecting the first object, again from standing position, he flexes the contralateral knee to pick up the second object	<i>Walking Sideways.</i> The exercise is done without sliding foot or twisting body. The actor stands with feet close together. Then, stepping sideways, he moves one feet to the side first and brings the contralateral to join it
<i>Walking in a Straight Path with Upper Limbs Abducted at 90°.</i> Initially, the actor walks back and forth with arms at his sides. The following sequence requires shoulder abduction to 90° wherever possible. Additional external cues, such as marked path, were avoided	<i>Overcoming an Obstacle (Tightrope to 15 cm from the Floor).</i> The actor is standing next to a tightrope to 15 cm (at least) from the floor. Firstly, he lifts up one feet placing it over the rope; then, he brings the opposite feet to join it. Subsequently, twisting his body, he returns to start position
<i>Walking in a Not Straight Path with Upper Limbs Abducted at 90°.</i> The actor walks on a curved path, first with his arms at his sides and then with shoulders abducted up to maximum 90°. The patient is asked to walk so that he draws an imaginary "8" on the floor	<i>Getting Round Obstacles (Pins).</i> The pins are placed in series across the floor at distances of 40 cm. The actor walks through them trying to avoiding them. Arrived at the last one pin, he turns around to restart the exercise

measures, was used. The evaluation was performed at the same time in the morning, during ON condition (<2 hours after the intake of the dopaminergic medication). Among primary outcome measures, Berg Balance Scale (BBS) is a 14-item (0–4 points per task; high = best performance) validated scale that evaluates balance abilities during sitting, standing, and positional changes. Total scores are indicative of overall balance abilities, with a score of 0 to 20 indicating high fall risk; a score of 21 to 40 indicating medium fall risk; and a score of 41 to 56 indicating low fall risk [17]. A score of 43.5 or below suggests risk of falls [18]. The Activities-Specific Balance Confidence Scale (ABC-16) was administered to investigate the self-perceived level of balance confidence while performing 16 daily living activities rated 0 to 100 each. Patients with a score below 75.6 are at risk for falls [18].

2.3. Secondary Outcomes Measures. These outcome measures included Unified Parkinson's Disease Rating Scale, part III (UPDRS III) [19], 10-Meter Walk Test (10MWT) [20], and the Timed Up and Go Test (TUG) [21]. The Unified Parkinson's Disease Rating Scale (UPDRS) with four sections (I: Non-motor Experiences of Daily Living; II: Motor Experiences of Daily Living; III: Motor Examination; and IV: Motor Complications) is scored from 0 to 199 (199 represents the worst disability and 0 represents no disability). Part III has been used as secondary outcome (score ranges from 0 to 108). Items include rest tremor, action tremor, facial expressions, rigidity, bradykinesia, gait, and posture [19]. The 10MWT measures gait speed by the time required to walk 10 meters. The Timed Up and Go Test evaluates functional balance and basic mobility skills by measuring seconds when subject is asked to rise from sitting, walk 3 meters, return, and sit down [20]. Proposed cut-off score for prediction of falls in Pd is 11.5 seconds [21].

TABLE 2: Demographical and clinical characteristics of 15 patients with Parkinson's disease (PD) enrolled. Data are presented as mean \pm standard deviation (SD) or percentage.

Gender	
Female n (%)	9 (60)
Male n (%)	5 (40)
Age (years) mean \pm SD	68.9 \pm 4.7
Time from idiopathic PD diagnosis (years) mean \pm SD	3.5 \pm 1.9
H&Y score mean \pm SD	2.1 \pm 0.8
More affected body side (right/left)	10/5
FAC mean \pm SD	4.3 \pm 0.5
MMSE mean \pm SD	26.4 \pm 1.45

H&Y: Hoehn & Yahr stage; FAC: Functional Ambulation Category; and MMSE: Minimal State Examination.

2.4. Statistical Analysis. All variables and difference between baseline (t_0) and posttreatment outcome measure scores (t_1) were expressed as mean (95% confidence intervals (CIs)) and were compared using the Kruskal-Wallis test. The level of statistical significance was set as $p < 0.05$. Data analyses were performed using STATA MP 10.1.

3. Results

The PD patients aged between 60 and 77 years (mean = 68.9 \pm 4.7) had a mean disease duration of 3.5 \pm 1.9 months. The demographical and clinical characteristics of the 15 PD patients enrolled in the present study are shown in Table 2: 60% ($n = 9$) of the patients enrolled in the study were female. Table 3 showed primary (BBS and ABC-16) and secondary (UPDRS III, 10MWT, and TUG) outcome measure scores at baseline (t_0) and after 8 weeks of treatment (t_1), with score

TABLE 3: Functional findings of 15 patients with Parkinson's disease at baseline (t_0) and at the end of the 8-week program of action observation treatment (AOT) (t_1). Data are presented as mean \pm standard deviation (SD) and 95% confidence interval (95% CI).

Outcome measures	t_0	95% CI	t_1	95% CI	Score differences	p value
BBS	42.9 \pm 6.9	39.0–46.7	44.8 \pm 7.0	40.9–48.7	–1.93	0.3706
ABC-16	49.8 \pm 13.8	42.2–57.5	51.9 \pm 13.9	44.2–59.6	–2.09	0.5201
10MWT (s)	16.1 \pm 3.3	14.2–17.9	15.0 \pm 3.3	13.2–16.9	1.04	0.1645
TUGo (s)	15.3 \pm 4.2	12.9–17.6	14.1 \pm 4.1	11.8–16.3	1.21	0.3613
UPDRS III	23 \pm 13.1	15.7–30.2	22.1 \pm 13.0	14.8–29.2	0.93	0.8031

95% CI: 95% confidence interval; BBS: Berg Balance Scale; ABC-16: Activities-Specific Balance Confidence Scale; 10MWT: 10-Meter Walk Test; TUG: Timed Up and Go Test; UPDRS III: Unified Parkinson's Disease Rating Scale, part III.

differences along with 95% CIs. No statistically significant differences were observed in all primary and secondary outcome measures used in the present study.

4. Discussion

Imbalance and postural instability are among the most disabling issues of PD, still partly misunderstood. In the present prospective open-label feasibility study, we aimed to demonstrate the effect of AOT for postural instability and balance disorders in PD patients, as well as occurring of freezing of gait in these patients [10]. AOT is an innovative rehabilitative technique that has been successfully used especially for rehabilitation of stroke patients [7, 8]. Unfortunately, the present findings did not suggest an impact of this technique not effective in reducing balance impairments and postural instability in patients with mild to moderate PD.

Several studies and review articles focused on efficacy of AOT in PD patients [10, 22–25]. AOT combined with the repetition of the observed actions has a positive effect in terms of retention of information but only when observed movements are congruent with practiced movements. The observation of video just performed and the repetition of sequences of movements as occurred in AOT make it possible to stimulate the MNS involving basal ganglia. In fact, previous studies showed the detection of changes in local fields potentials (LFP) recorded from the subthalamic nucleus in PD patients during the observation of a movement performed by another person, whereas no LFP signals were detected during the observation of a static image. These changes were present in both “off” and “on” PD motor states and were similar to those observed during movement execution [26, 27]. These results can explain the effectiveness for the rehabilitation of bradykinesia or motor impairment in PD.

In particular, Pelosin and colleagues have shown that AOT has a positive additional effect on recovery of walking ability in PD patients with freezing of gait [10]. More specifically, the subjects enrolled in the study underwent a 60-minute physical therapy training for 3 sessions/week for 4 weeks. A group of PD patients watched 6 video clips showing strategies useful in circumventing freezing of gait episodes. During each training session, two video clips (with different sequences of actions) were presented twice. Another group of patients watched two video clips (presented twice) containing sequences of static pictures of mountains and seaside, countryside, and desert scenes without any living (human or animal) representations. Pelosin and colleagues

observed that subjects submitted to video with active movements improved for freezing of gait better than patients who watched “static” video [10], even if it is also as yet not clear whether it would be more effective for movement execution to be carried out simultaneously, or following AOT. A further meaningful result has been obtained for the reduction of bradykinesia after only one session of AOT in PD patients compared to subjects submitted to acoustic cue [28]. To the best of our knowledge, to date, no studies have investigated the role of AOT in reducing balance and postural disorders in PD patients.

The pathogenesis of PD-related balance disorders and postural instability is likely multifactorial: dystonia, rigidity, proprioceptive and sensorimotor disintegration, and peripheral degenerative processes have been proposed as causative factors. Therefore, it is possible that lesions in nondopaminergic systems can play a role in the pathophysiology of postural instability in PD [27]. Strategies exercises classically employed for improving balance include external forces against which to perform voluntary movement (and neuromuscular responses) as well as in response to an unexpected perturbation/stimulus in order to maintain the body's centre of mass within manageable limits of the base of support or in transit to a new base of support. Between several techniques of rehabilitation, global postural rehabilitation, functional static and dynamic standing balance training, computerized balance training using visual feedback, strengthening exercises, dance, yoga, vibration platform, Tai Chi, and sensorial cues can exert physiological effects at the cortical level, acting on intracortical inhibition or excitation in the areas controlling the flexor and extensor muscles [29]. A recent study showed that four-week indoor training and four-week outdoor rehabilitation are sufficient to improve balance and posture in PD patients [30]. The authors used postural reeducation, flexibility exercises, strength training with functional tasks, balance dance, modified Wing Chun (Chinese martial art), and Square Stepping Exercise with eight special patterns with progressive difficulty levels aiming at multidirectional balance and gait skills [30]. Another study showed that twelve weeks of rehabilitative training focused on progressive exercises targeting improvements in the function of the deeper trunk muscles were effective in improving clinical measures of balance in people with PD [31]. Moreover, similar exercises, when combined with aerobic exercises and stretching, were shown to significantly improve the strength and mobility of the trunk muscles in individuals with PD. The combination of postural rehabilitation

and Kinesio taping on trunk muscles, in a rehabilitative programme applied for four weeks, can be used for reducing axial postural disorders and risk of fall in PD [32].

The variability of the findings obtained in rehabilitative programmes and procedures confirms the absence of standard procedures to improve balance and posture in subjects affected by PD. In fact, the effect of several techniques is directed on impaired postural control systems, including flexibility and strength, anticipatory postural adjustment, postural responses sensory orientation, and stability in gait [33]. The purpose of the present study was to evaluate the effectiveness of AOT to reduce balance and postural disorders in PD patients. In the present study, the choice of the type of movements and therefore the content of the video to show were the result of numerous evaluations extrapolated from existing literature and also adapted to our population of PD patients. The motor sequences contained in the videos concerned the assumption of positions strictly linked to equilibrium when the PD patients are sitting, or when they are standing during ambulation. We focused on postural instability evaluated primarily with the BBS and treated with the AOT, a therapy that has been successfully integrated in numerous fields of neurorehabilitation. Hence, PD patients did not undergo traditional physical training programmes during the period of video-therapy training to avoid possible confounders examining possible effects of the AOT. To date, there is no evidence that AOT may be useful for reducing balance and postural disorders in PD patients. Our findings did not support the hypothesis to use this rehabilitative technique for this field. In fact, the analysis of outcome measures used to test patients at baseline and after two months of treatment showed only a slight improvement of clinical features of patients concerning balance and posture. The surprising effect of AOT in reducing freezing of gait episodes and bradykinesia [10, 28], as well as the recovery of the arm motricity in stroke survivors [7, 8], proved unsuccessful in reducing balance and postural disorders.

AOT is based on recruiting motor areas not only when actions are actually performed, but also when they are mentally rehearsed or simply observed. Mirror neurons are localized into premotor cortex and the adjacent area 44, the human homologue of area F5 [34, 35], first described in monkeys, so, they act on motor system improving upper or lower limb motricity. This could explain the reasons why our data did not significantly change after 8 weeks of AOT. Motor system is only partially involved in posture and balance control. It is a multifactorial process based on proprioceptive information (tactile, somatosensory, visual, and vestibular feedback) that by afferent pathways can modify efferent responses mediated by cerebellum and spinal cord on antigravitary muscles influencing muscle spindles, Golgi tendon organs, subcutaneous, somatosensory, and mechanoreceptors activity, and joints' position. All these components are involved to plan, organize, adjust, and execute postural and voluntary movements. Despite the possibility to increase the motor performances of PD patients submitted to our video for 8 weeks, our subjects did not report a statistically significant improvement of balance impairment and postural disorders measuring with primary and secondary outcome measures.

This result is, moreover, in accordance with the conclusion of a review article on the role of motor learning in PD [36]. Nieuwboer and colleagues argued that PD patients do seem to need more time to achieve learning, especially to achieve automatization, and, especially in the later stages of the disease, explicit learning methods, sensory information, and cues may be adopted to enhance learning [36]. However, even against the background of a neurodegenerative condition as PD affecting the basal ganglia, animal models of PD suggested that there is a dynamic interplay between degenerative and regenerative mechanisms of these structures, which are mediated by exercise and learning. Focused physical activity may tap into a variety of molecular repair mechanisms which not only appear to restore motor function but also promote neuroprotection at least in PD animal models [36].

5. Conclusion

Despite the growing evidence on the utilization of AOT in the field of neurorehabilitation, in the present study, no positive evidence was found in improving balance and posture related disorders in mild to moderate PD patients in 8-week training sessions. We must acknowledge some limitations of the present study. First of all, the small sample size and the possibility of including other forms of degenerative parkinsonism despite our accuracy could impact the obtained findings. Probably, more targeted and task-specific activities of the AOT programmes (i.e., daily actions divided into the component activities) would be required to achieve an effect on postural instability in PD patients. Furthermore, no long-term follow-up was considered. Again, no instrumental evaluation of balance skills, such as computerized static and dynamic posturography, was done and no cued training was applied to the participants. Finally, given the absence of a standardized protocol, about video and dynamic images for AOT, no firm conclusions concerning the efficacy of AOT in PD patients to reduce balance and postural impairment could be drawn. Although this was a feasibility study with a relatively low sample size, the outcomes and the data are still important to report and lend valuable information to the field. Future efforts will strive to refine processes and approaches, based on these results and experiences. Therefore, further studies with larger samples, longer follow-up period, and standardized protocols with AOT only or plus traditional physiotherapy are needed to investigate the effects of this rehabilitation technique to manage postural and balance disorders in PD patients.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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