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Parkinson's Disease Rehabilitation: Effectiveness Approaches and New Perspectives

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Abstract

Parkinson's disease has been considered one of the most important and common neurodegenerative diseases in the world. Its motor and nonmotor signs determine a huge functional loss, leading the individuals to lose their independence. Although the treatment requires a pharmacological approach, physical therapy has confirmed its importance in this process. Today, neurorehabilitation is indispensable to increase many of the cardinal signs of the disease. Using traditional or technological approaches, physical therapy has reached good results in improving motor and nonmotor functions, as well as the quality of life of Parkinsonians. However, it is important to develop and to fortify the physical therapy approach so that we can provide stronger evidence about our practice.

Keywords: Parkinson's disease, rehabilitation, physical therapy

1. Introduction

In this chapter, we will discuss some important topics about Parkinson's disease (PD), a progressive and neurodegenerative disease, that is characterized by many motor and nonmotor symptoms and with wide-reaching implications for patients and their families [1, 2]. It is neuropathologically characterized by nigrostriatal cell loss and the presence of intracellular α -synuclein-positive inclusions called Lewy bodies [3].

It is the most common movement disorder with approximately 1–2% of the population over 65 years of age suffering from PD. This percentage increases in people of 85 years of age and older, about 3–5% [3]. According to the World Health Organization, 6.1 million individuals have Parkinson's disease globally [4]. Some authors have shown that the burden of Parkinson's

disease has more than doubled over 26 years worldwide, from 2.5 million patients in 1990 to 6.1 million patients in 2016. So, we can expect that the trend will continue in the next 30 years having approximately more than 12 million individuals suffering from PD [5]. In 2016, there were 211,296 estimated deaths caused by Parkinson's disease [4].

PD is characterized mainly by four motor symptoms: resting tremor, bradykinesia, rigidity, and postural instability [1] with balance decrements and gait disruption [2]. It may present problems in performing personal activities of daily living, such as eating, drinking, cutting food, walking in the neighborhood, and writing [6].

The diagnosis of PD is based on medical history and a neurological examination since there are no blood tests, laboratory tests, or imaging examinations that have been proven to help in diagnosing PD [7], and its treatment is based on a pharmacological approach. The main 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 [8].

The traditional classification and disease progression of Parkinson's disease (PD) orient toward disease milestones that can be most obviously followed along motor domains. However, diverse nonmotor domains, quality of life, psychosocial burden, and stigma have been used as important domains for the course of PD and the outcome parameters of clinical trials [9].

At present, there is no cure for PD, but a variety of medications provide relief from the symptoms. Individuals who are affected usually are given levodopa combined with carbidopa. Levodopa helps in at least three-quarters of Parkinsonian cases; however, not all symptoms respond equally to the drug. Bradykinesia and rigidity respond best, while tremor may be only marginally reduced. Problems with balance and other symptoms may not be alleviated at all [7].

In this scenario, physiotherapy has a significant importance in a multidisciplinary team focused on the rehabilitation of individuals with PD, with the purpose of maximizing functional ability and minimizing secondary complications through movement rehabilitation within a context of education and to support the person as a whole [10].

The main focuses of physiotherapy for individuals with PD are transfers, posture, upper limb function, balance (and falls), gait, and physical capacity and activity. Physiotherapy also uses cueing strategies, cognitive movement strategies, and exercises to maintain or to increase independence, safety, and quality of life. The traditional and new strategies will be addressed in this chapter [10].

2. Pathophysiology of PD

Physiologically, the symptoms associated with Parkinson's disease are the result of the loss of a number of neurotransmitters, most notably dopamine. It is characterized neuropathologically by nigrostriatal cell loss and the presence of intracellular α -synuclein-positive inclusions called Lewy bodies [3, 11]. All these alterations change the function of the basal ganglia system, resulting in Parkinson's main movement disorders.

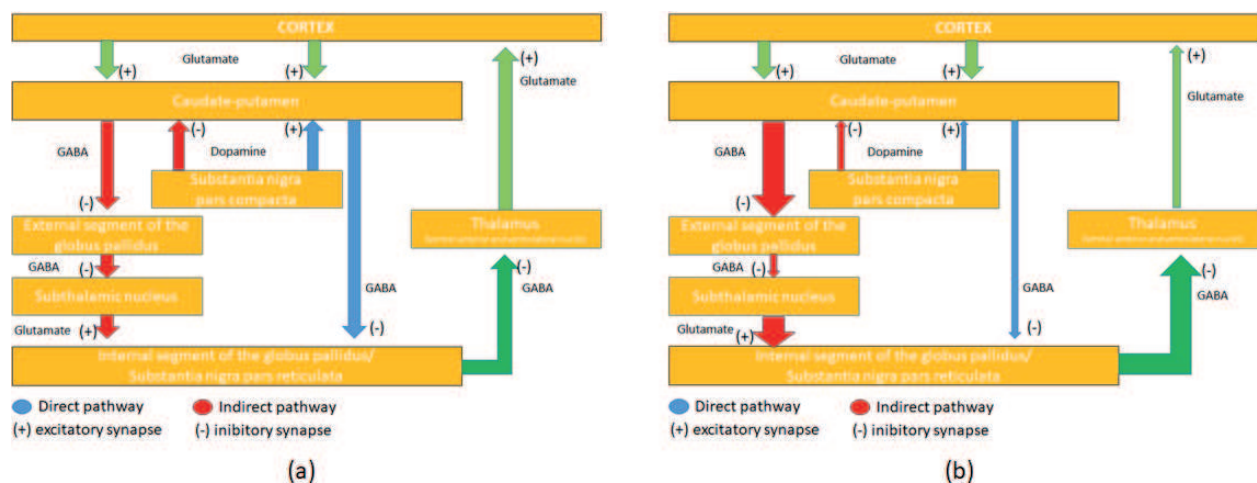


Figure 1. A schematic view of the functional anatomy of the basal ganglia. There are the normal direct and indirect pathways (panel a) and the alteration of direct and indirect pathways in Parkinson's disease (panel b). Modified from Magrinelli et al. [8] and Nitrini and Bacheschi [12].

Cell loss in the substantia nigra occurs in a region-specific manner, with the lateral ventral tier of the pars compacta being most affected. It is estimated that at least 50% of the nigral neurons must degenerate to produce symptoms, and, at autopsy, most cases show more than 80% reduction [8].

The basic basal ganglia circuitry and the balance between the direct and indirect striatal pathways provide a simple heuristic model for PD's main signs. According to this model, the pathophysiological hallmark of PD, hypokinetic signs are the prevalence of the indirect pathway over the direct one, consequently, resulting in increased neuronal firing activity in the output nuclei of the basal ganglia and leading to excessive inhibition of thalamocortical and brainstem motor systems, interfering with normal speed of onset movement and execution. On the other hand, overactivity in the direct pathway and imbalance with the indirect one may cause reduced inhibitory basal ganglia output and result in reduced basal ganglia filtering and parallel facilitation of multiple movement fragments. (See **Figure 1**) [8].

Another important region that has been linked to physiopathology of PD is the cerebellum. Its reciprocal connections with basal ganglia, especially with striatum and external segment of the globus pallidus, strengthens the hypothesis that it plays a role in the pathogenesis of some PD symptoms and signs [8].

Histopathology alterations can be described in this pathophysiological situation. There usually can be seen some histological characteristics not just in nerve tissue. The most important marker is called Lewy bodies. They are made of a protein called alpha-synuclein, which, in a healthy brain, plays a number of important roles in neurons, especially at synapses [13].

Lewy bodies can be found in many regions of the brain and some reports have suggested that the substantia nigra is not the first place where they form in Parkinson's disease [14].

Neither cell loss nor the formation of Lewy bodies is absolutely specific for PD, but both are required for a diagnosis of PD under current definitions. Additionally, it's necessary to consider that not all affected neurons in PD are dopaminergic. An example to be cited is the cholinergic neurons from the dorsal vagal nucleus. This variety of regions has been suggested to be responsible for the complex clinical picture in PD [13].

This pathophysiological situation seems to be multifactorial. It can be considered by genetic factors, inflammation, immune response, and environmental elements [14].

While having a family member with PD may increase a person's risk, PD is not normally considered a genetic disease. Variants in three genes (SNCA, UCHL 1, and LRRK 2) have been reported in familial PD. Mutations in three other genes (PARK 2, PARK 7, and PINK 1) have been found in sporadic PD [14, 15].

On the other hand, large population studies have suggested that individuals taking nonsteroidal anti-inflammatory drugs (NSAIDs) have less risk of developing idiopathic PD, which suggests that anti-inflammatory drugs may be a promising disease-modifying treatment for Parkinsonian patients [16].

Some reports have provided direct evidence of interactions between α -synuclein and environmental agents. Some options described in the literature are heavy metals (iron, copper, manganese, lead, and mercury), pesticides (including insecticides and herbicides), and illicit substances (amphetamine, methamphetamine, and cocaine) [17].

In a review, Di Monti et al. [18] describe some possibilities of multiple events and interactive mechanisms possibly responsible for alpha-synuclein alterations. These may include (i) the synergistic action of endogenous and exogenous toxins, (ii) the interactions of toxic agents with endogenous elements (e.g., the protein α -synuclein), (iii) the tissue response to an initial toxic insult, and (iv) the effects of environmental factors on the background of genetic predisposition and aging.

It's important to explain that the symptoms of Parkinson's disease sometimes can be seen outside the disease itself. In these cases, we call this clinical condition of parkinsonism, also known as "atypical Parkinson's," "secondary Parkinson's," or "Parkinson's syndrome." Parkinsonism often has an identifiable cause, such as exposure to toxins, methamphetamine, trauma, multiple strokes, other nervous system disorders, or illness. Generally, Lewy bodies are not seen in parkinsonism [14].

3. Parkinson's clinical signs, diagnosis, and rating scales

The three clinical motor cardinal signs of PD, a-/hypo-/bradykinesia, rest tremor, and rigidity, are directly related to the degeneration of dopaminergic neurons. However, other motor symptoms and signs, secondary to degeneration of nondopaminergic pathways, can be described such as loss of postural control, postural stability/balance, and gait disturbance. In addition, the most well-known nonmotor characteristic motor symptoms have also been described. There can be additional psychiatric and autonomic features found, as well as cognitive impairment, sleep disorders, olfactory dysfunction, and pain.

3.1. Clinical motor cardinal signs

1. A-/hypo-/bradykinesia: These terms are defined, collectively, as slowed voluntary movement. Separately, akinesia indicates the absence of voluntary movement, while hypokinesia

means smaller movements, and bradykinesia refers to slowness of movement. They usually determine any impairment in fine motor movements, facial expression (hypomimia), monotonic and hypophonic speech with a reduction of speed, and general motion amplitude. This can have an important impact in functional skills like arm swinging when walking, raising from a chair, handwriting, and general gesturing [14, 19].

This cardinal sign is one of the best that emerges from its origin of dysfunction, which is cited in this chapter (see **Figure 1**). It has been determined especially by a characteristic involving the movement programming of the cerebral cortex, in particular the supplementary motor area [8, 19].

It is possible to find two modulations of this cardinal sign of Parkinson's disease: freezing phenomenon and kinesia paradoxa. In the first one, the individual presents a sudden and transient motor block, mainly in the lower limbs during walking. This may include start hesitation, hesitation, or inability to move through the presence of contradictory visual cues (floors with different colors and small steps), when there is a need to change direction of gait or be still in open spaces. The second one, kinesia paradoxa, occurs under certain emotional circumstances where the patient is able to exhibit a sudden brief period of mobility (walking or even running and catching a ball). This phenomenon shows that, even though individuals with Parkinson's disease have their motor programs intact, the disease prevents them from accessing them in the correct way, requiring external stimuli for this to happen even if done poorly [19, 20].

2. *Rest tremor*: this sign is usually asymmetric, consisting of alternate contractions of agonist and antagonist muscles, including flexors, extensors, pronators, and supinators of the wrists and arms, resulting in the "pill rolling" movement of the hand. It has a medium frequency (3 to 6 Hz) and tends to disappear with action. The legs, lower jaw, or head may also be involved, resulting in an adduction-abduction movement of the lower limbs and yes-yes or no-no motion in the head [8, 21].

The pathophysiology of rest tremor is largely unknown. Clinical-pathological studies have demonstrated that patients with PD and prominent tremor have dysfunction of a subgroup of midbrain (A8) neurons and its magnitude seems to not be related to dopamine deficiency [8, 19].

3. *Rigidity*: it is a type of increase in muscle tone (also called plastic hypertonia), generally defined as an increased resistance to passive movement of a joint. Rigidity is more evident in the flexor muscles of the trunk and limbs and may be enhanced by voluntary movement. However, its presence usually determines a characteristic of stooped posture. Two types of rigidity can be described: cogwheel rigidity refers to resistance that stops and starts at the limb, the limb is moved through its range of motion, and it is the result of coexisting rigidity and tremor; lead-pipe rigidity is defined as a constant resistance to motion throughout the entire range of movement [8, 14].

It is unclear how rigidity is associated with dopamine deficiency and basal ganglia dysfunction. Nevertheless, evidence suggests that this cardinal sign has its pathogenesis in the passive mechanical properties of joints, tendons, and muscles, and spinal and supraspinal reflexes, which together determine an increased response to peripheral stimulation and an increased muscle elongation response [8].

3.2. Additional motor signs

1. *Posture disturbances*: individuals with Parkinson's disease usually develop abnormal axial postures as a result of bradykinesia, rigidity, and resting tremor. This abnormality leads to a flexed general posture, with hip and knee flexion, accompanied by shoulder and even elbow flexion. In the long term, this posture disturbance can determine severe postural deformities such as antecollis, scoliosis, camptocormia, and Pisa syndrome. Little is known about the cause of these deformities, which makes it unresponsive to most treatments [8, 19].
2. *Postural instability balance and gait disturbances*: postural instability and gait disturbances usually occur during the course of PD, generally being manifestations of the late stages of the disease. They represent a therapeutic challenge, since they show little change through traditional pharmacological treatment using dopaminergic drugs. These two impairments, especially if associated with the freezing phenomenon, are the most common cause of falls and fractures in Parkinsonians [19, 22].

One of the most important causes for these signs is the poor ability to integrate visual, vestibular, and proprioceptive inputs associated with a failure to activate central motor programs and their interaction with the mechanisms of sensitive feedback. Postural instability and gait disturbances have been associated with an akinetic-rigid syndrome, as well as an increased incidence of nonmotor features [8, 22].

3. *Other signs and symptoms*: in addition to the most important signs of Parkinson's disease, some other motor signs can be found, such as dysarthria, hypophonia, dysphagia, and sialorrhea. These signs occur as a result of bulbar dysfunction and as a result of orofacial-laryngeal bradykinesia and rigidity. We can still find some neuro-ophthalmological signs such as a decreased blink rate and blepharospasm, among others. Other important disturbances are linked with the respiratory system and usually contribute strongly to morbidity and mortality in PD. The obstructive or restrictive respiratory complications are probably due to the presence of the rigidity present in the trunk area [19].

3.3. Nonmotor signs and symptoms

The current literature suggests there is a prodromal or premotor stage of Parkinson's disease before the onset of motor symptoms. Nonmotor signs and symptoms of Parkinson's disease include cognitive, neuropsychiatric, sleep, autonomic, and sensory dysfunctions, which are typically not treated by the dopaminergic therapy. Patients who go on to develop Parkinson's disease commonly have experienced depression, constipation, anosmia, and rapid eye movement sleep behavior disorder in the years preceding their diagnosis. So, the presence of nonmotor features has contributed during the diagnosis process of Parkinson's disease. However, if these nonmotor signs were not evaluated well enough during the diagnostic process, they may delay the diagnosis [23, 24].

More specifically, there can be subtle cognitive deficits found affecting attentional, executive, visuospatial, and memory functions. Neuropsychiatric symptoms are also common and include

depression, anxiety, apathy, and psychosis. Autonomic dysfunction can manifest as urinary frequency or urgency, constipation, orthostatic hypotension, drooling, erectile dysfunction, or

Neuropsychiatric symptoms	Depression
	Dementia
	Anxiety
	Anhedonia
	Apathy
	Psychosis (hallucination and delusion)
	Cognitive dysfunction
	Attention deficit
	Off-period-related panic attacks
	Confusion
Sleep disorders	Insomnia
	Excessive daytime sleepiness
	Nonrapid eye movement sleep-related movement disorders
	Sleep-disordered breathing
	Periodic limb movement disorder
	Rapid eye movement sleep behavior disorder
	Vivid dreaming
	Restless legs syndrome
Autonomic symptoms	Urgency
	Frequency
	Orthostatic hypotension
	Nocturia
	Erectile dysfunction
Gastrointestinal symptoms	Sweating
	Dribbling of saliva
	Ageusia
	Nausea
	Dysphagia
	Reflux and vomiting
	Constipation
	Diarrhea
	Fecal incontinence
	Unsatisfactory voiding of bowel

Sensory symptoms	Primary pain
	Secondary pain
	Fluctuation-related pain
	Paresthesia
	Olfactory disturbance
Other symptoms	Visual dysfunction
	Fatigue
	Ankle swelling
	Nonmotor fluctuations
	Blurred vision

Table 1. Nonmotor signs and symptoms of Parkinson’s disease [23–25].

abnormal sweating. These clinical manifestations can have a substantial impact on the patient’s quality of life [25]. We can see a long list of nonmotor signs and symptoms in **Table 1**.

Some of the most important nonmotor signs and symptoms for physiotherapists, which require special attention, are fatigue, pain, urinary bladder control, and anal sphincter control. We will discuss how physical therapy functions with these aspects of the disease later in this chapter.

3.4. Diagnosis of Parkinson’s disease

During the diagnostic process of Parkinson’s disease, one of the first components to be established is the presence of “parkinsonism.” This clinical condition is established by the presence of the cardinal signs of the disease, of which bradykinesia is an indispensable criterion jointly with one of the other two signs [25], associated and exclusionary symptoms, atypical features in the history and on examination, and response to levodopa.

The presence of nonmotor features is important, as these may be prominent even early in the disease’s course. Some diagnostic criteria have been developed by some organizations like the UK Parkinson’s Disease Society Brain Bank, the National Institute of Neurological Disorders and the Stroke (NINDS), and Movement Disorder Society. All of them ask for the presence of the cardinal signs, the application of exclusion criteria and some supportive criteria [25, 26]. They can be consulted in **Table 2**.

However, the reliability and validity of them have not been clearly established. In this way, it is common to have a misdiagnosis of Parkinson’s disease. The most common causes of misdiagnosis that are described in literature are Alzheimer’s disease, essential tremor, and vascular parkinsonism. It should be remembered that rigidity, bradykinesia, and gait disturbance can be found during normal aging period or can be determined by other medical conditions of aging [25, 27, 28].

United Kingdom Parkinson's Disease Society Brain Bank's	National Institute of Neurological Disorders and Stroke (NINDS)	Movement Disorder Society
Step 1	Group A features (characteristic of Parkinson's disease)	1. Diagnosis of parkinsonism
Bradykinesia	Resting tremor	a. Bradykinesia, plus one of
At least one of the following criteria:	Rigidity	b. Tremor
Rigidity	Asymmetric onset	c. Rigidity
4-6 Hz rest tremor	Group B features (suggestive of alternative diagnoses)	2. Exclusion criteria
Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction	Features unusual early in the clinical course	d. Cerebellar abnormalities
Step 2	Prominent postural instability in the first 3 years after symptom onset	e. Supranuclear gaze palsy
Exclude other causes of parkinsonism	Freezing phenomenon in the first 3 years	f. Diagnosis of behavioral variant of frontotemporal dementia or primary progressive aphasia within 5 years of disease onset
Step 3	Hallucinations unrelated to medications in the first 3 years	g. Parkinsonian features restricted to the lower limbs for more than 3 years
At least one of the following supportive (prospective) criteria:	Dementia preceding motor symptoms or in the first year	h. Treatment with a dopamine receptor blocker or dopamine-depleting agent consistent with drug-induced parkinsonism
Unilateral onset	Supranuclear gaze palsy (other than restriction of upward gaze) or slowing of vertical saccades	i. Absence of a response to high-dose levodopa despite at least moderate disease severity
Rest tremor	Severe, symptomatic dysautonomia unrelated to medications	j. Cortical sensory loss, clear limb ideomotor apraxia, or progressive aphasia
Progressive disorder	Documentation of condition known to produce parkinsonism and plausibly connected to the patient's symptoms (such as suitably located focal brain lesions or neuroleptic use within the past 6 months)	k. Normal function imaging of the dopaminergic system ("DAT scan")
Persistent asymmetry primarily affecting side of onset	Criteria for definite Parkinson's disease	1. Diagnosis of alternative condition causing parkinsonism that could be causing the symptoms
Excellent response (70-100%) to levodopa	All criteria for probable Parkinson's are met and	3. Supportive criteria

(Continued)

United Kingdom Parkinson's Disease Society Brain Bank's	National Institute of Neurological Disorders and Stroke (NINDS)	Movement Disorder Society
Severe levodopa-induced chorea (dyskinesia)	Histopathological confirmation of the diagnosis is obtained at autopsy	m. Clear beneficial response to dopaminergic therapy
Levodopa response for 5 years or more	Criteria for probable PD	n. Presence of levodopa-induced dyskinesia
Clinical course of 10 years or more	At least three of the four features in group A are present and	o. Rest tremor of a limb
	None of the features in group B is present (note: symptom duration ≥ 3 years is necessary to meet this requirement) and	p. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy (although the latter is rarely done in current practice)
	Substantial and sustained response to levodopa or a dopamine agonist has been documented	4. Red flags
	Criteria for possible Parkinson's disease	q. Rapid progression of gait impairment leading to wheelchair use within 5 years
	At least two of the four features in group A are present; at least one of these is tremor or bradykinesia and	r. Absence of progression of motor symptoms over 5 years, unless related to treatment
	Either none of the features in group B is present or symptoms have been present ≤ 3 years and none of the features in group B is present and	s. Early bulbar dysfunction
	Either substantial and sustained response to levodopa or a dopamine agonist has been documented or the patient has not had an adequate trial of levodopa or a dopamine agonist	t. Inspiratory respiratory dysfunction
		u. Severe autonomic failure within the first 5 years of disease
		v. Recurrent falls because of impaired balance within 3 years of onset
		w. Disproportionate anterocollis or contractures within 10 years of disease onset
		x. Absence of any of the common nonmotor features despite 5 years of disease
		y. Unexplained pyramidal signs
		z. Bilateral symmetrical parkinsonism
		For the diagnosis of clinically established Parkinson's disease

United Kingdom Parkinson's Disease Society Brain Bank's	National Institute of Neurological Disorders and Stroke (NINDS)	Movement Disorder Society
		27. Parkinsonism
		28. Absence of exclusion criteria
		29. At least 2 supportive criteria
		For the diagnosis of clinically probable Parkinson's disease
		30. Parkinsonism
		31. Absence of exclusion criteria
		32. Balanced numbers of supportive criteria and red flags

Table 2. Options of diagnostic criteria for Parkinson's disease.

3.5. Rating scales for Parkinson's disease

A rating scale is a means of providing information on a particular feature by assigning a value to it. Parkinson's rating scales are a means of assessing the symptoms of the condition. They provide information on the course of the condition and/or assess quality of life. They may also help to evaluate treatment and management strategies, which can be useful to researchers, medical doctors, physiotherapists, and other healthcare professionals, as well as to people with Parkinson's and their caregivers [29].

In Parkinson's disease, there are a number of rating scales used. Often, more than one scale is used to give a broader picture of symptoms. The most important and used rating scale for this disease is the Unified Parkinson's Disease Rating Scale (UPDRS). The scale has three sections that evaluate key areas of disability, together with a fourth section that evaluates any complications of treatment, as shown below:

Part 1: Nonmotor experiences of daily living

Part 2: Motor experiences of daily living

Part 3: Motor examination

Part 4: Motor complications

The UPDRS features sections that require independent completion by people affected by Parkinson's and their caregivers, and sections to be completed by the clinician. The UPDRS is often used with two other Parkinson's rating scales: The Hoehn and Yahr, and the Schwab and England Activities of Daily Living (ADL) scales [20, 30].

In **Table 3**, there is a list of rating scales available and recommended by the European Parkinson's Disease Association and by the International Parkinson and Movement Disorder Society [29, 30].

MDS-owned rating scales	The European Parkinson’s Disease Association (EPDA)
Global assessment scale for Wilson’s disease	Unified Parkinson's disease rating scale (UPDRS)
Global dystonia scale	Hoehn and Yahr scale
MDS-unified Parkinson’s disease rating scale (MDS-UPDRS)	Schwab and England activities of daily living (ADL) scale
Modified bradykinesia rating scale	PDQ-39
Nonmotor symptoms scale (NMSS)	PD NMS questionnaire
Nonmotor symptoms questionnaire (NMSQ)	NMS survey
PKAN disease rating scale (PKAN-DRS)	Parkinson’s disease composite scale
Quality of life essential tremor questionnaire	King’s PD pain scale
Rating scale for psychogenic movement disorders	Parkinson's disease sleep scale-PDSS-2
Rush dyskinesia rating scale	Lindop Parkinson's assessment scale
Rush video-based tic rating scale	Short-form 36 (SF-36)
UFMG Sydenham's Chorea Rating Scale (USCRS)	Sickness impact profile (SIP)
Unified dyskinesia rating scale (UDysRS)	Mini-mental state examination (MMSE)
Unified dystonia rating scale (UDRS)	Montreal cognitive assessment scale (MoCa)
Unified multiple system atrophy rating scale (UMSARS)	Caregiver strain index (CSI)

Note: Based on the European Parkinson’s Disease Association [29] and International Parkinson and Movement Disorder Society [30] websites.

Table 3. Recommended rating scales for Parkinson’s disease.

It is important to note that many of these scales and questionnaires are owned and licensed by some organization. Hence, it is necessary to require a rating scales permission request form before working with them.

In a nonclinical way, Braak and coworkers [31] proposed staging procedures of the pathology of Parkinson’s disease, based on central nervous system involvement. Their proposal has six stages:

Stage 1: Premotor period in which typical pathological changes, Lewy neurites, and Lewy bodies spread from the olfactory bulb and vagus nerve to lower brainstem regions (medulla oblongata and pontine tegmentum).

Stage 2: Additional lesions in the raphe nuclei and gigantocellular reticular nucleus of the medulla oblongata, locus coeruleus in the pontine tegmentum.

Stage 3: The symptomatic period when pathological changes involve the midbrain including substantia nigra pars compacta, basal nuclei of Meynert. Structures affected in stages 1 and 2 develop more Lewy bodies.

Stage 4: Severe dopaminergic cell destruction in the pars compacta with additional mesocortex and allocortex involvement, especially seen in amygdala and subnuclei of the thalamus.

Stage 5: There are initial changes in neocortex (cortical lobes). Cellular death can be seen in the substantia nigra, the dorsal motor nucleus of the vagus nerve, the gigantocellular reticular nucleus, and the locus coeruleus.

Stage 6: Neocortex entirely affected (motor and sensory areas).

This kind of rate is totally based on histological development of the disease. It is important to remember that, historically, the definitive diagnosis of Parkinson's disease is closed in a postmortem autopsy [32].

4. Parkinson's disease treatment

Drug treatment: traditionally, the drugs that have shown good effects on the motor signs and symptoms of Parkinson's disease are the dopaminergic drugs.

Among them, the most used in clinical practice is levodopa or levodopa plus dopa-decarboxylase inhibitors (DDC-I), designed to replace the dopamine in the depleted striatum, undoubtedly, the most efficient medication for Parkinson's disease [33]. They improve motor functions in a cyclic way during the day period. When they reduce the motor impairment, the period is called "on time." When the motor signs and symptoms start to return, the period is called "off time" or "wearing-off period." However, during the "wearing-off period," symptoms may not be related only to movement. It is also usual for patients to report increased anxiety, fatigue, mood changes, difficulty thinking, restlessness, and sweating [29].

Initially, levodopa offers a stable alleviation of PD symptoms so it is usual for it to be offered in low doses, being well-tolerated by patients. This period of treatment is called the "honeymoon." However, as the disease becomes more advanced, the effect of the drug usually wears off quickly, and an increased frequency of dosing is often required. This marks the end of the "honeymoon" period. After some years (4–6 years), patients begin to experience, most strikingly, its intense side effects [33, 34].

These long-term complications included many kinds of motor fluctuations. In addition to the on-off phenomenon, already described above, the patients may also experience delay on, when medication takes a longer period to take its effect; freezing phenomenon, which was already discussed during the motor signs presentation; and dyskinesia, which is determined by the presence of hyperkinetic involuntary movements, including twitches, jerking, twisting, or simple restlessness but no tremor, occurring when the drug is at its peak dose, during the wearing-off period or even during off-periods of the medication [29, 34]. Several new formulations of levodopa have been developed to provide a more stable levodopa plasma concentration, reducing some of the side effects, including dyskinesia. Among them, as aforementioned is a levodopa/carbidopa combination [33].

Other drugs on treatment of motor signs are dopaminergic agonists, amantadine, dopamine receptor agonists, catechol-O-methyltransferase (COMT), and monoaminoxidase (MAO) inhibitors. Recently, new pharmacological treatment has been studied such as the use of cannabis (to reduce mainly the three cardinal signs) and the angiotensin IV ligand-based compound, which influences motor and nonmotor signs (memory) [33].

Since Parkinson’s disease is not considered a pure movement disorder anymore, the treatment of nonmotor signs and symptoms is justified. However, the treatment of nonmotor symptoms is still an unsatisfactory field for patients and their families [35]. A cholinesterase inhibitor has been used for dementia treatment, while noradrenergic medications (like tricyclic antidepressants) have shown some effect in depression and serotonergic agonists (like clozapine) in psychosis. Amantadine is used with some success in the management of levodopa-induced dyskinesia. For autonomic dysfunction, there are many options such as mineralocorticoid, fludrocortisone and adrenergic agents, the noradrenaline precursor for orthostatic hypotension, antimuscarinics for urinary urgency or incontinence, and prokinetic drugs to treat constipation [35].

Surgical treatment: lesioning procedures, such as pallidotomy and thalamotomy, were used to reduce the motor signs and symptoms of Parkinson’s disease. For a period, these procedures were abandoned because of good results with pharmacological treatment using dopaminergic drugs. However, nowadays, the surgical procedures are reviving as a result of the complications of pharmacological therapies.

The technological advances in the area of medicine have led to the development of a new kind and nonablative surgical procedure: deep brain stimulation (DBS). It involves sending electrical impulses to certain parts of the brain by a neurostimulator device that is a brain implant known as a ‘brain pacemaker.’ The general procedure of this surgery is an intracranial electrode precisely implanted in the target area (see **Table 4**), followed by implantation of lead extension wires that connect the intracranial leads to a power-generating and programming source and, then finally, the implantation of an internal pulse generator (**Figure 2**). The main target areas can be seen in **Table 4** such as the signs/symptoms that are most prominently modulated by DBS [36, 38]. When PD symptoms are very severe and medications cannot moderate them, surgery and deep brain stimulation can be considered as the final options of treatment.

Subthalamic nucleus	Disabling motor symptoms Dyskinesia Motor fluctuations
Globus pallidus internus	Improvement of motor symptoms in general
Ventral intermediate thalamic nucleus	Tremor
Pedunculopontine nucleus	Gait instability Gait freezing phenomenon

Note: Based on Dallapiazza et al [36].

Table 4. Main target areas for deep brain stimulation (DBS) in Parkinson’s disease.

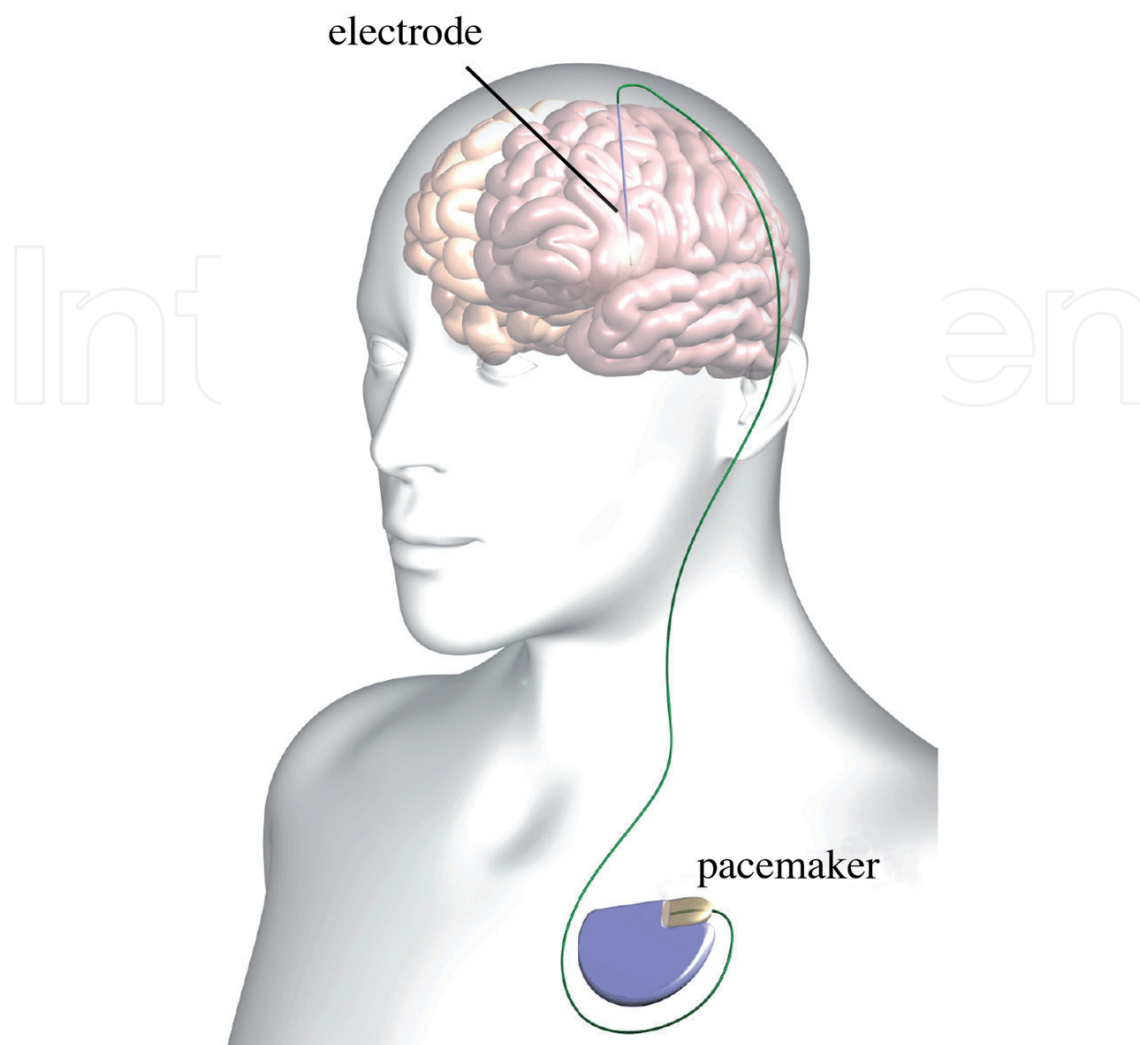


Figure 2. Typical deep brain stimulation setup. The electrode is placed in the brain and connected to a brain pacemaker permanently placed under the skin of the chest. Source: Shamir et al. [37] the use, distribution or reproduction in other forums is permitted.

Other treatments: other alternatives to Parkinson's disease management include a group of therapies other than a pharmacological approach. There is a vast variety of techniques available for this purpose, such as tai chi, yoga, massage, acupuncture, dance, traditional herbs, and molecular targeted therapies, among others.

Physical therapy shows a number of different strategies that has been frequently used in rehabilitation of Parkinson's disease patients, having the most important goal to enhance the quality of life of these individuals.

4.1. Physical therapy in Parkinson's disease treatment

Physiotherapists are members within a multiprofessional team, which has the purpose of maximizing functions and abilities and minimizing secondary complications of several diseases. They use movement rehabilitation within a context of education and support for the person

as a whole. In patients with Parkinson's disease, physical therapy focuses on many functions such as transfer, posture, balance improvement and fall prevention, gait, upper limb functions, and physical capacity (including cardiorespiratory capacity) essential to carry out activities of daily life. All of these goals, worked together with cueing strategies, cognitive movement and exercises, increased independence, and safety, as a consequence, improve quality of life [10].

Some evidence presented in the literature supported that therapeutic exercises applied in individuals with Parkinson's disease were effective in improving both the motor and nonmotor impairments [39, 40]. This improvement may be linked to a number of plasticity-related physiological events including synaptogenesis, angiogenesis, and neurogenesis. This process can be mediated by use-dependent expression of endogenous neurotrophic factors. In an unedited systematic review and meta-analysis, Hirsch and his coworkers show aggregated evidence that physical exercise training increases brain-derived neurotrophic factor (BDNF) blood levels in individuals with Parkinson's disease. This BDNF increase results in concomitant reduction in motor signs and symptoms, measured by UPDRS, confirming possible effects on dopaminergic pathways [41].

Together with neuroplasticity, there is some evidence pointing to the participation of motor modules (coordinated patterns of muscle activity that combine to produce functional motor behaviors) like a physiological theory for good results of physical therapy in Parkinson's disease. For this purpose, it is proposed to consider five neuromechanical principles: motor abundance, which means that for any given task, many equivalent motor solutions are possible; motor structure, which means that motor modules reflect biomechanical task relevance; motor variability, which means that variations on motor modules are higher as much as the motor output is lower; individuality, which means that different motor repertory must be considered among different individuals; and multifunctionality, which means that muscle activity can generate a large number of different actions. It is important to emphasize that in Parkinson's disease the basal ganglia dysfunction supposedly leads to inappropriate selection of motor modules [8].

It is still important to remember that motor rehabilitation is a motor relearning practice and training where it is essential to reacquire motor skills. Although individuals with Parkinson's disease show preserved motor learning abilities, the basal ganglia dysfunction may impair the consolidation of them. Therefore, the basic rules of neural plasticity practice must be used to be successful in the rehabilitation process. It includes intensity, repetition, specificity, difficulty, and complexity of practice [8, 42].

Several rehabilitative approaches have been proposed in Parkinson's disease.

4.1.1. Resistance training and muscle strength

In the last two decades, exercise, such as resistance training, has shown to be beneficial for the improvement of both motor and nonmotor signs and symptoms. It increases low strength determined by hypokinesia and disuse, besides playing a neuroprotective effect in individuals with Parkinson's disease. Its effect is probably determined by an increase of mitochondrial

respiration and of neuroplasticity mechanisms, improving the recruitment of motor unit and generating selective activation of the muscles [14, 43, 44].

However, there is no consensus about the parameters for resistance training prescription for individuals who have Parkinson's disease [43]. In a systematic review and meta-analysis, Saltychev and his coworkers [45] concluded that there is no evidence on the superiority of progressive resistance training compared with other treatments to support the use of this approach in rehabilitation procedures.

On the contrary, it is possible to find successful directions to use this therapeutic strategy in rehabilitation of individuals with Parkinson's disease from other systematic reviews, meta-analysis, and clinical research. Studies shows that low (2 times per week over 12 weeks) to moderate (2–3 times per week over 8–10 weeks) intensity resistance training appears to be effective in people with early, mild-to-moderate Parkinson's disease. They still show that this specific approach resulted in gaining muscle strength, balance, Parkinson's motor symptoms, and quality of life, with low or no improvement in gait performance, freezing phenomenon, and the number of falls [43, 44, 46, 47]. The load of the exercises can be chosen using the test of maximal strength (1-RM). The number of sets may vary between 2 and 3 during initial periods. The retest of 1-RM can provide additional information to adjust the load and sets along the rehabilitation period. The resting time between the sets can be controlled by cardiovascular parameters and can vary from 30 seconds up to 3 or 4 minutes [43, 44].

There are numerous ways to work with resistance training, and it is up to the physiotherapists to choose the most appropriate one for the individual under their care. In resistance training, the following examples of exercises can be used: bench press, lat pulldown, military press, seated row, leg 45°, barbell squat, leg curl, leg extension, calf raises, lower abdominal exercises, and manual or external (theraband, barbell, ankle-weight, and pulley system) resistance in active movement. Treadmill and bicycle intervention can be used when performing against resistance [43–45, 47]. Da Silva and her coworkers [48] suggest a long-term effect in nonmotor signs and symptoms of Parkinson's disease, especially in cognitive aspects, in individuals performing treadmill training, just as Ferreira and her coworkers [49] showed that resistance training was an effective intervention in the reduction of anxiety symptoms and improved the quality of life in this population.

4.1.2. Transcutaneous electrical stimulation to control resting tremor

Even if the treatment of Parkinson's disease tremor focuses on medication, and there is indication to deep brain stimulation for those patients with tremor recalcitrant using oral medication, electrotherapy has been shown to be beneficial to control this special cardinal sign.

Few studies have been performed to provide further evidence on the effects of electrotherapy on Parkinson's tremor reduction. The theory supporting the use of this strategy is based on evidence revealing that propriospinal neurons in the C3–4 spinal cord mediate voluntary commands from the motor cortex (in Parkinson's disease, these commands are oscillating

and give rise to resting tremor) and project directly to forelimb motor neurons. This proposal assumes the importance of propriospinal neurons to interfere in tremor signal transmission, especially because there are a rich variety of afferents, including cutaneous afferents [6].

Based on this concept, Xu and coworkers [50] hypothesize that cutaneous afferents evoked by surface stimulation could produce an inhibitory effect on propriospinal neurons, which in turn could suppress tremor signals passing through the propriospinal neurons.

Additionally, evidence shows benefits of electrical stimulation, especially when applied to the superficial cutaneous radial nerve area, in reduction refractory resting tremor. This effect is possibly mediated by cutaneous reflex via premotor neuron interneurons, through a disynaptic inhibitory postsynaptic potential. Some initial research was performed to confirm this theory using transcutaneous electrical nerve stimulation (TENS), with good results [6, 52]. The position of the electrodes can be verified in **Figure 3**.

The parameters used for TENS stimulation were 200 μ s pulse width at 250 Hz pulse frequency. The pulse amplitude of stimuli must be adjusted during the stimulation period. First, it is necessary to discover the radiating threshold of the patient. It occurs when the patient refers to a radiating sensation, such as a paresthesia, running from the dorsal skin to the fingers. This radiating threshold has been used as a sensory marker because it indicates that the superficial radial nerve is actually activated by electrical stimulation. After detecting the radiating threshold, the intensity of electrical stimulation must be adjusted to 1.5–1.75 times radiating threshold to produce better effects on tremor control [6].

Nowadays, researchers have been studying a way to detect the tremors and control them simultaneously and automatically by electrostimulation. They already developed and tested a closed-loop system for tremor suppression by transcutaneous electrical nerve stimulation

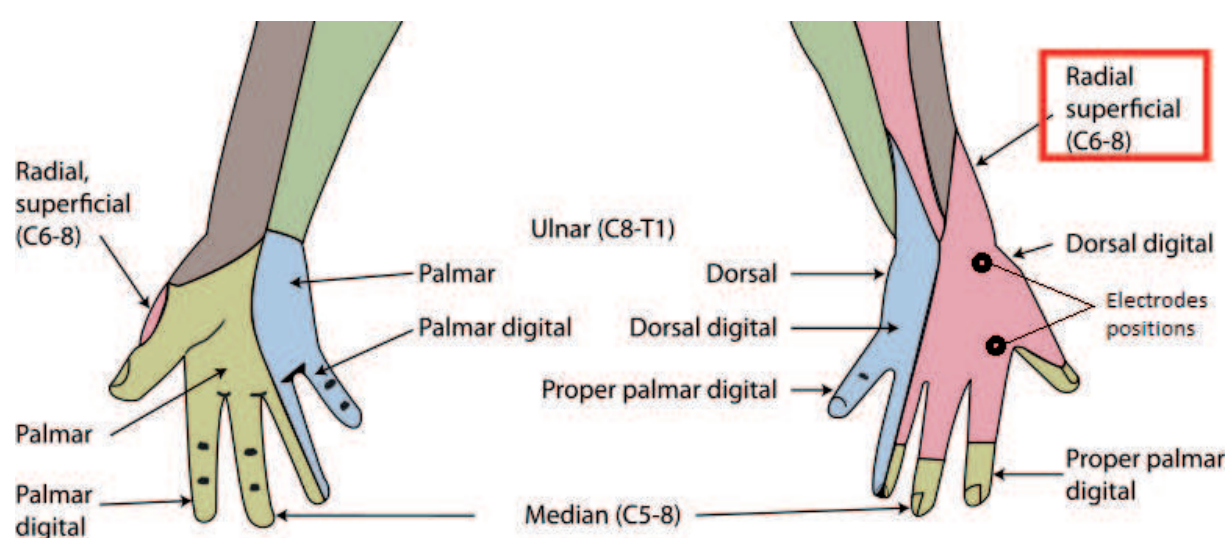


Figure 3. Use of transcutaneous electrical nerve stimulation to reduce resting tremor in Parkinson's disease. The figure brings cutaneous superficial radial nerve area and electrodes position for transcutaneous electrical nerve stimulation (TENS). Source: Modified from Gray [56]. Picture is public domain.

(TENS) using EMGs of the forearm muscles. Through this record, when a tremor is detected, a command signal triggers a stimulator to output TENS pulses to a pair of surface electrodes positioned just as described in **Figure 3**. The preliminary results showed that a closed-loop system can detect tremor properly and suppress significantly the tremor, by electrical stimulation of cutaneous afferents, in Parkinson's disease patients. Within this new concept, a tremor's glove was developed reaching also good results [50–52].

4.1.3. *Aerobic training: treadmill, cycling, free walking, dance, and tai chi*

It's known that aerobic exercises can reduce inflammation, suppress oxidative stress, and stabilize calcium homeostasis in the brain. So, it has been prescribed as an important activity for the elderly. The form of aerobic exercise used may be adapted to the capability of the individual. In individuals with Parkinson's disease, these exercises show important functions, once they can trigger plasticity-related changes, including synaptogenesis, enhanced glucose utilization, and neurogenesis [2, 53].

In general, aerobic training has been reported to improve both motor and nonmotor signs and symptoms of Parkinson's disease. The motor effects are extensively known and have been studied the most so far, showing the most unequivocal benefits on health across the life span. Furthermore, the neural mechanisms involving dopaminergic pathways are studied and suggest a significant preservation of nigrostriatal neuronal connections as well as striatal dopamine levels in experimental models. As a result, exercise-dependent plasticity following aerobic exercises acts on the brain in a similar manner as dopaminergic-derived treatments, using the same pathways to produce symptomatic relief [54].

In nonmotor signs and symptoms, aerobic training promotes positive and significant effects on global cognitive function, processing speed, sustained attention and mental flexibility, memory, and mood disorder aspects (anxiety and depression) in patients who are considered in a moderate stage of Parkinson's disease [49]. In sleep disorder, present in Parkinson's disease, aerobic exercise has been shown to have small-to-moderate effects. The mechanism involved in these effects evolved increased dopaminergic signaling and a wide variety of effects on nondopaminergic neurotransmitter systems, including serotonergic, noradrenergic, and GABAergic systems, which is relevant for depression, anxiety, and sleep [53, 54].

The most common and studied form of aerobic training is using a treadmill. In some systematic reviews, the majority of articles considered in analyses use treadmills for aerobic training. This approach can be used with or without a body-weight-support system, depending on the motor difficulties of the individual with Parkinson's disease. It may be related with improvement in motor signs like motor action, balance, and gait, although the evidence is not so strong [2, 48].

In the same way, free walking and Nordic walking (a total body version of walking performed with specially designed walking poles similar to ski poles) also have good effects on motor and nonmotor domains of Parkinson's disease and must be stimulated and used in physical therapy practice in rehabilitation of individuals with Parkinson's disease [55].

Similar to the aerobic training used on the treadmill, moderate intensity of interval training for cycling has shown several beneficial effects on the DA-dependent motor and nonmotor signs that compromise Parkinson's disease patients. Researchers have reported improvement on bimanual motor control, automatic interlimb coordination, executive functions, and neurological (UPDRS) symptoms [56].

An interval protocol template that can be used can be the following: from 8 to 12 weeks of training, 3 times per week, 1-hour session training with 10 minutes of warm-up, 40 minutes of aerobic training, and 10 minutes of cooldown). During the 40 minutes of aerobic training, the patient can perform 8 sets of 3 minutes of cycling or treadmill at 60–80 rpms and 2 minutes of less than 60 rpms. The heart rate also can be used as a parameter to improve effort during the training period. Hence, the physiotherapist may adjust the resistance to ensure the patient is cycling at 60–75% of his/her maximal heart rate. This effort can increase gradually during the training period [56]. A guideline with some exercise modes to be used in Parkinson's disease was provided by Meng and coworkers in a systematic review and meta-analysis [57].

Other forms of aerobic exercises have been stimulated in the rehabilitation process in Parkinson's disease. Several data have shown that dance can provide increased activation of the reward system, determining better mood aspects in people. In patients with Parkinson's disease, practicing dance has induced better responses and a substantial relevant improvement in motor symptoms (such as static and dynamic balance, freezing phenomenon, and gait) and functional mobility. This improvement determines also a better quality of life in performers. It probably occurs because rhythmic stimulation leads to time-perception compensation due to the synchronization of movement with rhythm [58, 59].

To get these effects, a dance program must include visual and auditory cues, rhythm tasks, and recreational activities that motivate socialization. Another important aspect is to reach the ideal heart rate during practice, just as discussed previously in the aerobic training protocol [58].

Oriental martial arts, such as tai chi, have been successfully used in treatment of individuals with Parkinson's disease. Tai chi combines deep breathing and slow movements and studies have provided moderate evidence that tai chi improves balance and functional mobility, reducing the number of falls, but with no significant effect in gait velocity, step length, and gait endurance improvement [33, 60, 61]. A systematic review and meta-analysis showed that tai chi, plus medication, showed greater gains than medication alone or another therapy plus medication in motor function and balance. Presumably, these gains were due to the development of new motor programs, which allow faster reactions responding to postural challenge promoting better behavioral recovery through new synaptic connections [62]. It is necessary to know and practice this technique before using it on patients.

4.1.4. Multimodal exercise program

The aim of the multimodal exercise program is to develop the patients' functional capacity, cognitive functions, posture, and locomotion. It's comprised of a variety of activities that

simultaneously focus on the components of functional capacity, such as muscular resistance, motor coordination, and balance [14]. It's a 6-month program, performed 3 times per week, 1 hour per session. Each session consists of five parts (warm-up, pre-exercise stretching, the exercise session, the cooldown, and postexercise stretching). The program is divided into six phases with different uses of coordination, muscular resistance, and balance strategies [63, 64]. A description of each phase can be seen in **Table 5**.

The little data that are available in the literature point to improvement in some kinematic gait parameters of mild-to-moderate idiopathic PD patients using multimodal exercise programs [63, 64].

Phases	Capacities		
	Coordination	Muscular resistance	Balance
Phase 1	Upper and lower limb movements.	Exercises without weights.	Recreational activities that stimulated the vestibular system.
Phase 2	Trunk movements were added to upper and lower limb movements.	Light-weight equipment (hoops, ropes, and batons).	Recreational activities that stimulated the visual and vestibular systems.
Phase 3	Trunk movements were substituted by head movements.	Heavier equipment (barbells, ankle weights, and medicine balls).	Recreational activities that stimulated the visual and somatosensorial systems.
Phase 4	Head, trunk, and upper and lower limb movements.	Load was again increased with heavier equipment for resistance training (increase of intensity) or increased repetitions (increased volume).	Recreational activities integrated the vestibular, visual, and somatosensorial systems.
Phase 5	Four different movement sequences, two of which were the same for upper and lower limbs and two other sequences that alternated movements for upper and lower limbs in place and in movement.	Exercises were done with weights: leg press, pulley, seated cable rows, peck deck, and bench press. Load was adjusted according to patients' convenience (in two series of 15 repetitions).	Recreational activities included static balance, dynamic balance, half-turn, and complete turn (all with visual cues).
Phase 6	Four sequences of different movements, two sequences of alternating movement for upper and lower limbs, and two sequences of different movement for upper and lower limbs, with or without trunk movement and equipment (balloons, balls, hoops, and rope).	The same exercises with load increase. Series of 15 repetitions were added.	Recreational activities were composed of activities with tactile cues.

Note: Based on Vitório and coworkers [63].

Table 5. Multimodal exercise program in Parkinson's disease.

4.1.5. *Acupuncture*

Several data show acupuncture and electroacupuncture (still performed on animal models) as beneficial strategies in Parkinson's disease treatment, used either isolated or combined with other treatments. It has been described as showing improvement in the UPDRS total score and in its subsections after an acupuncture session. So, even motor and nonmotor signs and symptoms, including pain, can be improved with the use of acupuncture [65–67]. However, the most important source of data that proves the beneficial effects of acupuncture in treatment of signs and symptoms in Parkinson's disease is provided from functional neuroimaging studies. These studies have shown huge modifications in neural functions after acupuncture sessions [68, 69].

As tai chi use was previously discussed, acupuncture requires previous academic training so that it can be used in an accurate way in the treatment of Parkinsonian individuals.

4.1.6. *Hydrotherapy*

Hydrotherapy has been widely used to treat individuals with Parkinson's disease. It has been proven to be effective for different gait rehabilitation programs, as well as to improve balance and quality of life, and reduce pain and falls. The warm property of water used for hydrotherapy potentially also reduces rigidity [70, 71].

In water, innumerable forms of exercises can be performed including warm-up exercises (like jumping and walking), stretching exercises, gait training, cooldown exercises, trunk mobility, balance, coordination and proprioceptive exercises, the Halliwick method, posture exercises, the Ai Chi method, aerobic exercise, the Bad Ragaz method, motor dexterity exercises, and swimming exercises, among others [71].

4.1.7. *Virtual reality and exergames: integrative techniques*

Virtual reality potentially optimizes motor learning in a safe environment, and by replicating real-life scenarios, it could help to improve functional activities of daily living in individuals with Parkinson's disease. However, the use of commercially available devices makes this tool contiguous to many other physical therapy instruments, leading to low evidence in the results [72]. Despite this, several studies have reported greater improvement in many signs and symptoms such as balance, gait, functional capacity, and self-confidence, improving quality of life and reducing the risk of falling [73–75].

As an example of specific virtual reality developed for Parkinson's disease rehabilitation, Gomez-Jordana and coworkers [76] developed visual cues that could be presented in an immersive, interactive virtual reality environment. With this, they created different forms of spatial and temporal information where black footprints presented at a prespecified distance apart could recreate different step lengths (spatial cues), and by controlling when the black footprints changed color to red, they could convey information about the timing of the foot

placement (temporal cues). With this device, they could get significantly improved gait performance in participants.

Additionally, exercise-based video gaming (exergaming), a form of physical training that is delivered through virtual reality technology, facilitates motor learning and is efficacious in improving balance in aged populations. This approach can use commercial devices such as Nintendo Wii Fit System®, X-box 360° with Kinect®, or rehabilitation-specific software program like Jintronix® [70, 74, 77].

These devices usually combine automated game instructions as well as visual and auditory and tactile inputs to correct performance and sustain motivation levels during and following game play. Therefore, exergames employ visual and auditory feedback techniques to create a quasi-immersive environment that can facilitate motor and cognitive learning. Since individuals with Parkinson's disease are dependent on sensory cues to maintain postural stability and show difficulties with long-term consolidation of new motor skills, this sensorial integration provided by using exergames may help to upregulate neuroplasticity and facilitate motor skill acquisition and retention [77].

These resources can be used isolated or associated in a clinical approach or in a telerehabilitation program like a home-based virtual reality or home-based exergame [74].

4.1.8. Group approach

Groups are used in physical therapy to improve global health status and bring relief from typical disability symptoms of several diseases, competing with individual rehabilitation at least in short-term follow-up. Therapeutic groups have been beneficial to the health care system by decreasing the cost and time spent on rehabilitation.

Similar to other techniques, group therapy can use several kinds of exercise goals such as general mobility, using muscular strength, free movement, and relaxation exercises; trunk control, using trunk displacement and rotation during dynamic exercises performed in a sitting posture; static balance, using the same strategies for trunk control but in a standing position; dynamic balance and gait, using free gait; and gait with obstacles, stairs, ramp, uneven ground, performed in and outside the room. The use of hearing and visual cues during the procedure provides several stimulus associations for the patients. This approach was reported to improve gait, balance, and activity of daily life performance in patients with PD [78].

4.1.9. Mental imagery

Mental imagery is the cognitive process of creating visual, auditory, or kinesthetic experiences in the mind with or without overt physical execution. In many people, this procedure can help or improve motor performance. This strategy has the potential to increase the function of both the motor cortex and the spinal neurons, resulting in improved muscle function [79, 80]. Thus, it is an important technique in motor learning and control,

and although it has its origin in sports science, it has been introduced into the field of neurorehabilitation.

In a few sources about mental imagery in Parkinson's disease rehabilitation, some data show a better muscle recruitment measured by electromyography or other form or neurophysiologic register. But available data are, sometimes, contradictory [80, 81].

Specifically in individuals with Parkinson's disease, this approach has shown to be beneficial to motor (measured by UPRDS-III-motor signs) and cognitive functions [79].

4.1.10. Applications (apps in cell phones or tablets): a new generation of physical therapy approach

Since smartphones became popular, numerous health-related apps have been developed for professionals, patients, and the general population. However, many of these apps are not validated, so their efficacy may be not satisfactory. Nowadays, this resource still has been used as a complementary treatment [82].

It is a well-known fact that it is important to emphasize that apps are a democratic source of information and rehabilitation, since they maintain the main principles of usability, accessibility, and equal opportunities for healthcare professionals, patients, relatives, and caregivers [82].

For Parkinson's disease, there are a few apps available, and just one with some data partially published. On the Parkinson's UK webpage, we can find a list of apps reviewed and recommended for individuals with Parkinson's disease. There are apps for sleep, volume of voice, mood, swallowing, memory (recording stories of patients), mobility, speech, and dexterity [83].

Another source from the International Parkinson's Community recommended eight extra apps. They focus on measurement and tracking the patient's symptoms, give information about Parkinson's disease, record and measure the magnitude of tremor and speech, and manage and track the individual's health condition. The only one that has some physical approach is the Parkinson's home exercise [84].

The Parkinson's Home Exercise®, promoted by the European Foundation for Health and Exercise, was easy-to-use and designed to be used by patients and physiotherapists. It provides advice and instructions for daily exercises and movements through over 50 videos and text instructions. It has a cost involved [85]. There are no references in literature about its efficacy.

Another app, developed by TEVA Pharmaceutical Industries, named Parkinsounds®, is a free app that helps patients with Parkinson's disease to find their gait rhythm using music and rhythmic beats (like a metronome). They use a predetermined music list or one that can be linked to Spotify®. Once the rhythm is chosen, Parkinsounds is able to find music that combines with the preselected rhythm adding beats in the music. The physiologic base for

this strategy is centered on the synchronic activation of neurons provided by the music and the rhythmic stimulus, added to an increase of dopamine liberation [86].

Our group has been developing research using this specific app in rehabilitation of gait in Parkinson's disease. The partial data were already presented at the World Confederation of Physical Therapy Conference (research data are not still available). However, a huge acute effect could be seen in the gait of Parkinsonians using Parkinsounds, even in a long-term period of rehabilitation. We could see an improvement in width and length of gait, with a reduction of base and number of steps, which were measured in a 10 meters' route, after 10 weeks of treatment. It is important to emphasize that the walking test was performed with and without Parkinsounds® use for patients at the moment of evaluation (initial and final), and in both cases, the improvement was significant. So, it can be considered an important feature for gait rehabilitation in Parkinson's disease.

4.1.11. Whole body vibration

According to the literature data, there is no apparent consistency in the effect of whole body vibration shown on mobility, balance, and gait in individuals with Parkinson's disease [87]. However, the majority of the studies point to a favorable effect of this therapeutic strategy [87, 88].

Disregarding the differences between the various types of equipment, a lot of research has proposed some parameters that are useful in improving mobility and balance in individuals with Parkinson's disease. The majority recommend orthostatic position and 7 to 14 mm amplitude with a frequency ranging between 3 and 25 Hz, in cycles of 5 bouts of 1 minute each. Until now, there is no consensus about which frequency is better [87]. So, it is recommended that the physical therapist evaluate these functions constantly after using this resource.

The effect of whole body vibration on tremor is less prominent [87]. Moreover, it also does not appear to lead to better cardiovascular conditions reducing the feeling of fatigue when compared to treadmill training [89].

The physiological mechanism involved in the effects of whole body vibration on reducing some of the motor signs of Parkinson's disease remains elusive. Some theories suggest that whole body vibration provides tactile and proprioceptive stimulus to the whole body originated from the vertical oscillating mechanical movement or the movement along the horizontal axis, which through neuromuscular activation and metabolic mechanism may bypass dysfunctional basal ganglia, resulting in better adjustments for postural stability and gait [88, 90].

5. Conclusion

In this chapter, we can notice how profound the discussions about Parkinson's disease are, especially about treatment. Physical therapy has increased its participation in Parkinson's disease treatment. However, research is still lacking to substantiate its real effectiveness. It is

imperative that further research be done to strengthen performance and the excellent results obtained with physical therapy in treating individuals with Parkinson's disease.

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