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Review

Parkinson's Disease: Insights into Epidemiology, Experimental Models, and Novel Therapeutic Approaches

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder that primarily affects motor functions, with symptoms such as tremors, bradykinesia, rigidity, and postural instability. Non-motor symptoms, including cognitive impairment and mood disorders, also contribute to the disease burden. While the exact etiology remains unclear, both genetic and environmental factors play a role in its onset and progression. The prevalence of PD is increasing, particularly among aging populations, with men being more affected than women. Various experimental models, including chemically induced and genetic animal models, are used to study PD pathophysiology and evaluate potential treatments. Current therapeutic approaches focus on symptom management through pharmacological treatments such as levodopa, dopamine agonists, and MAO-B inhibitors, as well as non-pharmacological interventions like physiotherapy, cognitive therapy, and deep brain stimulation (DBS). Despite advancements in understanding PD, no cure exists, and research continues to explore disease-modifying treatments and early diagnostic methods. This review highlights key epidemiological trends, experimental research, and current therapeutic strategies, emphasizing the need for multidisciplinary approaches to improve patient outcomes and quality of life.

Keywords: Parkinsons disease, neurodegeneration, motor symptoms, levodopa, dopamine, deep brain stimulation, experimental models, therapy.

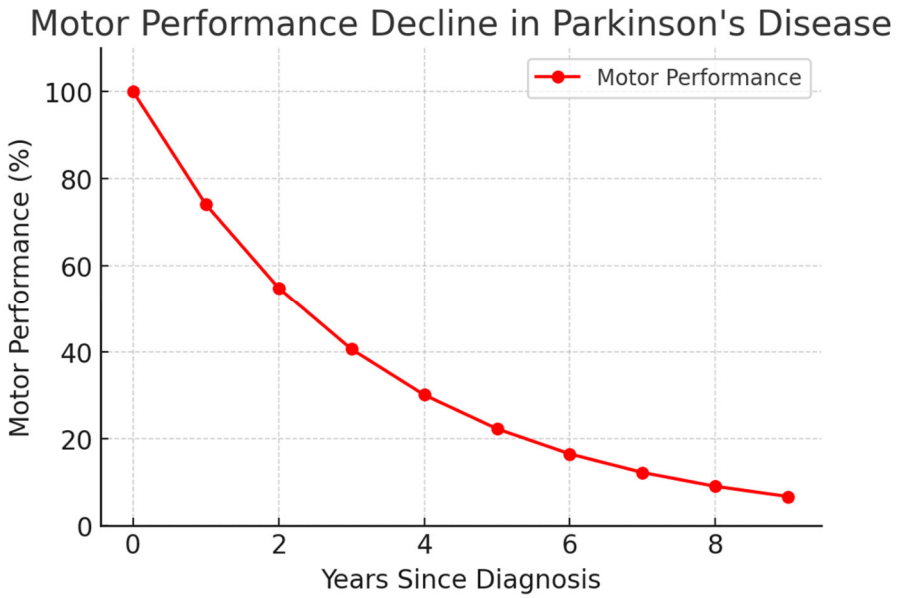
INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder of unknown origin that affects both motor and non-motor functions. It is a progressive condition that primarily affects older individuals, though it can also develop in younger patients. As the second most prevalent neurodegenerative disease, PD significantly impacts the nervous system. (1) Other neurodegenerative disorders can resemble idiopathic Parkinson's disease (PD). These conditions include Dementia with Lewy Bodies (DLB), Corticobasal Degeneration (CBD), Multiple System Atrophy (MSA), and Progressive Supranuclear Palsy (PSP). However, this review will primarily

concentrate on idiopathic PD, excluding these other parkinsonism-like syndromes. Parkinson's disease has been acknowledged since the early 1800s, when the physician after whom it is named first described it. Often referred to as "paralysis agitans," PD is relatively rare in younger individuals, particularly those under the age of 40. (2) Parkinson's disease affects approximately one million Americans, with nearly 60,000 new cases diagnosed annually. Globally, an estimated 7 to 10 million people are believed to be living with the condition. Men are 1.5 times more likely to develop PD than women. (3) A population-based study of U.S. Medicare beneficiaries found a mean prevalence of 1.6% for Parkinson's disease among individuals aged 65 and older. Fewer Black and Asian American individuals are affected compared to White individuals. Higher rates of PD are observed in the Midwest/Great Lakes region and along the northeastern U.S. seaboard, with exposure to environmental toxins in these areas proposed as a potential contributing factor. (4,5) The prevalence of Parkinson's disease is projected to increase significantly over the next 20 years as the U.S. population continues to age. As a result, it will remain a major health concern and a substantial economic burden due to both direct and indirect costs. This economic and human toll could be particularly significant in developed nations, where life expectancies are steadily rising. (6) Parkinson's disease (PD) was first described by Dr. James Parkinson in 1817 as "shaking palsy." It is a chronic, progressive neurodegenerative disorder characterized by both motor and nonmotor symptoms. The disease has a significant clinical impact on patients, families, and caregivers due to its gradual effects on mobility and muscle control. The motor symptoms of PD are primarily caused by the loss of dopaminergic neurons in the striatum, although the presence of nonmotor symptoms suggests degeneration in non-dopaminergic regions as well. The term "parkinsonism" refers to the motor features of PD, which include resting tremor, bradykinesia, and muscular rigidity. While PD is the most common cause of parkinsonism, other secondary causes exist, such as diseases that mimic PD and drug-induced conditions. (7) Research suggests that the pathophysiological changes associated with Parkinson's disease may begin before the onset of motor symptoms and can include a variety of nonmotor manifestations, such as sleep disturbances, depression, and cognitive changes. The evidence supporting this preclinical phase has sparked growing interest in research aimed at developing protective or preventive therapies. (8)

The Parkinson's Disease Foundation reports that approximately 1 million Americans currently have the disease. The incidence of PD in the U.S. is approximately 20 cases per 100,000 people per year (60,000 per year), with the mean age of onset close to 60 years. The prevalence of PD is reported to be approximately 1% in people 60 years of age and older and increases to 1% to 3% in the 80-plus age group. However, an important caveat associated with these numbers is that they do not reflect undiagnosed cases. (9) While Parkinson's disease is primarily associated with the elderly, it can also develop in individuals in their 30s and 40s. Gender differences in the incidence of PD are evident, with a 3:2 male-to-female ratio. The later onset of PD in females is thought to be related to the neuroprotective effects of estrogen on the nigrostriatal dopaminergic system. (10)

The variable yet pronounced progression of Parkinson's disease significantly affects patients, families, and society. In advanced and end-stage disease, serious complications, such as pneumonia, often arise and can be associated with death. Current treatments primarily focus on managing symptoms. Evidence indicates that patients with PD may also benefit from a multidisciplinary approach to care, involving movement specialists, social workers, pharmacists, and other healthcare professionals. (11)



Various risk factors and genetic mutations are linked to Parkinson's disease. These risk factors include oxidative stress, free radical formation, and exposure to environmental toxins. Although data on genetic associations with PD are limited, several gene mutations have been identified. Interestingly, there is an inverse relationship between cigarette smoking, caffeine intake, and the risk of developing PD. The protective effects of tobacco smoking may be explained by the inhibition of the enzyme monoamine oxidase (MAO), while the benefits of caffeine may stem from its activity as an adenosine antagonist. (12) The varying prevalence of Parkinson's disease worldwide suggests that environmental and genetic factors, along with ethnic differences, may all contribute to the disease's development. Ongoing biomedical research in individuals with PD continues to explore additional risk factors and could help inform future prevention and treatment strategies. (13)

EPIDEMIOLOGY

The epidemiology of Parkinson's disease exhibits significant variations across time, geography, ethnicity, age, and sex. Globally, the prevalence has risen beyond what would be expected from demographic changes alone. Several factors may contribute to this increase, including a decline in other competing causes of death. However, whether the incidence is rising particularly among women or in many low- and middle-income countries, where high-quality data is scarce remains uncertain. (14)

Age

Parkinson's disease is more common in older people and men. PD prevalence is increasing with age and PD affects 1% of the population above 60 years.(15) Parkinson's disease is more common in older people and men, and a variety of environmental factors have been suggested to explain why, including exposure to neurotoxic agents.(14) the age-specific prevalence rates showed a rapid increase after the 50th year of age. the greatest prevalence was shown by the age group 70–79 years of age in which almost 0.8 per cent of the population are affected. Age-specific incidence rates also displayed an increase after the 50th year of age. the greatest incidence was observed in the age group 70–79 years of age in which almost 1 per 1,000 of the population are annually affected by the disease. (16)

Gender and ethnic disparities

Observational studies show that Parkinson's disease (PD) generally affects males more often than females, though the underlying reasons remain unclear. In certain regions, such as South Korea, Japan, and Bolivia, the male predominance of PD is less noticeable. A study by Pringsheim et al. revealed that the male-to-female prevalence ratio of PD increases with age. (17) In women with Parkinson's disease (PD), the progression of symptoms is often delayed due to higher levels of physiological dopamine at the Nigro-striatal level, which is influenced by estrogen activity. Ethnic differences may also play a role in the motor complications related to PD treatment. While dyskinesia and 'wearing off' have been extensively studied in North American and European PD populations, research on these issues is limited in other parts of the world, particularly in multi-ethnic cohorts. Asian patients, for example, appear to experience dyskinesia more frequently, leading to recommendations for lower doses of dopaminergic medications. An international survey showed that Japanese physicians reported the lowest prevalence of dyskinesia among their patients. However, they were also the least likely to use levodopa monotherapy, preferring a combination of dopamine agonists and levodopa, which may contribute to this difference. (18)

Geography

The geographic clustering of Parkinson's disease could offer more compelling evidence of the environmental factors involved in its development. A limited number of studies have examined geographic variation in Parkinson's disease, with many focusing on rural living as a potential risk factor. While some case-control studies indicate a higher risk of Parkinson's disease in rural areas, others point to an increased prevalence in industrial regions, or show no significant difference. However, these studies are often constrained by inconsistent definitions of rurality and small sample sizes. (19)

BEHAVIORAL ANIMAL MODEL STUDIES OF PARKINSON'S DISEASE

Animal models play a crucial role in preclinical drug discovery research. Chemically-induced Parkinson's disease (PD) models typically involve rats treated with chemicals that are toxic to dopaminergic neurons. In contrast, genetic models of PD focus on altering or knocking out genes associated with familial forms of the disease. However, as discussed later, rodent models have encountered challenges, particularly in terms of lacking strong construct and/or face validity, as well as facing limitations related to species differences and strain variability. (20)

1.ELEVATED PLUS MAZE

Anxiety-like behavior was assessed using the elevated plus maze, as previously described by Pego et al. (2008). The apparatus consisted of two open arms (50.8 × 12 cm) and two enclosed arms (50.8 × 12 × 40.6 cm), all extending from a central platform (10 × 10 cm) and elevated 72.4 cm above the ground. Each animal was

individually placed on the central platform, facing the open arm, and allowed to explore the maze freely for 5 minutes. After each session, the apparatus was cleaned with 10% ethanol. The test was recorded using a video camera, and behavioral analysis was performed with The Observer Basic 3.0 software. The parameters recorded included the number of entries into both the open and closed arms, as well as the percentage of time spent in the open and closed arms, and at the intersection of the arms. The percentage of time spent in the open arms was used as an indicator of anxiety-like behavior, while the number of entries into the closed arms served as a measure of locomotor activity, which is considered a more reliable metric than the total number of arm entries.

2.FORCED SWIM TEST

The forced swim test was employed to assess depressive-like behavior, following the method outlined by Leite-Almeida et al. (2009). Rats were placed in a cylinder filled with water at 24°C for 5 minutes. The session was recorded using a video camera, and the latency to immobility and the total time spent immobile were measured. A depressive-like state was characterized by an increase in the duration of immobility and a reduction in the latency to immobility.

3.MORRIS WATER MAZE

Cognitive function was evaluated using the Morris Water Maze test, which includes tasks for working memory, spatial reference memory, and reversal learning. These tasks were performed as described by Cerqueira et al. (2007). Briefly, the test was conducted in a circular black tank (170 cm in diameter), filled with water at 24°C to a depth of 31 cm, placed in a dimly lit room with external spatial cues on the walls. The tank was divided into imaginary quadrants, with an invisible platform located in one of them. Data collection was done via a video camera mounted on the ceiling above the center of the tank, connected to a video tracking system (View Track v.2.6., Viewpoint Life Sciences Inc.). The platform's location varied depending on the task. Each day, animals underwent four trials to find the platform. At the start of each trial, the animals were placed in the periphery of the chosen quadrant, facing the wall of the maze. A trial was ended automatically once the animal found the platform, or if it failed to do so within 120 seconds, it was gently guided to it. A 20-second rest period on the platform followed each trial. Time taken to reach the platform and the distance traveled were automatically recorded.

The working memory task assessed the animal's ability to learn the platform's location and retain this information across four consecutive trials. This task was performed over four days, with the platform hidden in a different location each day. The final day of the working memory task marked the beginning of the spatial reference memory task, designed to evaluate the animal's ability to learn the platform's location over three consecutive days. In this phase, the platform remained in the same position ("old" quadrant) across all three days. The reversal learning task took place on the seventh day, testing for cognitive flexibility. During this task, the platform was moved to the opposite quadrant ("new" quadrant), and animals were tested through four trials. On the final day of testing, a fifth trial, the probe trial, was added. In this trial, the platform was removed from the tank, and the animal was tested for 120 seconds, with the distance swum in each quadrant recorded across all five trials.

4.ROTAROD

The motor performance was performed at 8 weeks post-surgery using the rotarod equipment (3376O4R, TSE Systems) as previously described (Monville et al., 2006). The unit consists of a rotating spindle, a power source for turning the spindle and grids beneath the rotating roller where the rat can fall without injury. All animals were pre-trained on the rotarod apparatus in order to reach a stable performance. The training consisted of four sessions on 3 consecutive days, under an accelerating protocol starting at 4rpm and reaching 40rpm in 5min; each session included three separate trials, with at least 20min of rest between trials. At the fourth day the final test was performed under the same accelerating protocol and the latency to fall was recorded.

5.SUCROSE PREFERENCE TEST

Anhedonia was evaluated using the sucrose preference test, as described by Carvalho et al. (2013). The test involved depriving animals of food and water for 18 hours, followed by the presentation of two pre weighed bottles: one containing a 3% sucrose solution and the other containing tap water. The animals were allowed to choose between the two bottles for 1 hour. Sucrose preference was calculated using the following formula: **Sucrose preference = (sucrose intake / (sucrose intake + water intake)) × 100**. A reduced preference for sucrose is indicative of anhedonia and, by extension, depression-like behavior. Additionally, the total consumption of sucrose and water was recorded to compare overall fluid intake across groups.

6.OPEN FIELD

Locomotor behavior was assessed using the open field test, following the method described by Leite-Almeida et al. (2009). The rat was placed at the center of a square arena (43.2 cm × 43.2 cm) (ENV-515, Med Associates Inc.) and allowed to explore the area for 5 minutes. Using tracking software (SOF-811, Med Associates

Inc.), data on the total distance traveled, time spent resting, number of readings, and ambulatory episodes were recorded. The arena was cleaned with 10% ethanol between each animal to avoid scent contamination.

7.SKILLED PAW REACHING TEST

Skilled paw reaching was evaluated using a double staircase box (80300, Campden Instruments Ltd.), designed similarly to the apparatus described by Montoya et al. (1991). This setup is intended to assess independent forelimb use in skilled reaching and grasping tasks. The apparatus consists of a clear chamber with a hinged lid, connected to a narrow compartment with a central platform running along its length. A removable double staircase, with 7 steps on each side, can be inserted between the platform and the walls of the box. Three food pellets were placed in each well of the double staircase. During the first two days, the rats were familiarized with the test, with pellets being available for 5 minutes on the first day and 10 minutes on the second. In the test session, the animals were placed in the box and given 15 minutes to reach, retrieve, and consume the pellets placed on the steps. All sessions were conducted at the same time of day with food-restricted animals. After the test period, the animals were removed from the box, and the remaining (leftover) pellets were counted.

8.IMMUNOHISTOCHEMISTRY

IHC was performed on free-floating mesencephalic axial frozen sections (35 μm). A chromogenic IHC assay was used to identify dopaminergic neurons. To block nonspecific antibody binding, the sections were incubated for 60 minutes in PBS with 10% fetal calf serum (FCS) containing 0.1% Triton X-100. Endogenous peroxidase activity was quenched by a 10-minute incubation in 1% H2O2. Sections were then incubated overnight at 4°C with a mouse anti-tyrosine hydroxylase (TH) antibody (1:1000; Transduction Laboratories) diluted in PBS with 1% FCS. Following this, the sections were incubated for 1 hour at room temperature with a biotinylated secondary antibody, goat anti-mouse IgG (1:200; Vector Laboratories), diluted in PBS. The sections were then incubated with avidin peroxidase (1:1000 in PBS; Vector Laboratories) for 50 minutes at room temperature. Finally, the reaction product was visualized using diaminobenzidine (DAB, Sigma) in TBS with 0.0024% H2O2.

9.QUANTITATIVE ANALYSIS OF THE POSITIVE CELLS

The immunohistochemically processed sections were used to assess the total number of TH-immunoreactive cells within the substantia nigra pars compacta (SNpc). In the mesencephalic sections, the region containing the TH-positive cells, corresponding to the SNpc, was delineated, and the total number of TH-positive cells was counted across the entire structure in each section. Every sixth section covering the full extent of the SNpc was included in the counting procedure. To estimate the total number of TH neurons, the following formula was applied: $\mathbf{N = V(SNpc) \times (Q / V(sect))}$, where **N** represents the estimated number of cells, **V(SNpc)** is the total volume of the SNpc, **Q** is the total number of cells counted in the sections, and **V(sect)** is the total volume of the counted sections.

10.STATISTICAL ANALYSIS

All datasets were examined for normality using the Shapiro-Wilk test before any statistical analysis. Data are presented as mean ± standard error of the mean (s.e.m.). Statistical analysis was carried out using the student's t-test, Mann–Whitney nonparametric test, or one-way/repeated measures analysis of variance (ANOVA), depending on the nature of the data. Post hoc comparisons between groups were conducted using Dunnett's or Bonferroni's tests. A p-value of 0.05 was considered statistically significant. All statistical procedures were performed using GraphPad Prism, version 4.(21)

11.CYLINDER TEST

The cylinder rearing test was adapted for use in mice to assess forelimb usage during spontaneous behavior. This test is commonly used to evaluate motor impairments in experimental models of Parkinson's disease, including those with unilateral 6-OHDA injections. Hemi lesioned animals exhibit significant forelimb asymmetry due to the lesion in the nigrostriatal pathway. While healthy mice typically use both forelimbs equally, dopamine-lesioned mice show a preference for using the forelimb ipsilateral to the lesion. Each mouse was placed in the cylinder, as described previously, and forelimb contacts were recorded (20 contacts). The number of contacts made with the impaired and paired forelimbs was calculated as the percentage of contralateral paw use during the observation period. All behavioral assessments were conducted the day before the animals were sacrificed.

12.ELEVATED BODY SWING TEST

The Elevated Body Swing Test (EBST) is another sensitive method for evaluating motor asymmetry in the unilateral model of Parkinson's disease. For the EBST, animals were carefully held by the base of the tail, and the number of swings (to the left or right) was recorded until 20 swings were completed, as previously described. (22)

EX VIVO EXPERIMENTAL STUDIES

Ex vivo gene therapy approaches offer significant potential for treating neurodegenerative diseases, many of which currently lack effective cures or adequate treatments. This review primarily focuses on the application of ex vivo gene transfer techniques in Parkinson's disease models. However, the issues discussed and the approaches outlined are also relevant to other neurodegenerative disorders.

1.MIDBRAIN CELL CULTURE

Fresh brain slices can be prepared from various strains of wild-type and genetically modified mice and rats, depending on the objectives of the study and the specific practices of the laboratory. Parkinson's disease (PD) is characterized by the accumulation of intracellular protein aggregates, known as Lewy bodies and Lewy neurites, which are primarily composed of the protein α-synuclein. As such, PD is classified as the most prevalent synucleinopathy. The motor symptoms of the disease are caused by the degeneration of neurons in the midbrain region, leading to a deficit in dopamine. (23)

2.MITOCHONDRIAL ANALYSIS

Mitochondrial dysfunction has been proposed as a key component of the pathophysiological cascade in Parkinson's disease (PD), based on autopsy findings. However, direct evidence for mitochondrial dysfunction in living patients remains limited. Since the disease is thought to initiate at the enteric level, we focused on studying the ganglionic and mitochondrial morphology of enteric neurons. Pathological changes in the submucosal colon nerve layer have been observed in early-stage PD patients, suggesting that these abnormalities in enteric neurons may represent an early manifestation of the disease. Additionally, animal studies of enteric neurons indicate that mitochondrial dysfunction may play a direct role in PD progression. (24)

3.IMMUNE SYSTEM ANALYSIS

The interrelated and disease-associated compartment of T-cell populations in the periphery warrants further investigation. T-cell populations from patients with Parkinson's disease (PD) and healthy controls were examined using flow cytometry and RNA gene expression analysis after isolation from peripheral blood. No significant differences were found in the numbers of CD3+, CD4+, and CD8+ T cells between PD patients and controls (Fig. 2a). However, when analyzing the phenotypes and functions of T cells, a reduction was observed in the T effector (Teff) cell population (CD4+ CD25-) in PD samples (Fig. 2b). RNA isolation and RT-PCR analysis revealed that the Teff population in PD patients was polarized toward a pro-inflammatory state, as indicated by elevated levels of pro-inflammatory transcripts such as tnf, ifnγ, and il2. Additionally, the master transcription factors for T helper type 1 (Th1) and T helper 17 (Th17), namely tbx21 and rorc, were found to be upregulated in PD patients compared to controls. (25)

MOTOR ASSESSMENT IN PARKINSON'S DISEASE

BALANCE AND POSTURE IN PD

Many individuals with Parkinson's Disease (PD) experience balance and posture issues, leading to a higher risk of falls. Over 50% of PD patients are affected by falls. To assess balance, several tests are commonly used, such as the Timed Up and Go Test (TUG), Berg Balance Scale (BBS), and Functional Reach Test (FRT). The TUG test has been confirmed as useful for detecting mobility changes in PD patients, and the Berg Balance Scale helps assess balance. Other tests, such as the Balance Evaluation Systems Test (Bes test) and its shorter version, MiniBES Test, evaluate various aspects of balance. Posturometric and stabilometric evaluations have also advanced, revealing that patients with PD show increased sway ratios compared to healthy individuals. Research suggests that even early PD affects postural control strategies, and PD patients exhibit deficits in motor learning and task performance, particularly when performing multiple tasks simultaneously.

ARM AND HAND FUNCTION

There are various tests and studies related to arm and hand function, particularly focusing on Parkinson's Disease (PD). It mentions well-known skill tests such as the Purdue Pegboard Test, Nine-Hole Peg Test, Jebsen and Taylor test, and others. Key motor function scales, including the Fugl-Meyer Motor Assessment Scale (FMA) and Södring Motor Evaluation (SMES), are highlighted. The Finger-Tapping Test (FTT), developed by Shimoyama in 1990, is noted for its ability to assess fine motor skills and correlate with the MDS-UPDRS scores, aiding in monitoring PD progression and treatment response, including deep brain stimulation (DBS).Studies on muscle activity in PD patients (e.g., Marusiak et al. 2009) reveal that PD patients show altered muscle responses compared to controls, with changes in the amplitude and frequency of mechanomyography (MMG) and electromyography (EMG) signals. MMG was found useful in distinguishing PD from healthy controls.

Research by Fernandez-Del-Olmo (2013) and Berardelli et al. (1986) highlights how PD patients' response times and movement characteristics differ from those of healthy individuals. Specifically, PD patients showed a startle reaction effect during wrist movements, and the study of wrist flexion movements suggested that changes in movement velocity are not always indicative of the clinical state in PD patients.

WALKING IN PD

Studies on walking and mobility in Parkinson's Disease (PD) have identified several key findings and tools. According to Rochester et al. (2004), PD patients walk significantly slower (26.5% slower) and have reduced step length (23% shorter) than controls. Elbers et al. (2013) highlighted that timed walking tests are valid for predicting community walking in PD, although fear of falling should also be assessed. The 12-Item MS Walking Scale (MSWS-12), developed by Hobart's team in 2003, has been shown to be useful for evaluating PD patients, while Stina Bladh et al. (2012) noted that the Walk-12G walking scale meets the criteria for clinical trials. King et al. (2013) explored the effects of exercise interventions and found that both Agility Boot Camp and treadmill training improved mobility, with the ABC group showing greater postural sway improvements. They concluded that outcome measures at the structure/function level were the most effective at detecting changes after exercise. Additionally, Klucken et al. (2013) developed the eGaIT system, a biosensor-based gait analysis tool that successfully distinguished PD patients from controls with 81% accuracy in UPDRS-III classification. The text also mentions a table of commonly used tests for assessing walking in PD.

THREE-DIMENSIONAL MOTION ASSESSMENT OF GAIT IN PD

The text outlines several studies and methods for assessing gait and mobility in individuals with Parkinson's Disease (PD). Mirek et al. (2007) used three-dimensional movement analysis to assess gait in 32 PD patients across stages I-III of the disease. They found significant differences between PD patients and controls in spatiotemporal gait parameters, with PD patients exhibiting slower cadence, reduced walking speed, shorter step length, and longer times for single and double support. Additionally, PD patients had reduced lower limb joint movement ranges and delayed swing phases compared to controls. Lewek et al. (2010) studied early PD patients and found that although gait velocity and arm swing magnitude were similar between PD patients and controls, PD patients exhibited significantly greater arm swing asymmetry, with an asymmetry angle of 13.9%, compared to 5.1% in controls. This asymmetry was a distinguishing factor between early PD patients and healthy individuals. Morris et al. (2005) used three-dimensional gait analysis to investigate whether PD patients have a central amplitude regulation disorder, finding evidence for such a disorder in PD patients, particularly in response to medication and attentional strategies. Speciali et al. (2013) conducted a study with PD patients and healthy controls, comparing gait under free walking and dual-task (DT) conditions. They found significant gait impairment in the PD group during DT walking, with a noticeable difference in Gait Deviation Index (GDI) between the groups.

Tomlinson et al. (2014) reviewed physiotherapy techniques for PD and highlighted a range of outcome measures commonly used in PD assessments, including gait outcomes (e.g., walk tests, walking speed, cadence, stride length), functional mobility and balance outcomes (e.g., Timed Up and Go, Berg Balance Scale), and fall-related data (e.g., fall diaries, Falls Efficacy Scale). These outcome measures are widely used to evaluate mobility and balance in PD patients and are critical for monitoring disease progression and treatment effectiveness. (26)

ACTIVITIES-SPECIFIC BALANCE CONFIDENCE SCALE [ABC SCALE

The Activities-Specific Balance Confidence (ABC) Scale is a subjective tool used to measure a patient's confidence in maintaining balance during various everyday tasks without falling or feeling unsteady. It consists of a 16-item questionnaire, where each item is rated on a scale from 0 to 100, with 0 indicating a lack of confidence and 100 representing complete confidence. The total score is calculated by summing the individual item scores and dividing by the number of tasks. Psychometric evaluations of the ABC scale have been conducted in PD patients, typically during the mild to moderate phases of the disease. Studies have shown excellent test-retest reliability in some cases, while others have reported moderate to good sensitivity and specificity. There were no floor or ceiling effects observed. However, the correlation between the ABC scale and functional clinical tests has been found to be poor to moderate. Advantages of the ABC scale include its simplicity, ease of administration, quick completion time, and relevance to daily living activities. It does not require special equipment. However, as a subjective measure, it carries a higher risk of error. It is not strongly correlated with most functional balance tests and does not provide insights into the specific type of balance issues a patient may face. Additionally, the ABC scale is not suitable for use with cognitively impaired patients. The ABC scale is recommended by the Neurology section of the American Physical Therapy Association for patients in stages 1-3 of the Hoehn and Yahr scale, as well as by The Movement Disorders Society Rating Scales Committee.

BERG BALANCE SCALE

The Berg Balance Scale (BBS) is a 14-item objective tool used to assess balance in adults during common daily activities, such as sitting, standing, and changing positions. Each task is rated based on the patient's ability to perform it independently, with scores ranging from 0 to 4, where 4 indicates the highest level of function. The maximum possible score is 56 points. The BBS is frequently used in Parkinson’s Disease (PD) patients, particularly in mild to moderate stages. It is relatively easy to implement but requires some equipment. Studies have reported excellent interrater reliability (ICC = 0.84–0.95), test-retest reliability (ICC = 0.80), and internal

consistency (Cronbach's alpha = 0.92–0.95). However, floor effects can occur in stages 4 and 5 of the Hoehn and Yahr (H&Y) scale, and a ceiling effect is evident in the early stages, making the BBS less effective for assessing postural instability in the early stages of PD. Despite its widespread use, the BBS has limitations. It was originally designed for elderly populations and may not be the best tool for evaluating PD patients, as it fails to effectively identify those at risk of falling. Studies by Leddy et al. (19) and Duncan et al. (21) showed that while the BBS has moderate reliability, its sensitivity and specificity in distinguishing fallers from non-fallers are not particularly strong. Additionally, the BBS focuses primarily on static balance and does not assess reactive postural control, which is essential for fall prevention. The Movement Disorders Society Rating Scales Committee recommends the BBS, acknowledging both its advantages, such as ease of administration and quick assessment time, and its limitations, including the ceiling effect, limited scope, and equipment requirements.

BALANCE EVALUATION SYSTEMS TEST

The BES Test (Balance Evaluation Systems Test) is a comprehensive 36-item clinical tool designed to assess balance disorders. It evaluates postural control through six distinct subscales: mechanical constraints, limits of stability, anticipatory postural adjustments, postural response to induced loss of balance, sensory orientation, and gait. Each item is scored from 0 (indicating the worst performance) to 3 (indicating the best performance), with the total score being the sum of all items. Additionally, each category provides its own score, which helps identify specific mechanisms of postural control that may be impaired. The authors offer paper and video instructions to ensure proper administration, with a full assessment taking approximately 30 minutes, although it can take longer in clinical practice, especially when evaluating Parkinson's Disease (PD) patients, with assessments sometimes exceeding 40 minutes. For clinical settings requiring quicker assessments, there are two shorter versions of the BES Test: the Mini-BES Test and the Brief-BES Test. These versions are less time-consuming and may offer more practical utility in clinical practice. The Brief-BES Test includes one item from each category of the full version, totaling six items.

FULLERTON ADVANCED BALANCE SCALE

The FAB (Four Square Step Test) Scale is designed to assess both static and dynamic balance under various sensory conditions. It was initially developed to measure balance in higher-functioning, active elderly adults. The scale consists of 10 items, each rated on a 5-point ordinal scale, and evaluates static and dynamic postural control. The total score ranges from 0 to 40 points, with higher scores indicating better balance. Detailed administration instructions can be found in the original publication. Although the FAB scale has been used in a few studies on Parkinson's Disease (PD), it has mainly been assessed in patients with mild to moderate disease. The scale demonstrates excellent test-retest reliability in PD patients, and no ceiling effect has been reported. However, it has been primarily used in specific research settings, with only a limited number of studies employing it to assess postural control in PD patients. The advantages of the FAB scale include its simplicity, ease of administration, and the fact that it is quicker to perform than other tools like the BBS or Mini-BES Test. It also helps assess postural control under daily activity conditions, providing insights into the efficiency of various postural control mechanisms. However, there is conflicting information about the scale's sensitivity and specificity in distinguishing between fallers and non-fallers in PD, which may be seen as a limitation. Additionally, the Movement Disorders Society Rating Scales Committee does not recommend the FAB scale due to insufficient clinometric evidence in PD.

FUNCTIONAL REACH TEST

The Functional Reach Test (FRT) is designed to assess balance in adult populations by measuring the maximum distance a person can reach forward while standing in a fixed position. This test has been widely used in Parkinson's Disease (PD) patients, primarily for individuals in stages 1 to 3 of the Hoehn and Yahr scale. Clinometric properties of the FRT have shown variable results. According to Lim et al. (34), the interrater reliability was moderate (ICC = 0.64). Test-retest reliability has been reported as excellent in some studies (ICC = 0.84–0.93), particularly for patients with a history of falls, but lower (ICC = 0.42) for non-falling patients. Kerr et al. (8) found a significant difference in FRT scores between fallers and non-fallers in PD patients ($p < 0.05$). However, Behrman et al. (38) reported that the sensitivity of the FRT for predicting fall risk was only 30%, though it had a high positive predictive value (90%) for individuals with a positive history of falls. The test's specificity was 92% for patients without a history of falls, indicating that it could effectively identify those at low risk. The FRT has several advantages: it is easy to administer and requires minimal equipment. However, its ability to discriminate between fallers and non-fallers in PD is debated, as shown by the varying sensitivity and specificity results. Despite this limitation, the FRT is recommended by the Neurology Section of the American Physical Therapy Association (for stages 2–3 of the Hoehn and Yahr scale) and the Movement Disorders Society Rating Scales Committee.

PUSH AND RELEASE TEST

The Push and Release Test is an updated version of the retropulsion or pull test, developed to offer a more sensitive and consistent assessment of postural stability in Parkinson's Disease (PD) patients. Foreman et al. noted that the pull test was not effective at predicting falls in PD patients, whereas the Push and Release Test provided better results. During the test, an examiner places their hands on the patient's back, prompting the patient to lean back. The examiner then suddenly removes their hands, and the patient's postural response is rated on a scale from 0 to 4, with 0 indicating the best response (no fall) and 4 indicating the worst (fall).The Push and Release Test is noted for its adequate interrater reliability, good to excellent validity, and high sensitivity and specificity in differentiating between fallers and non-fallers. Its advantages include being easy to administer, time-efficient, and requiring no special equipment. However, the test has limitations: it assesses only one aspect of balance and does not provide insight into the specific types of balance problems the patient may experience. Despite these limitations, the test is recommended by the Neurology section of the American Physical Therapy Association (APTA) and is part of the Unified Parkinson's Disease Rating Scale (UPDRS).

TINETTI BALANCE SCALE

The Tinetti Test, also known as the Performance-Oriented Mobility Assessment (POMA) or Tinetti Mobility Test (TMT), was developed by Mary Tinetti to assess gait, balance, and the risk of falling in elderly individuals. It takes approximately 10 minutes to complete, during which the patient is asked to perform 16 functional tasks, 9 of which focus on balance assessment. The total score is 16 points. According to Contreras et al., the Tinetti Balance Scale is correlated with the occurrence of falls. Some research has shown excellent interrater reliability (ICC = 95%), regardless of the researcher's age or experience. However, a floor effect is observed at stages 4 and 5 of Hoehn & Yahr. In the Korean version of the Tinetti Mobility Test, interrater reliability for the balance assessment section ranged from 0.94 to 0.98, with an ICC of 0.97, indicating excellent reliability. The test-retest reliability also had an ICC of 0.97. A balance score of 14 has been identified as the cutoff with the highest sensitivity (81%) and specificity, useful for predicting falls in PD patients (75%). The advantages of the Tinetti Test include its simplicity, ease of administration, and use of basic equipment. However, it has limitations, including limited clinometric evidence in PD populations and the presence of a floor effect at later stages of the disease. Another version, the Tinetti Falls Efficacy Scale, is used to measure a patient's fear of falling, although it is less commonly used in PD research. The Movement Disorders Society Rating Scales Committee has suggested caution in using the Tinetti test due to the lack of clinometric evidence in PD.

TIMED UP AND GO

The Timed Up and Go (TUG) test involves the patient sitting in a chair with their back against the seat. The patient is then instructed to walk 3 meters at a normal speed, turn around, and walk back at a comfortable and safe pace. The time it takes from start to finish, measured by a stopwatch, is recorded when the patient's buttocks touch the seat again. This test was originally designed to measure mobility in elderly individuals and has proven to be a useful tool for assessing locomotor performance in people with Parkinson's disease. The TUG test is characterized by excellent interrater reliability and adequate to excellent test-retest reliability. It has good sensitivity and specificity in predicting fall risk. Its advantages include simple administration, time-effectiveness, and the lack of need for special equipment. However, a major disadvantage is that the test does not provide a comprehensive assessment of balance, as it primarily evaluates feedforward postural control, without addressing feedback control aspects. Despite this, the TUG test is recommended by the Movement Disorders Society Rating Scales Committee for use in clinical practice. (27)

CURRENT TREATMENT AND MANAGEMENT OF PARKINSON'S DISEASE

1.Pharmacological Treatment

Levodopa

The cornerstone of current Parkinson's disease (PD) treatment is levodopa-based therapy, which aims to replenish the dopamine levels in the depleted striatum. As mentioned earlier, dopamine cannot cross the blood-brain barrier (BBB) and thus cannot be directly used to treat PD. However, its precursor, levodopa, can cross the BBB and is used as a therapeutic agent. Once it is absorbed and crosses the barrier, levodopa is converted into dopamine by the enzyme DOPA decarboxylase.

Dopamine agonists

Dopamine receptor agonists were introduced in 1978 for the treatment of Parkinson's disease (PD). The most commonly used agonists contain an ethanolamine group and can be classified into two categories: ergot-derived and non-ergot-derived, depending on their receptor specificity. These medications enhance dopamine system function by binding directly to dopaminergic receptors and, unlike levodopa, they do not require conversion into dopamine.

Monoamine Oxidase B (MAO-B) inhibitors

Other medications for Parkinson's disease (PD) work by inhibiting enzymes involved in dopamine metabolism, thereby preserving the levels of endogenous dopamine. One such class is the MAO-B inhibitors. MAO-B is a key enzyme responsible for the breakdown of dopamine, and inhibiting its activity increases dopaminergic activity within the striatum, mediated by the body's own dopamine. The use of these inhibitors helps alleviate motor symptoms in PD patients.

Amantadine

Amantadine (Symmetrel) was originally developed as an antiviral medication for treating the flu, but it has since been repurposed for Parkinson's disease (PD) treatment. It can help manage symptoms such as rigidity, rest tremor, and occasionally fatigue, providing short-term improvements in PD symptoms. (28)

AGENT	TYPICAL INITIAL DOSE	DAILY DOSE RANGE
Levodopa Formulations		
1.Carbidopa/Levodopa	25 mg carbidopa+100 mg Levodopa ,2-3 daily	200-1200 mg Levodopa
2.Carbidopa/Levodopa sustained-release	50 mg carbidopa+200 mg Levodopa, 2 daily	200-1200 mg Levodopa
3. Carbidopa-Levodopa orally disintegrating tablets	25 mg carbidopa+100 mg Levodopa, 2-3 daily	200-1200 mg Levodopa
COMT Inhibitors		
1.Entacapone	200 mg with each dose of Levodopa/ Carbidopa	600-2000 mg
2.Tolcapone	100 mg with Carbidopa /Levodopa	100-300 mg
DA Agonists		
1.Apomorphine	2 mg subcutaneous	6-18 subcutaneous
2.Bromocriptine	1.25 mg	2.5-15 mg daily
MAO Inhibitors		
1.Rasagiline	1 mg daily	0.5-1 mg
2.Selegiline	5 mg 2 daily	2.5-10 mg
Other medications		
1.Trihexyphenidyl HCl	1 mg 2 daily	2-15 mg
2.Amantadine	100 mg 2 daily	100-200 mg

2.Non-pharmacological Treatment

Non-pharmacological interventions for individuals with Parkinson's disease (PD) have traditionally been viewed as supplementary or "add-on" treatments primarily aimed at alleviating motor symptoms. While physiotherapy, speech-language therapy, and occupational therapy have increasingly become integral to the overall management of Parkinson's disease (PD), other non-pharmacological approaches, such as cognitive training, cognitive behavioral therapy, and art or light therapy, have remained somewhat unconventional and are only now beginning to be incorporated into therapy guidelines.

Physical perspectives

The importance of early physical training delivery is underscored by the recently published consensus statement from the Parkinson's Foundation task force. Patient compliance is a central focus in training-based interventions, particularly long-term adherence, which is essential if non-pharmacological approaches are to effectively contribute to secondary or tertiary disease prevention in the prodromal or clinically manifest phases of Parkinson's disease (PD). Therefore, this section offers valuable, in-depth insights into how to address the daily challenges of securing patient engagement in exercise therapy.

Mental perspectives

The high prevalence of cognitive impairment and affective disorders in people with Parkinson's disease (PD) significantly impacts both quality of life and caregiver burden. Pharmacological treatments often provide limited relief for these symptoms and may even have adverse effects on cognition or alertness. As a result, it is promising to see increasing attention being given to non-pharmacological interventions, with the hope that these approaches will play a key role in the future management of non-motor symptoms. (29)

CONCLUSION

Parkinson's disease (PD) is a progressive neurodegenerative disorder that primarily affects movement, manifesting as tremors, rigidity, bradykinesia, and postural instability. While its exact cause remains unclear, both genetic and environmental factors play a significant role in its onset and progression. Although there is currently no cure for PD, existing treatments, including medication, physical therapy, and surgical interventions like deep brain stimulation (DBS), offer symptomatic relief and help improve quality of life for individuals living with the disease.

Ongoing research continues to explore better treatment options, early detection methods, and potential disease-modifying therapies. Ex vivo models and animal studies are crucial in providing valuable insights into the disease mechanisms and testing new therapeutic approaches. Increasing awareness, early diagnosis, and a multidisciplinary approach to care are essential in improving outcomes. As research advances, there is hope for more effective, personalized treatments that not only manage symptoms but also slow or halt disease progression, ultimately enhancing the lives of those affected by Parkinson's disease.

REFERENCES

1. 1.Sherer TB, S Chowdhury, K Peabody, D Brooks:Overcoming obstacles in Parkinson's Disease. *Movement Disorders* 27(13), 1606-1611 (2012).
2. Chou K: Clinical manifestations of Parkinson Disease.*UpToDate*. Retrieved on 7/22/2013 from www.uptodate.com. (2013).
3. Parkinson's Disease Foundation: Statistics on Parkinson's. Retrieved from http://www.pdf.org/en/parkinson_statistics. (2013).
4. Fritsch T, K Smyth, M Wallendal, T Hyde, G Leo, D Geldmacher: Parkinson Disease: Research update and clinical management. *Southern Medical Association* 105(12), 650-656 (2012).
5. Wright Willis A, B Evanoff, M Lian, S Criswell, B Racette: Geographic and ethnic variation in Parkinson Disease: A population-based study of US Medicare Beneficiaries. *Neuroepidemiology*, 34, 143-151 (2010).
6. Chinta S, C Lieu, M Demaria, R Laberge, J Campisi, J Anderson: Environmental stress, ageing, and glial cell senescence: A novel mechanistic link to Parkinson's Disease? Journal of Internal Medicine 273, 429-436 (2013).
7. 7.Parkinson J. An Essay on the Shaking Palsy. London: Sherwood, Neely, and Jones; 1817.
8. 8.Schrag A, Horsfall L, Walters K, et al. Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. Lancet Neurol. 2015;1:57–64
9. 9.Parkinson's Disease Foundation Statistics on Parkinson's.
10. 10.Rumayor MA, Arrieta O, Sotelo J, et al. Female gender but not cigarette smoking delays the onset of Parkinson's disease. Clin Neurol Neurosurg. 2009;111:738–741.
11. 11.Simonson W, Hauser RA, Schapira AHV. Role of the pharmacist in the effective management of wearing-off in Parkinson's disease. Ann Pharmacother. 2007;41:1842–1849.
12. 12.Liu R, Guo X, Park Y, et al. Caffeine intake, smoking, and risk of Parkinson disease in men and women. Am J Epidemiol. 2012;175:1200–1207
13. 13.Soreq L, Ben-Shaul Y, Israel Z, et al. Meta-analysis of genetic and environmental Parkinson's disease models reveals a common role of mitochondrial protection pathways.
14. Prof Yoav Ben-Shloma,Sirwan Darweesh et al ;The epidemiology of Parkinson's disease , The Lancet. 2024 Jan 20:P283-292
15. Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. J Neural Transm (Vienna). 2017 Aug;124(8):901-905.
16. Mabtrila RJ, Rinne UK. Epidemiology of Parkinson's disease in Finland. *Acta Neurologica Scandinavica*. 1976;53(2):125-130.
17. Zirra A, Rao SC, Bestwick J, Rajalingam R, Marras C, Blauwendraat C, Mata IF, Noyce AJ. Gender differences in the prevalence of Parkinson's disease. *Mov Disord Clin Pract*. 2023;10(1):86–93. doi: 10.1002/mdc3.13584.
18. Ben-Joseph A, Marshall CR, Lees AJ, Noyce AJ. Ethnic variation in the manifestation of Parkinson's disease: A narrative review. *J Parkinsons Dis*. 2020;10(1):31–45. doi: 10.3233/JPD-191763.
19. 19.Willis AW, Evanoff BA, Lian M, Criswell SR, Racette BA. Geographic and ethnic variation in Parkinson disease: A population-based study of US Medicare beneficiaries. *Neuroepidemiology*. 2010; 34(3):143–151. doi: 10.1159/000275491.
20. Gamber KM. Animal models of Parkinson's disease: New models provide greater translational and predictive value. *Biotechniques*. 2018;64(3):210–211.

21. Willis AW, Evanoff BA, Lian M, Criswell SR, Racette BA. Geographic and ethnic variation in Parkinson disease: A population-based study of US Medicare beneficiaries. *Neuroepidemiology*. 2010;34(3):143–151. doi: 10.1159/000275491.
22. Antonosante A, Castelli V, Sette M, Alfonsetti M, Catanesi M, Benedetti E, Ardini M, Cimini A, d'Angelo M. Neuroprotective effects of the PPARβ/δ antagonist GSK0660 in in vitro and in vivo Parkinson's disease models. *Biol Res*. 2023;56:27. doi: 10.1186/s40659-023-00438-1.
23. Loryan I, Fridén M, Hammarlund-Udenaes M. The brain slice method for studying drug distribution in the CNS. Fluids Barriers CNS. 2013;10(1):6.
24. Baumuratov AS, Antony PMA, Ostaszewski M, He F, Salamanca L, Antunes L, Weber J, Longhino L, Derkinderen P, Koopman WJH, Diederich NJ. Enteric neurons from Parkinson's disease patients display ex vivo aberrations in mitochondrial structure. Neurobiol Dis. 2016; 94:33-44. doi: 10.1016/j.nbd.2016.08.004
25. Thome AD, Atassi F, Wang J, Faridar A, Zhao W, Thonhoff JR, Beers DR, Lai EC, Appe SH. Ex vivo expansion of dysfunctional regulatory T lymphocytes restores suppressive function in Parkinson's disease. npj Parkinson's Dis. 2021;7:41. doi:10.1038/s41531-021-00188-5
26. Opara J A, Małecki A, Małecka E, Socha T. Motor assessment in Parkinson`s disease. Ann Agric Environ Med. 2017; 24(3): 411–415.
27. Krzysztoń K, Stolarski J, Kochanowski J. Evaluation of balance disorders in Parkinson's disease using simple diagnostic tests—not so simple to choose. Front Neurol. 2018; 9:932.
28. Zahoor I, Shafi A, Haq E. Pharmacological Treatment of Parkinson's Disease. In: Stoker TB, Greenland JC, editors. Parkinson's Disease: Pathogenesis and Clinical Aspects Brisbane (AU): Codon Publications; 2018 Dec 21. Chapter 7.
29. Kalbe E, Bloem BR, Nieuwboer A, et al. Special issue: Non-pharmacological interventions for people with Parkinson's disease: are we entering a new era? *J Parkinsons Dis*. 2024;14(s1)