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Cognition and Quality of Life in Parkinson's Disease

Parkinson Hastalığında Biliş ve Yaşam Kalitesi

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ABSTRACT

Parkinson's disease is a neurodegenerative disease known for its progressive prognosis which may be associated with delay in diagnosis. Its etiology can be composed of different modalities involving genetic, psychiatric, and social factors. Findings and observations from clinical settings, motor symptoms such as bradykinesia, tremor, and rigidity have been reported. In addition, non-motor symptoms, such as depression and cognitive dysfunctions have been demonstrated. Moreover, decrease in quality of life has been reported in people with Parkinson's disease diagnosis. Although multidisciplinary studies on Parkinson's disease indicated general the molecular and radiological findings of the disease, inconsistent data are reported in terms of modalities such as cognitive functioning, depression, and quality of life. The present study aims to present the current perspective in the context of quality of life by examining the findings reported in the cognitive and psychiatric context of Parkinson's disease. According to the findings of this study, cognitive impairments that can be identified based on the course of the disease, manifesting in various forms such as attention, memory, and visual-spatial skills, negatively impact the quality of life for patients. The emergence of depression or depression-like symptoms can further decrease the overall quality of life for individuals diagnosed with Parkinson's disease.
Keywords: Parkinson's disease, cognitive impairment, quality of life

ÖZ

Nörodejeneratif bir hastalık olan Parkinson hastalığının yavaş ve ilerleyici olması tanıda gecikmeler yaşanması ile ilişkili olabilmektedir. Genetik, psikiyatrik ve çevresel faktörler gibi farklı değişkenlerin dahil olduğu kompleks bir etiyolojiye sahiptir. Klinik bulgularında bradikinezi, tremor ve rijidite gibi motor semptomlarının yanı sıra depresyon ve bilişsel bozulmalar gibi non-motor semptomlar bildirilmiştir. Bilişsel bozukluklar ve yaşam kalitesinde düşüşlerin de seyredebileceği Parkinson hastalığı hakkında yapılan multidisipliner çalışmalar hastalığın moleküler ve radyolojik bulgularını raporlasa da bilişsel disfonksiyon ve depresyon gibi modaliteler bakımından tutarsız veriler sunulmuştur. Bu çalışmada, Parkinson hastalığının bilişsel ve psikiyatrik bağlamda bildirilen bulguların irdelenerek güncel perspektifin yaşam kalitesi bağlamında sunulması amaçlanmaktadır. İncelemeler doğrultusunda; hastalığın seyrine bağlı olarak görülebilen ve dikkat, bellek, görsel-uzamsal beceriler gibi farklı modalitelerde ortaya çıkan bilişsel bozuklukların hastaların yaşam kalitesini olumsuz yönde etkilediği raporlanmıştır. Depresyon veya depresyon benzeri semptomların ortaya çıkması, Parkinson hastalığı tanısı konan bireylerin genel yaşam kalitesini daha da düşürebilir.
Anahtar sözcükler: Parkinson hastalığı, bilişsel bozukluklar, yaşam kalitesi

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, following Alzheimer's disease. It was initially identified by James Parkinson in 1817 and termed as shaking palsy. Neurologists Jean Martin Charcot and William Gowers made significant contributions to the understanding of the disease in the 19th century, coining the term "Parkinson" (Voon et al. 2011, Zhao et al. 2018). PD affects approximately 3% of the population up to the age of 65, and around 5% of individuals aged 85 and above, on average (Thomas et al. 2017). The incidence and progression rates of the disease have been reported to be higher in men compared to women. However, it has been noted that the mortality rate is higher in women, and the disease tends to progress more rapidly in this demographic. Moreover, the response to treatment for both motor and non-motor symptoms, as well as the risk factors associated with the disease, manifest differently in men and women (Cerri et al. 2019).

When examining the psychiatric medical histories of individuals diagnosed with PD, approximately 15% have been reported to have a family history of PD. Mutations are observed to occur either in an inherited familial

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manner or sporadically, with approximately 5% to 10% of individuals with the disease being identified as carriers (Chu et al. 2021). The majority of mutations are sporadic, and evidence suggests a significant role of genetic factors in the pathogenesis of the disease. Genetic factors have been found to be associated with the age of onset, with patients whose disease onset occurs at age 50 or earlier being reported to have a more influential genetic component (Singleton et al. 2013). In cases observed sporadically, there is a 20-25% incidence of PD among first-degree relatives. The etiology of PD is multifactorial, involving a combination of genetic, environmental, and neurobiological factors. While the underlying mechanisms of PD are not fully understood, significant progress has been made in elucidating key factors in understanding its pathogenesis. Research indicated that that both environmental and genetic factors play a crucial role in the development of PD (Payami et al. 2002). Homozygous mutations in the PARKIN gene, particularly in PARKIN mutations, are among the most common causes of juvenile PD (Shulman et al. 2011). Additionally, sources highlight the PINK1 (PARK 6) mutation as one of the primary causes of early-onset PD. The frequency of this mutation varies across cultural differences, ranging from 1% to 9% (Bonifati et al. 2005). Structural deletions in these mutations are reported to be rare (Trinh and Farrer 2013). PINK1, in conjunction with PARKIN mutations, is responsible for regulating mitochondrial morphology. The mutation of PINK1 has been identified as leading to mitochondrial dysfunction, resulting in the occurrence of PD (Chu et al. 2021). Mitochondrial dysfunction plays a significant role in both sporadic and familial PD. While various theories have been proposed to understand its pathogenesis, investigating mitochondrial dysfunction holds promise for providing new insights into treatment. PD is reported to result from a deficiency of dopamine, a neurotransmitter released from the pars compacta region of the substantia nigra in the midbrain (Klein and Westenberger 2012, Dalle and Mabandla 2018). Symptoms of PD typically have a gradual onset and can progress with age (Simon et al. 2020). In this context, it is noted that there are different clinical motor and non-motor symptoms that can vary between individuals. Motor symptoms commonly include tremor, bradykinesia, and rigidity. Non-motor symptoms may manifest as a decrease in sense of smell, sleep disturbances, or cognitive impairments (Balestrino and Schapira 2020). Cognitive impairments encompassing deficits in attention, memory, and executive functions are common non-motor symptoms of PD.

Recent research has focused on the potential connection between melatonin and cognitive function in PD patients (Tchekalarova and Tzoneva 2023). Melatonin receptors, distributed widely throughout the brain, including regions involved in cognitive processes, have been implicated in PD. Changes in melatonin receptor density and function observed in Parkinson's patients suggest a potential link between melatonin signaling and cognitive decline (Guo et al. 2023). However, the relation is not clear yet. Studies have reported cognitive dysfunction symptoms developing in up to 50% of patients during the course of the disease (Goldman et al. 2020). Furthermore, it has been emphasized that a majority of Parkinson's patients with a prolonged disease duration will suffer from dementia (Hely et al. 2008, Åström 2022). However, the uncertainty of predicting the occurrence of cognitive impairments has maintained ambiguity in the relationship with PD. Apart from comorbid processes, the importance of these symptoms responding to dopaminergic treatment is highlighted when examining the treatment plan. Six main classes of drugs are commonly used to treat motor symptoms of Parkinson's: levodopa, dopamine agonists (DAs), monoamine oxidase type B (MAO B) inhibitors, catechol-O-methyltransferase (COMT) inhibitors, amantadine, and anticholinergic drugs (Fox et al. 2018, Mansuri Reddy et al. 2022). The sensitivity of motor symptoms to levodopa treatment has been emphasized as a significant quality for treating Parkinson's (Postuma et al. 2012). Indeed, the dopamine deficiency, a distinguishing feature of PD, not only contributes to motor symptoms but also plays a crucial role in the development of cognitive deficits. The complex interplay between dopamine pathways, brain regions involved in cognition, and the effects of medications highlights the need for comprehensive approaches to understand and manage cognitive dysfunction in PD.

Apathy often perceived as a decrease in motivation, is commonly observed in PD, and is believed to have a negative impact on quality of life (den Brok et al. 2015, Cong et al. 2022). The indifference present in the behavioral, social, and emotional domains in PD, despite its high prevalence, remains uncertain in terms of its impact. These states of apathy often exhibit similar symptoms associated with changing motivation in patients, particularly in the context of depression, and are related to different comorbid conditions such as anhedonia (Kirsch et al. 2011, Leentjens et al. 2008). Although the findings suggest a potential mechanism between the pathology and cognition of PD, illuminating studies are needed on its relationship and impact on the patient's overall quality of life and comorbid symptoms. This study aims to discuss and address PD in the context of cognitive impairments, depression, and quality of life.

Parkinson's Disease and Non-Motor Symptoms

Non-motor symptoms, observed in nearly all individuals diagnosed with PD, often manifest in a prodromal

manner several years before the onset of motor symptoms (Pfeiffer 2016, Schapira et al. 2017). Although PD is primarily defined as a movement disorder, the presence of non-motor symptoms also shapes the clinical profile of the disease (Goldman and Guerra 2020). These symptoms include a decrease in the sense of smell (hyposmia), anxiety, apathy, fatigue, psychosis, depression, cardiovascular issues, cognitive impairments, sleep disturbances, vision problems, gastrointestinal problems, urinary system issues, and sexual problems (Pfeiffer 2016). A decrease in the sense of smell is observed in more than 90% of individuals with PD. Moreover, the accumulation of Lewy bodies in brain regions related to olfaction has been emphasized as a potential contributor to hyposmia or reduced olfactory ability (Schapira et al. 2017). According to the hypothesis proposed by Braak and colleagues in 2003, PD originates from a pathogen that enters the body through the nasal cavity, later reaching the intestines through swallowing, initiating Lewy pathology in the nose and digestive system (Braak et al. 2003). In this context, it has been debated whether a prion-like process could mediate the progression of PD, suggesting that the disease may start in the peripheral system.

The frequency of cardiovascular problems is known to be at least 50%, with orthostatic hypotension being the most common, increasing the risk of falls (Amara and Memon 2018). Vision problems, such as impaired color discrimination, reduced contrast sensitivity, and dry eye syndrome, are encountered in approximately 73% of Parkinson's patients on average (Pfeiffer 2016, Schapira et al. 2017). In PD, classic insomnia often involves difficulties in maintaining sleep rather than falling asleep (Ratti et al. 2015). These problems, observed in 60-76% of individuals with PD, may be associated with disruptions in the sleep-wake cycle, depression, anxiety, dementia, tremor, dyskinesia, and other motor complications (Iranzo 2016). Also, this may represent a structural indicator of functional impairments in brain networks sustaining visual perception and attention abilities, which could contribute to visual hallucinations. Indeed, voxel-based morphometry studies have demonstrated an association between decreased gray matter in the occipital, temporal, and frontal regions and visual hallucinations (Pezzoli et al. 2021).

Anxiety and depression are neuropsychiatric symptoms that can be observed at any stage of the disease. Indeed, these conditions negatively impact the quality of life of individuals with PD (Balestrino and Martinez-Martin 2017). Considering all non-motor symptoms, a decline in the quality of life is expected for individuals affected by the disease. In the pursuit of enhancing the quality of life, it is valuable to inquire not only about prominent motor symptoms but also about non-motor symptoms that may be overlooked in the clinical picture but directly affect the patient's quality of life. Factors such as the presence of Lewy bodies, gray matter reduction, and other considerations can provide insights into understanding and explaining sleep disorders, visual hallucinations, cognitive impairments, and the profile of dementia observed in the course of the disease. Therefore, the recognition and exploration of non-motor symptoms are crucial for a comprehensive understanding of PD and for efforts aimed at improving the overall well-being of individuals affected by the condition.

Parkinson’s Disease and Cognitive Impairments

The most prevalent cognitive impairments observed in PD are associated with attention, executive function, and visual-spatial processing stages (Biundo et al. 2017a). Bradyphrenia that is characterized by slowed thinking or prolonged information processing time, has been reported as a prominent feature of subcortical dementias, progressing in parallel with the highlighted bradykinesia in PD (Biundo et al. 2017a). It was reported that the PD group required significantly longer time than the healthy control group to complete the A and B sub-forms of the Trail Making Test in which attention, motor speed and executive functions can be examined (Çekok et al. 2023). Moreover, the problems in executive functions in the disease can be considered indicative of early alterations in dopaminergic stimulation in the frontal cortex (Bronnick et al. 2011). Additionally, impairments in visuo-spatial processes have been shown to pose a higher risk of dementia in Parkinson's, with direct associations to the posterior neuropathological disposition of the temporal and parietal cortex (Çorakcı and Hanoğlu 2021).

Experiencing cognitive impairments, unfortunately, may have an impact on motor symptoms in PD, as well. Therefore, a functional decline is generally observed in individuals who develop dementia in the later stages of the disease. To accurately discern this bidirectional interaction, comprehensive neuropsychological assessment is recommended. Moreover, cognitive impairments observed in the PD significantly influence its prognosis and management, both at the onset and throughout its progression (Çorakcı and Hanoğlu 2021). The pathology in PD dementia can spread in a manner that extensively affects the cerebral cortex, including visual cortex areas. It was speculated that the transition of pathology from subcortical to cortical regions may execute a significant role in explaining the progression of dementia in PD (Armstrong 2017).

Dual tasks, also referred to as simultaneous or associated tasks, are prerequisites for the functional performance of various daily life activities. Typically, during the execution of daily life activities, the simultaneous and automatic performance of both motor and cognitive tasks is expected. However, in the presence of motor or cognitive impairments, a considerable amount of attention is required to fulfill even basic daily life activities (Floriano et al. 2015). Similarly, impaired mobility and cognition, along with automatically executed movements, demand increased attention to sustain. Consequently, impairments in dual-task abilities may occur (Friz et al. 2016). The diminished attention capacity and difficulties in sustaining attention in PD can lead to secondary issues in cognitive and motor tasks during daily life activities. Indirectly, this situation is believed to adversely affect the quality of life skeptically.

Lewy body dementia (LBD) is a neurodegenerative disorder encompassing memory impairment and various other cognitive dysfunctions in addition to memory problems (Abeysuriya and Walker 2015). Visual hallucinations and fluctuations in parkinsonism are observed in LBD (Hovendon and Kaufman 2015). Clinically, cognitive impairment, behavioral and psychiatric disorders, along with physical symptoms, characterize the disease (Donaghy and McKeith 2014, Jellinger 2018). PD and LBD are closely related neurodegenerative disorders sharing overlapping clinical and pathological features. Abnormal accumulations of α-synuclein protein, known as Lewy bodies (LBs), are distinguishing features of both PD and LBD, and their presence in specific brain regions contributes to similarities between these disorders. Cognitive impairments in PD may manifest early in the course of the disease and progress over time. Executive function impairment, attention deficits, and impaired visual-spatial abilities are common cognitive dysfunctions in PD. These impairments are attributed to the spread of LBs beyond the Substantia Nigra into cortical areas, affecting crucial brain networks essential for cognitive processing. In LBD, cognitive symptoms are a fundamental characteristic, specifically visual hallucinations, and fluctuations in attention. The widespread distribution of LBs in cortical regions forms the basis of cognitive dysfunction, disrupting neurotransmitter systems and cellular pathways contributing to cognitive impairment. The relationship between PD, LBD, and cognitive dysfunction may stem from the presence of LBs and their effects on neural networks. The observed cognitive impairments in the spectrum of these disorders emphasize the importance of considering underlying neuropathology in diagnosing, treating, and managing cognitive dysfunction.

Cognitive fluctuations generally arise from alterations in cognition, attention, and arousal similar to delirium. Additional symptoms associated with these changes include behavioral inconsistency, problems in speech, and fluctuating attention (McKeith et al. 2017). Fluctuations in attention or alertness have been reported to be directly related to thalamic damage and cholinergic imbalance in the studies (Delli et al. 2015, Erskine et al. 2017, Jellinger 2018). This condition disrupts visual-perceptual and attention functions, potentially leading to the emergence of visual hallucinations as symptoms (Yoshizawa et al. 2013, Jellinger 2018, Pezzoli et al. 2021,). Approximately 80% of individuals with Lewy body dementia (LBD) experience recurrent, complex visual hallucinations, serving as a clinical marker for this diagnosis (McKeith et al. 2017).

The brain's default network is a set of regions that is spontaneously active during passive moments. As the severity of cognitive impairment increases, a decrease in connectivity within the Default Mode Network (DMN) is observed in neuroimaging findings (Baggio et al. 2015). However, two distinct studies investigating the continuity of cognitive impairment associated with Parkinson's disease (PD) have reported findings suggesting an increase in DMN connectivity. In the PD-MCI (Parkinson's Disease with Mild Cognitive Impairment) group, compared to both PD-NC (Parkinson's Disease without Cognitive Impairment) and healthy control (HC) groups, functional connectivity of DMN's midline and frontal/temporal components with posterior components of the Dorsal Attention Network (DAN) and Frontoparietal Network (FPN) was observed to increase. However, this hyperconnectivity was found to have a negative relationship with visual-spatial function scores. Nevertheless, in this study, connectivity increase was primarily observed in inter-network connections. Rather than a direct increase in connectivity, the partial observed effect may be mediated by reduced connectivity between DAN nodes and core networks. This could result in components less connected to other DAN regions losing the expected negative correlation with the DMN of the network (Baggio et al. 2015). The increase in the DMN in people with PD-MCI may contribute to understanding the fluctuations in attention and other cognitive components.

In a study conducted by Ruppert and colleagues, an investigation of the Default Mode Network (DMN) through the Independent Component Analysis (ICA) revealed a reduction in PD-NC (PD without cognitive impairment) compared to healthy control participants. However, in PD-MCI (Parkinson's Disease with Mild Cognitive Impairment), increased DMN connectivity was found compared to both healthy controls and PD-NC. It was noted that general cognition scores, visual-spatial function scores, and attention scores exhibited a significant negative relationship with DMN intra-connectivity, while emphasis was placed on the positive relationship with

executive function scores (Ruppert et al. 2021). In the previous study by Ruppert et al., metabolic changes related to PD were highlighted (Ruppert et al. 2020).

Depression and Anxiety in Parkinson's Disease

PD and the accompanying depression or depressive mood are subjects of ongoing research to determine whether they stem from psychosocial difficulties or neurodegenerative changes. The pathologic depressive mood experienced by individuals can be associated with a more negative evaluation of motor symptoms by the patients themselves (Klein and Westenberg 2012). Depression is commonly observed in individuals with PD, increasing the burden of the disease, causing insomnia, and decreasing the overall quality of life (Marinus et al. 2018). Anxiety and depression are neuropsychiatric symptoms that can occur at any stage of PD (Pfeiffer 2016, Amara and Memon 2018). In a study with Parkinson's patients, it was reported that non-motor symptoms such as anxiety and depression were more prevalent in women compared to men (Lee and Gibert 2016, Georgiev et al. 2017). Anxiety disorders are the second most commonly observed psychiatric condition in PD, following depression. Studies have reported an incidence rate of 30-40% for anxiety disorders in individuals with PD (Lo et al. 2019). It has been noted that the prevalence of anxiety disorders is five times higher in Parkinson's patients who show symptoms of depression and receive a diagnosis compared to those who exhibit only depression symptoms (Qureshi et al. 2012).

The relationship between anxiety, depression, and PD remains complex, involving both psychosocial factors and potential neurodegenerative changes, and further research is needed to unravel these intricacies. PD is also characterized by disruptions in frontostriatal and mesocorticolimbic dopaminergic circuits, which play a significant role in depression and anxiety in PD. The loss of noradrenergic and serotonergic neurons in PD can contribute to mood problems. Additionally, levodopa, while primarily acting on dopaminergic systems, can lead to serotonin and norepinephrine deficiency through non-dopaminergic pathways, potentially resulting in depression and anxiety (Ehgoetz et al. 2017). It is essential to be mindful of potential mood-related side effects, particularly with prolonged levodopa use. Considering these potential side effects, it is crucial to recognize the possibility of mood problems in individuals receiving levodopa treatment. Therefore, in approaches to individuals undergoing levodopa therapy, the evaluation of depression and anxiety concerning the adaptation and participation in the rehabilitation process should not be overlooked. In the treatment of depression and anxiety, antidepressants often constitute the first-line pharmacological intervention. However, non-pharmacological methods such as exercise and cognitive-behavioral therapy can also be utilized in the treatment procedure. Cognitive-behavioral therapy, in particular, is noted to be effective in managing depression and anxiety in individuals with PD (Egan et al. 2015).

Therefore, a comprehensive approach that combines pharmacological and non-pharmacological strategies is often recommended to address mood-related issues in individuals with Parkinson's disease. Studies emphasized that there may be a bidirectional relationship between imbalance in microbial processes in the gut and psychological disorders. Dietary modalities such as probiotic intake may play an active role in resolving this situation. Moreover, the intake of probiotic bacteria is reported to have significant effects on influencing the gut-brain axis, alleviating functionality in psychiatric disorders, and reducing mood, cognition and pain sensitivity (Van Hemert et al. 2016). The microbial balance within the gut microbiota, which plays a role in both physical and psychological health, can be maintained through the inclusion of probiotics. The establishment of this balance is known to influence the process of treating anxiety and depression (Doğan et al. 2018).

The hypothalamic–pituitary–adrenal (HPA) axis is the primary neuroendocrine response system to stress. It has been reported that the HPA axis affects the composition of the gut microbiota and may also increase gastrointestinal permeability. This imbalance in the gut microbiota may cause overactivation of the HPA axis. The disruption and overactivation of the HPA axis lead to a decrease in neurotrophic factors. With this situation, neurochemical order may be disrupted and many psychiatric diseases, especially depression, is likely to occur (Stahl and Muntner 2021). Each probiotic to be taken in sufficient amounts may cause changes in the mood of the person and will also affect the comfort zone in daily life activities. Therefore, balancing gastrointestinal functions with the probiotic mechanism will provide improvements in tackling depressive mood and so quality of life.

Parkinson’s Disease and Quality of Life

Researchers working in the field of health sciences prefer to define the concept of quality of life (QoL) as the individual's feeling of well-being, perception of one’s own health status, and especially self-evaluation regarding

his/her condition in general terms (Opara et al. 2012, Kuhlman et al. 2019). Since chronic and progressive disorders influence an individual's life in multiple ways, QoL related to health status is especially taken into consideration while managing such diseases (Kuhlman et al. 2019). Accordingly, it has been shown that both motor and non-motor symptoms of PD directly or indirectly influence patients' QoL. Especially, the impact of non-motor symptoms may have more severe effects on QoL (Kuhlman et al. 2019). While the severity of disease, sleep disorders, fatigue, and fluctuations in motor functions have influence on QoL, it is reported that depression, anxiety, and cognitive impairments may have worse impact on QoL (Lee and Gilbert 2016). Furthermore, in individuals diagnosed with PD, tremor, known as the major motor symptom, prominently stands out among the primary obstacles to the functional execution of daily life tasks, while the presence of depressive mood and anxiety can potentially diminish the quality of life. Severity of motor and non-motor symptoms may differ depending on the progression of the disease. Therefore, it is emphasized that when understanding QoL, the necessity of taking into account the different stages of the disease should be acknowledged (Çolakoğlu 2014).

In the PD, the frequency of functional problems in the upper extremity, which encompasses the shoulder, elbow, wrist, and fingers and is a complex structure, is reported to be 70% (Alreni et al. 2017). Moreover, impairments in physical functions related to the upper extremities are observed due to symptoms such as bradykinesia, tremor, and rigidity. As the disease progresses, these impairments lead to limitations in daily life activities such as dressing and eating (de Freitas et al. 2017, Kalkan et al. 2020). Such symptoms observed in individuals with PD diagnosis, may result in delay in initiating an action/behavior, difficulty in accomplishing sequential tasks, and reduction in speed and strength of a movement. Accordingly, impairments of functions in upper extremities are likely to occur (Mak et al. 2015, Kalkan et al. 2020). From another perspective, due to impairment of such functions, the socioeconomic burden of both the patient and the society increases and accordingly, in turn, the QoL decreases (Alreni et al. 2017). Skill is situated within the realm of upper extremity functions. The occurrence of impairments in manual dexterity is well-documented, particularly at various levels of PD (Hwang and Song 2016, Soke et al. 2019). Difficulties in using fingers and hands either singly or together are reported to be prevalent in almost every stage of the disease. Furthermore, it is noted that as the disease progresses, factors such as fatigue and cognitive impairments accompany the challenges experienced in daily activities (de Freitas et al. 2017, Proud et al. 2013). Significant disruptions in daily life activities are observed during episodes of severe tremor (Campbell et al. 2015). Accordingly, the psychological impact on individuals, including feelings of shame, depression, and anxiety, arises from the impairments in activities due to tremor-related effects, contributing to a decrease in the individual's overall quality of life (Chandran and Pal 2013). As the disease progresses into advanced stages, dementia may manifest, and motor symptoms can become more pronounced. Cognitive decline in PD-dementia encompasses a range of deficiencies, including primary memory impairment, executive function dysfunction, and difficulties in visual-spatial skills. These multifaceted impairments, alongside motor symptoms, can adversely affect the quality of life for patients. Carefully planned treatment and cognitive rehabilitation, taking into account the course of the disease, can positively contribute to enhancing life with PD. Undoubtedly, the management of psychiatric symptoms such as depressive mood and anxiety can also be achieved as the quality of life improves and is sustained in patients.

Treatment and Cognitive Rehabilitation

PD is considered one of the most successful neurodegenerative diseases in terms of medical treatment. However, there is currently no effective treatment method that halts or slows down the progression of the disease (Kakkar and Dahiya 2015). Treatments for PD primarily include pharmacological therapy, device-assisted therapy, and rehabilitation (Armstrong 2020). The efficacy of drug treatments has been investigated, with a focus on examining various psychotropic drug types. However, different psychotropic drug types directly associated with Parkinson's have not been simultaneously or in terms of usage patterns (Goldstein et al. 2018). Particularly, women are considered a high-risk group for the use of psychotropic drugs in the treatment of conditions such as depression, anxiety, and sleep problems that occur after menopause (Girgus et al. 2017, Sarwar 2018). McFarthing et al. have initiated a study with the aim of halting or slowing down PD and have reviewed existing clinical trials in the literature. Through this review, they have identified 145 registered and ongoing studies. Among these, 57 clinical trials aim to develop disease-modifying treatments in the long term and focus on achieving symptomatic relief. Analyses have shown that only one-third of trials targeting symptomatic relief specifically address non-motor symptoms. This finding emphasizes the importance of research and development for the treatment of non-motor symptoms since it is highly correlated to the overall quality of life of patients. Studies indicating that non-motor symptoms are as widespread and severe as motor symptoms highlight that untreated non-motor symptoms negatively impact the quality of life of patients. By all means, this does not

encompass the treatment of non-motor symptoms using symptom-targeted drugs regardless of the presence of PD (McFarthing et al. 2020).

Due to the prominence of cholinergic deficiency in dementia with Lewy bodies (DLB), the potential role of cholinesterase inhibitors can be considered. In this regard, Rivastigmine has been demonstrated to be effective for cognitive and psychiatric features. Evidence for other acetylcholinesterase inhibitors and memantine is mostly supportive, but a definitive framework has not yet been established. Research on treatment options for cognitive impairments in DLB is ongoing (Phillips et al. 2023).

Latterly, two clinical studies conducted in Australia and China have explored the use of embryonic stem cell (ESC) therapy for Parkinson's disease (PD) (Garitaonandia et al. 2016, Wang et al. 2018). Additionally, a clinical study has been initiated in Japan, aiming to achieve positive outcomes through the use of induced pluripotent stem cell (iPSC)-derived dopaminergic neurons. In this treatment approach, transplanted cells have been reported to survive for an extended period (presumably until the patient's demise) and function as dopaminergic neurons. As a result, it is emphasized that there is a need for more robust risk management compared to other studies utilizing mesenchymal stem cells. Furthermore, the study highlights that dopaminergic progenitors did not exhibit any tumor formation or toxicity. Additionally, results from trials with 6-hydroxydopamine (6-OHDA) lesions suggest improvements in abnormal behaviors. Consequently, the safety and validity of clinical research involving dopaminergic progenitors derived from iPSCs have been affirmed (Doi et al. 2020).

PD is commonly treated with another method known as deep brain stimulation (DBS) applied to the subthalamic nucleus (Savaş and Akbostancı 2014). DBS involves the placement of metal conductor pieces called electrodes, which deliver electrical currents, into regions of the brain associated with movement. Stimulation of the brain is achieved through a brain pacemaker connected to the electrodes. The brain pacemaker is an electronic device designed to control the excessive activity of brain regions resulting from dopamine deficiency. Patient selection is crucial in the use of the brain pacemaker, as it significantly influences the outcomes of surgical treatment. The first 3-4 years of PH are not suitable for the use of deep brain stimulation because positive responses are usually obtained from medications during this period. Additionally, some other neurodegenerative diseases may exhibit symptoms similar to early-stage PD. Moreover, patients of advanced age (70 and above), those with moderate or advanced dementia, and those with primary psychosis do not form a suitable patient profile for DBS (Yiğit and Arıcıoğlu 2015). The most suitable period for DBS is the "mid-term" when deterioration occurs, and motor fluctuations emerge as a result of levodopa use (Savaş and Akbostancı 2014). DBS can be used for the treatment of motor fluctuations, tremor, and dyskinesia. Findings have indicated its superiority over medication in treatment and improvement of quality of life (Giugni and Okun 2014). As long as the pacemaker is active, improvements in tremor symptoms or their near absence contribute to the enhancement of the patients' quality of life, addressing conditions such as anxiety and depressive mood. It is believed that the improvement in mood will positively impact individuals' self-confidence. However, as with any treatment plan, DBS has associated side effects, including speech problems (e.g. aphasia), gait disturbances, and balance problems. The lifespan of the pacemaker is approximately 5-7 years, requiring replacement when this period elapses (Yiğit and Arıcıoğlu 2015). When considering quality of life, the positive effects of DBS are almost inevitable.

Medical treatments developed for PD, including medications and Deep Brain Stimulation (DBS), unfortunately, may not fully address walking and balance problems, necessitating the exploration of alternative solutions. One such treatment approach is engaging in exercise (Gage and Storey 2004), and also dance is considered one form of exercise. Exercise programs tailored for individuals with PD have the potential to positively impact their quality of life. The balance and walking functions developed in these programs also provide benefits in daily life. Additionally, the social nature of dance is a crucial aspect that should not be overlooked. The social aspect can contribute to the improvement of an individual's quality of life. Through the creation of social networks, individuals with PH can participate in dance therapies over the long term. Therefore, dance is associated with increased motivation (Song et al. 2004).

Cognitive rehabilitation is an intervention and treatment method aimed at enhancing the quality of life by focusing on individuals' impaired cognitive functions. On the other hand, the term “rehabilitation of individuals with cognitive impairments” may more accurately capture the emphasis on individuals targeted for cognitive rehabilitation, as opposed to the term 'cognitive rehabilitation (Sohlberg and Mateer 2001). Non-pharmacological interventions (e.g. cognitive training) may be the most effective in individuals with mild or moderate cognitive impairment rather than severe disorders. Cognitive training (CT) is based on the concept that repeated execution of cognitive tasks can lead to improvement in cognitive functions. CT is often implemented using individually tailored 'game-like' tasks, including paper-pencil exercises or computer-based activities that provide feedback and motivate patients to engage in treatment. Results obtained from imaging

studies have shown that a cognitive training program offered within the scope of cognitive rehabilitation improved the cognitive performance of people with PD diagnosis who are involved in the training, specifically in terms of reaction time and accuracy scores on the Stroop test during magnetic resonance imaging (MRI) compared to a non-participating patient group (Nombela et al. 2011). The application of cognitive rehabilitation protocols in PD has been primarily focused on executive-frontal functions, which are crucial for successful daily functioning and quality of life but vulnerable in Parkinson's. These protocols target fundamental executive functions, including working memory, planning, set shifting, response inhibition, and recall. While dopaminergic therapy may temporarily improve some mild frontal function-based abilities, existing pharmacological treatments can be largely ineffective. Moreover, cognitive impairments are often underdiagnosed or inadequately treated. In the past decade, alternative approaches have been developed to enhance cognition in PD, including computer-based cognitive training (CBT) and physical therapy techniques. Findings suggest that a computer-based CT program (administered 3 to 4 times per week for 4 weeks) may be beneficial for vulnerable visual-spatial and executive functions in PD (Biundo et al. 2017b). Furthermore, current research demonstrates that cognitive rehabilitation is a beneficial tool in improving specific cognitive impairments observed in PD and underscores the need for individualized adaptation based on patients' specific impairments (Giustiniani et al. 2022).

Due to the variability in disease progression and clinical features among individuals, rehabilitation goals should be individually determined. Supportive approaches, such as improving disease symptoms, patient education, psychological support, stress reduction, organizing exercise and nutrition programs, increasing social interactions, enhancing physical fitness, and maintaining daily life activities, are crucial for the quality of life of patients (Buetow et al. 2008). Among the rehabilitation goals, increasing patients' physical activities, instilling exercise habits, and preventing falls in activity levels should be prioritized. Rehabilitation involves a learning process where patients are taught how to move more easily and achieve postural stability using their cognitive functions (Morris et al. 2010).

Physical therapy applications are tailored based on the patient's physical functions. When designing exercise programs, the patient's tolerance should be taken into account, and group exercises are often recommended. In patients in the moderate stage of the disease, the focus should be on teaching therapeutic exercises. In the advanced stage, the treatment aims to teach compensatory strategies to both the patient and their caregivers. Studies comparing the quality of life between exercise programs conducted under the guidance of a physiotherapist and individually applied home exercise programs have been conducted. These studies highlight the greater effectiveness of exercise programs conducted with the guidance of a physiotherapist. Controlled studies have shown that rehabilitation approaches include lower extremity strength training programs, aerobic exercises, strategies focusing on attention and perception, sensory cues, active axial rotation exercises, and repeated specific tasks (Dereli and Yaliman 2010, Gracies 2010).

Relaxation exercises, aerobic exercises, respiratory exercises, strength exercises, balance and coordination exercises, and dance therapy may be included in the exercise program (Yaliman and Şen 2011). Relaxation exercises can significantly reduce rigidity, facilitating easier progress in the rehabilitation program. Regularly performed aerobic exercise has been shown to improve higher-level cognitive functions such as attention and memory in patients after a six-month exercise program, thought to be beneficial in preventing brain tissue loss (Tanaka et al. 2009).

Discussion

In the present review, the aim was to examine cognitive impairments that can be observed depending on the course of PD while considering psychiatric symptoms such as depression and anxiety in the context of the quality of life of patients. In this regard, based on the conducted reviews, it has been found that individuals diagnosed with PD often experience depressive mood and anxiety; sleep disorders emerge due to the pathophysiology of the disease, and cognitive function may play a crucial role in problems related to daily functioning. In the context of the examined variables, the quality of life can be negatively affected both indirectly and directly by both motor and non-motor symptoms. Understanding the impact of motor and non-motor symptoms on the lives of individuals diagnosed with PD is crucial for their adaptation to everyday life. Additionally, it should be noted that genetic transmissions are among one of the essential factors contributing to the risk of developing the disease. Therefore, given the slow and insidious nature of the disease, clinical presentations should be thoroughly examined and monitored. As in all diseases, early diagnosis is highly valuable in PD as well.

Recent genetic and biochemical data indicate that the ubiquitin-proteasome systems affected by genetic or environmental factors have been implicated as a mechanism responsible for the pathogenesis of PD. Protein

accumulation associated with the dysfunction of this mechanism is a prominent pathological feature in the profile of dementia. Also, it was indicated that homozygous mutations in the PARKIN mutation are among the most common causes of juvenile PD. As the profile of dementia is often observed in the course of Parkinson's disease, especially, family members should closely monitor potential changes in the individual's ability to carry out daily tasks. Neuropsychological assessment allows for the identification of major problems in patients, and personalized cognitive rehabilitation methods can enhance overall quality of life of patients. The severity of motor and non-motor symptoms affects the progression of the disease. Therefore, when evaluating the quality of life, consideration should be given to the different stages of the disease. Changes in melatonin receptor density and function, among other pathological elements in PD, suggest a connection between melatonin signaling and cognitive decline, although findings are inconsistent.

The most common cognitive impairments observed in PD are associated with attention, executive function, and visual-spatial processing stages. It is believed that the disturbances in executive functions in the disease are an early sign related to changes in dopaminergic stimulation in the frontal cortex. Indeed, when the neuropsychological profile of Parkinson's patients is assessed, impairments in sustaining attention and problems with spatial orientation stand out among the prominent daily issues. This situation is parallel to the neuroimaging findings of the disease. In the later stages, PD can be accompanied by Lewy body dementia, a neurodegenerative disease encompassing various cognitive impairments, including primary memory deficits.

The finding that depression in PD more negatively affects motor symptoms, is reported. Additionally, individuals diagnosed with PD are reported to experience more psychosocial stress after diagnosis. When looking at the literature, anxiety disorder in PD has not been investigated in as much detail as depression. It is thought that the difference from depression may be due to the phenomenon and the side effects of medications. When examining psychotic disorders in PD, they can develop with dopaminergic stimuli depending on mesolimbic and mesocortical dopamine receptors. The difference from schizophrenia is attributed to the observation of more visual hallucinations. Another common disorder in PD is sleep disturbances, noted as one of the most frequent complaints associated with the disease.

Considering the course of the disease, planned treatment and cognitive rehabilitation can contribute positively to living with PD. Undoubtedly, the treatment of psychiatric symptoms such as depressive mood and anxiety can be achieved in patients with improved and sustained quality of life. One of the most commonly applied methods in the treatment of PD is DBS applied to the subthalamic nucleus. Patient selection in the application is crucial as it significantly affects the outcomes of surgical treatment. The first 3-4 years of PD are not suitable for the use of deep brain stimulation. The optimal period for deep brain stimulation is the 'middle period' where deteriorations occur in response to levodopa usage, and motor fluctuations emerge. Concurrently, personalized cognitive rehabilitation interventions can contribute to the treatment of patients and their integration into daily life. Another treatment modality, dance, has been shown to have positive effects on individuals with PD.

The cognitive impairment spectrum associated with PD is commonly defined as a continuum ranging from mild cognitive impairment in PD (PD-MCI) to PD dementia (PD-D). Additionally, it is emphasized that approximately 39% of newly diagnosed PD patients also experience subjective cognitive impairment (PD-SCI). Due to the heterogeneous nature of PD and variations in comorbidities, future studies with designs incorporating histological and molecular levels, supported by brain imaging and neuropsychological evaluations, hold promising potential to provide enlightening results regarding the pathogenesis and prognosis of the disease. Longitudinal research is considered necessary for connectivity analyses and determination of biomarkers for cognitive dysfunctions in PD. There is significant interest in cell-based therapeutic approaches that offer the possibility of renewing and replacing dopaminergic neurons.

Conclusion

The presence of hypotheses attempting to explain the neuropathological mechanisms of PD has been a fundamental indicator of its complex etiology, involving layered and diverse variables. Multidisciplinary and multidimensional studies, conducted with animal models or patient data, continue to emphasize environmental and psychological factors, particularly for sporadic cases, in addition to the presence of genetic elements. A biopsychosocial perspective provides valuable insights into understanding the disease both at the molecular and neuropsychological levels. Furthermore, a thorough understanding of specific motor and non-motor symptoms reflecting the disease's profile will guide the development of rehabilitation and intervention programs aimed at improving the quality of life for individuals affected by PD. The fundamental outcome obtained through our study is that motor symptoms (such as tremor) and comorbid cognitive dysfunctions (including attention,

executive functions, and visual-spatial skill problems) negatively impact the overall quality of life of people dealing with PD. Indeed, these symptoms may be associated with the observation of other psychiatric indicators, such as depression and anxiety. However, it is crucial to note that the decline in the quality of life may adversely affect psychiatric, cognitive, and motor symptoms. The interplay of symptoms emerging from or accompanying PD can mutually influence each other negatively, highlighting the necessity for PD researchers to examine the relationship in the context of these variables from different perspectives. In addition to a physician-monitored treatment plan, individual-centered cognitive and physical rehabilitation processes, along with professional psychological support based on neuropsychological profiling and the severity of motor symptoms, can positively impact patients' quality of life and, consequently, their overall well-being. Our study has the limitation of not encompassing the cognitive and psychological status of primary caregivers for individuals with Parkinson's disease. Validating the reported findings requires further research, particularly to determine the longitudinal impact of caregiver quality of life and potential protective factors. Longitudinal studies should also consider the cognitive and psychological changes in caregiver individuals, taking into account its effects on both caregivers and individuals with Parkinson's disease, including outcomes such as institutionalization.

References

Abeysuriya R, Walker Z (2015) Dementia with lewy bodies. Br J Neurosci Nurs, 11:146-149.

Alreni AS, Harrop D, Gumber A, McLean S (2017) Measures of upper limb function for people with neck pain: A systematic review of measurement and practical properties. Musculoskel Sci Pract, 29:155-163.

Amara AW, Memon AA (2018) Effects of exercise on non-motor symptoms in parkinson's disease. Clin Ther, 40:8-15

Armstrong MJ, Okun MS (2020) Diagnosis and treatment of Parkinson disease: a review. JAMA, 323:548-560.

Armstrong RA (2017) Visual dysfunction in Parkinson's. Int Rev Neurobiol, 134:921-946.

Åström DO, Simonsen J, Raket LL, Sgarbi S, Hellsten J, Hagell P et al. (2022) High risk of developing dementia in Parkinson's disease: A Swedish registry-based study. Sci Rep, 12:16759.

Baggio H, Segura B, Sala-Llonch R, Marti M, Valldeoriola F, Compta Y et al. (2015) Cognitive impairment and resting-state network connectivity in Parkinson's disease. Hum Brain Mapp, 36:199-212.

Balestrino R, Martinez-Martin P (2017) Reprint of "Neuropsychiatric symptoms, behavioural disorders, and quality of life in Parkinson's disease". J Neurol Sci, 374:3-8.

Balestrino R, Schapira AH (2020) Parkinson disease. Eur J Neurol, 27:27-42.

Biundo R, Fiorenzato E, Antonini A (2017a) Non-motor symptoms and natural history of Parkinson's disease: Evidence from cognitive dysfunction and role of noninvasive interventions. Int Rev Neurobiol, 133:389-415.

Biundo R, Weis L, Fiorenzato E, Antonini A (2017b) Cognitive rehabilitation in Parkinson's disease: is it feasible? Arch Clin Neuropsychol, 32:840-860.

Bonifati V, Rohe C, Breedveld G, Fabrizio E, Mari M, Tassorelli C et al. (2005) Early-onset parkinsonism associated with PINK1 mutations: Frequency, genotypes, and phenotypes. Neurology, 65:87-95.

Braak H, Rub U, Gai WP, Del Tredici K (2003) Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. J Neural Transm 110:517-36.

Bronnick K, Alves G, Aarsland D, Tysnes O, Larsen J (2011) Verbal memory in drug-naive, newly diagnosed Parkinson's disease. the retrieval deficit hypothesis revisited. Neuropsychology, 25:114-124.

Buetow S, Giddings LS, Williams L, Nayar S (2008) Perceived unmet needs for health care among Parkinson's Society of New Zealand members with Parkinson's disease. Parkinsonism Relat Disord, 14:495-500.

Campbell AM, Glover J, Chiang VL, Gerrard J, Yu JB (2015) Gamma knife stereotactic radiosurgical thalamotomy for intractable tremor: A systematic review of the literature. Radiother Oncol, 114:296-301.

Cerri S, Mus L, Blandini F (2019) Parkinson's disease in women and men: what's the difference? J Parkinsons Dis, 9:501-515

Chandran P, Pal PK (2013) Quality of life and its determinants in essential tremor. Parkinsonism Relat Disord, 19:62-65.

Chu Y, Tai C, Lin C, Wu, R (2021) Updates on the genetics of Parkinson's disease: clinical implications and future treatment. Acta Neurol, 30:83-93.

Cong S, Xiang C, Zhang S, Zhang T, Wang H, Cong S (2022) Prevalence and clinical aspects of depression in Parkinson's disease: A systematic review and meta-analysis of 129 studies. Neurosci Biobehav Rev, 141:104749.

Çekok FK, Kahraman T, Genç A, Duran G, Çolakoğlu BD, Yerlikaya D et al. (2023) Association between executive and physical functions in people with Parkinson's disease. Somatosens Mot Res, doi: 10.1080/08990220.2023.2186393..

Çolakoğlu B (2014) Parkinson hastalığında yaşam kalitesi ve ölçümü. Turk Noroloji Dergisi, 20:38-41.

Çorakcı Z, Hanoğlu L (2021) Parkinson hastalarında kognitif ve duyu işlemleme süreçlerinin incelenmesi. Türkiye Klinikleri Sağlık Bilimleri Dergisi, 6:467-475.

Dalle E, Mabandla O (2018) Early life stress, depression and Parkinson's disease: A new approach. Mol Brain, 11:18.

De Freitas PR, Lemos AE, Santos MP, Michaelsen SM, Corrêa CL, Swarowsky A (2017) "Test D'évaluation Des Membres Supérieurs Des Personnes Âgées" (TEMPA) to assess upper limb activity in Parkinson's disease. J Hand Ther, 30:320-327.

den Brok M, van Dalen J, van Gool A, van Charante E, de Bie, Richard B (2015) Apathy in Parkinson's disease: A systematic review and meta-analysis. Mov Disord, 30:759-769.

Delli PS, Franciotti R, Taylor JP, Thomas A, Tartaro A, Onofrj M et al. (2015) Thalamic involvement in fluctuating cognition in dementia with lewy bodies: Magnetic resonance evidences. Cereb Cortex, 25:3682-3689.

Dereli EE, Yaliman A (2010) Comparison of the effects of a physiotherapistsupervised exercise programme and a self-supervised exercise programme on quality of life in patients with Parkinson's disease. Clin Rehabil, 24:352-62.

Doğan A, Yaşar S, Kayhan S, Kırmızıgöz Ş, Kaplan A (2018) Bağırsak-beyin aksı. Türk Nöroşirürji Dergisi, 28:377-379

Doi D, Magotani H, Kikuchi T, Ikeda M, Hiramatsu S, Yoshida K et al. (2020) Pre-clinical study of induced pluripotent stem cell-derived dopaminergic progenitor cells for Parkinson's disease. Nat Commun, 11:3369.

Donaghy PC, McKeith IG (2014) The clinical characteristics of dementia with lewy bodies and a consideration of prodromal diagnosis. Alzheimers Res Ther, 6:46.

Egan SJ, Laidlaw K, Starkstein S (2015) Cognitive behavior therapy for depression and anxiety in Parkinson's disease. J Parkinsons Dis, 5:443-451

Ehgoetz Martens KA, Lewis SJ (2017) Pathology of behavior in PD: What is known and what is not? J Neurol Sci, 374:9-16.

Erskine D, Thomas AJ, Attems J, Taylor JP, McKeith IG, Morris CM et al. (2017) Specific patterns of neuronal loss in the pulvinar nucleus in dementia with lewy bodies. Mov Disord, 32:414-422.

Floriano EN, Alves JF, Almeida IA, de Souza RB, de Christofoletti G, Santos SM (2015) Dual task performance: A comparison between healthy elderly individuals and those with Parkinson's disease. Fisioterapia Em Movimento, 28:251-258.

Fox SH, Katzenschlager R, Lim SY, Barton B, de Bie RMA, Seppi K et al. (2018) International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. Mov Dis, 33:1248-1266.

Friz NE, Cheek F, Nichols-Larsen, DS (2016) Motor cognitive dual-task training in neurologic disorders: A systematic review. J Neurol Phys Ther, 39:142-153.

Jellinger KA (2018) Dementia with lewy bodies and Parkinson's disease dementia: current concepts and controversies. J Neural Transm, 125:615-650.

Garitaonandia I, Gonzalez R, Christiansen-Weber T, Abramihina T, Poustovoitov M, Noskov A et al. (2016) Neural stem cell tumorigenicity and biodistribution assessment for phase i clinical trial in Parkinson's disease. Sci Rep, 6:34478.

Gage H, Storey L (2004) Rehabilitation for Parkinson's disease: A systematic review of available evidence. Clin Rehabil, 18:463-482.

Georgiev D, Hamberg K, Hariz M, Forsgren L, Hariz GM (2017) Gender differences in Parkinson's disease: A clinical perspective. Acta Neurol Scand, 136:570-584.

Giugni JC, Okun MS (2014) Treatment of advanced Parkinson's disease. Curr Opin Neurol, 27:450-60.

Girgus JS, Yang K, Ferri CV (2017) The gender difference in depression: Are elderly women at greater risk for depression than elderly men? Geriatrics, 2:35.

Giustiniani A, Maistrello L, Danesin L, Rigon E, Burgio F (2022) Effects of cognitive rehabilitation in Parkinson disease: A meta-analysis. Neurol Sci, 43:2323-2337.

Goldman JG, Guerra CM (2020) Treatment of nonmotor symptoms associated with Parkinson disease. Neurol Clin, 38:269-292.

Goldstein DS, Kopin IJ (2018) Linking stress, catecholamine autotoxicity, and allostatic load with neurodegenerative diseases: A focused review in memory of Richard Kvetnansky. Cell Mol Neurobiol, 38:13-24.

Gracies JM (2010) Neurorehabilitation in Parkinsonian syndromes. Rev Neurol (Paris), 166:196-212.

Guo YL, Wei XJ, Zhang T, Sun T (2023) Molecular mechanisms of melatonin-induced alleviation of synaptic dysfunction and neuroinflammation in Parkinson's disease: A review. Eur Rev Med Pharmacol Sci, 27:5070-5082..

Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG (2008) The Sydney multicenter study of Parkinson's disease: The inevitability of dementia at 20 years. Mov Disord, 23:837-844.

Hovendon B, Kaufman M (2015) Dementia with lewy bodies: An overview. McGill Science Undergraduate Research Journal, 10:45-48.

Hwang S, Song CS (2016) Relationship between manual dexterity and the unified Parkinson's disease rating scale-motor exam. J Phys Ther Sci, 28:3403-3406.

Iranzo A (2016) Sleep in neurodegenerative Diseases. Sleep Med Clin, 11:1-18.

Kakkar AK, Dahiya N (2015) Management of Parkinson's disease: Current and future pharmacotherapy. Eur J Pharmacol, 750:74-81.

Kalkan AC, Kahraman T, Ugut BO, Colakoglu BD, Genc AA (2020) Comparison of the relationship between manual dexterity and postural control in young and older individuals with Parkinson's disease. J Clin Neurosci, 75:89-93.

Kirsch-Darrow L, Marsiske M, Okun MS, Bauer R, Bowers Ş (2011) Apathy and depression: Separate factors in Parkinson's disease. J Int Neuropsychol Soc, 17:1058-1066.

Klein C, Westenberger A (2012) Genetics of Parkinson's disease. Cold Spring Harb Perspect Med, 2:a008888.

Kuhlman GD, Flanigan JL, Sperling SA, Barrett MJ (2019) Predictors of health-related quality of life in Parkinson's disease. Parkinsonism Relat Disord, 65:86-90.

Lee A, Gilbert RM (2016) Epidemiology of parkinson disease. Neurol Clin, 5:14-28.

Leentjens AFG, Dujardin K, Marsh L, Martinez P, Richard H, Starkstein S et al. (2008) Apathy and anhedonia rating scales in Parkinson's disease: Critique and recommendations. Mov Disord, 23:2004-2014.

Lo C, Arora S, Baig F, Lawton MA, El Mouden C, Barber TR et al. (2019) Predicting motor, cognitive and functional impairment in Parkinson's. Ann Clin Transl Neurol, 6:1498-1509.

Mak MK, Lau ET, Tam VW, Woo CW, Yuen SK (2015) Use of Jebsen Taylor Hand Function Test in evaluating the hand dexterity in people with Parkinson's disease. J Hand Ther, 28:389-394.

Mansuri Z, Reddy A, Vadukapuram R, Trivedi, C, Amara A (2022) Pimavanserin in the treatment of Parkinson's disease psychosis: Meta-analysis and meta-regression of randomized clinical trials. Innov Clin Neurosci, 19:46-51.

Marinus J, Zhu K, Marras C, Aarsland D, van Hilten JJ (2018) Risk factors for non-motor symptoms in Parkinson's disease. Lancet Neurol, 17:559-568.

McFarthing K, Buff S, Rafaloff G, Dominey T, Wyse RK, Stott SRW (2020) Parkinson's disease drug therapies in the clinical trial pipeline. J Parkinsons Dis, 10:757-774.

McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D et al. (2017) Diagnosis and management of dementia with lewy bodies: Fourth consensus report of the DLB Consortium. Neurology, 89:88-100.

Morris ME, Martin CL, Schenkman ML (2010) Striding out with Parkinson disease: Evidence-based physical therapy for gait disorders. Phys Ther, 90:280-288.

Nombela C, Bustillo PJ, Castell PF, Sanchez L, Medina V, Herrero MT (2011) Cognitive rehabilitation in Parkinson's disease: Evidence from neuroimaging. Front Neurol, 2:82.

Opara JA, Brola W, Leonardi M, Błaszczyk B (2012) Quality of life in Parkinson's disease. J Med Life, 5:375-381.

Payami H, Zareparsi S, James D, Nutt J (2002) Familial aggregation of Parkinson disease: A comparative study of early-onset and late-onset disease. Arch Neurol, 59:848-850.

Pezzoli S, Sánchez-Valle R, Solanes A, Kempton MJ, Bandmann O, Shin JI (2021) Neuroanatomical and cognitive correlates of visual hallucinations in Parkinson's disease and dementia with lewy bodies: Voxel-based morphometry and neuropsychological meta-analysis. Neurosci Biobehav Rev, 128:367-382.

Pfeiffer RF (2016) Non-motor symptoms in Parkinson's disease. Parkinsonism Relat Disord, 22:119-122.

Phillips O, Ghosh D, Fernandez HH (2023) Parkinson disease dementia management: An update of current evidence and future directions. Curr Treat Options Neurol, 25:93-119.

Proud EL, Miller KJ, Martin CL, Morris ME (2013) Upper-limb assessment in people with Parkinson disease: Is it a priority for therapists, and which assessment tools are used? Physiother Can, 65:309-316.

Postuma RB, Aarsland D, Barone P, Burn DJ, Hawkes CH, Oertel W et al. (2012) Identifying prodromal Parkinson's disease: Pre-motor disorders in Parkinson's disease. Mov Disord, 27:617-626.

Qureshi SU, Amspoker AB, Calleo JS, Kunik ME, Marsh L (2012) Anxiety disorders, physical illnesses and health care utilization in older male veterans with Parkinson disease and comorbid depression. J Geriatr Psychiatry Neurol, 25:233-239.

Ratti PL, Nègre-Pagès L, Pérez-Lloret S, Manni R, Damier P, Tison F et al. (2015) Subjective sleep dysfunction and insomnia symptoms in Parkinson's disease: Insights from a cross-sectional evaluation of the French CoPark cohort. Parkinsonism Relat Disord, 21:1323-1329.

Ruppert MC, Greuel A, Tahmasian M, Schwartz F, Stürmer S, Maier F et al. (2020) Network degeneration in Parkinson's disease: Multimodal imaging of nigro-striato-cortical dysfunction. Brain, 143:944-959.

Ruppert MC, Greuel A, Freigang J, Tahmasian M, Maier F, Hammes J et al. (2021) The default mode network and cognition in Parkinson's disease: A multimodal resting-state network approach. Hum Brain Mapp, 42:2623-2641.

Sarwar AI (2018) Trazodone and parkinsonism: the link strengthens. Clin Neuropharmacol, 41:106-108.

Savaş A, Akbostancı C (2014) Parkinson hastalığında derin beyin stimülasyonu. Türk Nöroşirürji Dergisi, 24:168-72.

Schapira AH, Chaudhuri KR, Jenner P (2017) Non-motor features of Parkinson disease. Nat Rev Neurosci, 18:435-450.

Shulman JM, De Jager PL, Feany MB (2011) Parkinson's disease: genetics and pathogenesis. Annu Rev Pathol, 6:193-222.

Simon DK, Tanner CM, Brundin P (2020) Parkinson disease epidemiology, pathology, genetics, and pathophysiology. Clin Geriatr Med, 36:1-12.

Singleton AB, Farrer MJ, Bonifati V (2013) The genetics of Parkinson's disease: Progress and therapeutic implications. Mov Disord, 28:14-23.

Soke F, Colakoglu BD, Keskinoglu P, Genc A (2019) Reliability, validity and responsiveness of the squares test for manual dexterity in people with Parkinson's disease. Clin Neurol Neurosurg, 186:105542.

Sohlberg MM, Mateer CA (2001) Cognitive Rehabilitation: An Integrative Neuropsychological Approach. New York, Guilford Press.

Song R, June KJ, Kim CG, Jeon MY (2004) Comparisons of motivation, health behaviors, and functional status among elders in residential homes in Korea. Public Health Nurs, 21:361-371.

Stahl SM, Muntner N (2021) Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications, 5th ed. Cambridge, MA, Cambridge University Pres.

Tanaka K, Quadros AC, Santos RF, Stella F, Gobbi LT, Gobbi S (2009) Benefits of physical exercise on executive functions in older people with Parkinson's disease. Brain Cogn, 69:435-441.

Tchekalarova J, Tzoneva R (2023) Oxidative stress and aging as risk factors for Alzheimer's disease and Parkinson's disease: The role of the antioxidant melatonin. International Journal of Molecular Sciences, 24:3022.

Thomas KM, Redd LA, Wright JD, Hartos JL (2017) Sleep and mental health in the general population of elderly women. The Journal of Primary Prevention, 38:495-503.

Trinh J, Farrer M (2013) Advances in the genetics of Parkinson's disease. Nat Rev Neurol, 9:445-454.

Van Hemert S, Marlicz W, Szachta P, Pekelharing E, Ormel G, Loniewski I et al. (2016) The role of the gut microbiota in mood and behaviour. Whether psychobiotics can become an alternative in therapy in psychiatry? Eur Psychiatry, 33:26.

Voon V, Gao J, Brezing C, Symmonds M, Gao J, Symmonds M et al. (2011) Dopamine agonists and risk: Impulse control disorders in Parkinson's disease. Brain, 134:1438-1446.

Wang YK, Zhu WW, Wu MH, Wu YH, Liu ZX, Liang LM et al. (2018) Human clinical-grade parthenogenetic ESC-derived dopaminergic neurons recover locomotive defects of nonhuman primate models of Parkinson's disease. Stem Cell Reports, 11:171-182.

Yaliman A, Şen Eİ (2011) Parkinson hastalığı ve rehabilitasyonu. Turk J Phys Med Rehabil, 57:38-44.

Yiğit G, Arıcıoğlu F (2015) Günümüzde ve gelecekte Parkinson hastalığı için farmakolojik tedavi yaklaşımları. Klinik ve Deneysel Sağlık Bilimleri, 5:265-273.

Yoshizawa H, Von Sattel JPG, Honig LS (2013) Early neuropsychological discriminants for lewy body disease: an autopsy series. J Neurol Neurosurg Psychiatry, 84:1326-1330.

Zhao A, Qi L, Li J, Dong J, Yu H (2018) A hybrid spatio-temporal model for detection and severity rating of Parkinson's disease from gait data. Neurocomputing, 315:1-8.

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