The Princeton Journal of Interdisciplinary Research 2025 (Vol. 1, No. 2) - ISSN 3069-8200

A Literature Review of Dementia in Parkinson's Disease: From Risk Factors to Diagnostics and Treatments

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Abstract

Parkinson's Disease Dementia (PDD) is a neurodegenerative condition that affects a significant portion of individuals with Parkinson's disease (PD). This literature review synthesizes current research on the risk factors, underlying mechanisms, diagnostic criteria, treatment options, and emerging therapies for PDD to provide a foundational understanding of the disease and highlight debates within research.

A literature search was conducted through PubMed using keywords including "(Parkinson's Disease Dementia) AND (Risk factors), (Parkinson's Disease Dementia) AND (Diagnostic Criteria), (Parkinson's Disease Dementia) AND (Lewy Body Dementia), (Parkinson's Disease Dementia) AND (Pharmacological Treatment Methods), (Parkinson's Disease Dementia) AND (Clinical Criteria)" Studies published within the last 20 years were prioritized, focusing on clinical, pathological, and therapeutic insights.

Findings reveal that demographic factors (advanced age, longer disease duration, male gender), genetic mutations (GBA, SNCA), and environmental exposures (pesticides, traumatic brain injury) increase PDD risk. Mechanistically, PDD is characterized by cholinergic deficits, dopaminergic dysfunction, and the accumulation of alpha-synuclein aggregates called Lewy bodies, leading to mitochondrial dysfunction, oxidative stress, and synaptic transmission failure. Diagnosis is guided by the Movement Disorder Society (MDS) criteria, emphasizing

cognitive decline beyond motor impairments, including executive dysfunction, memory loss, visuospatial difficulties, and attention deficits. Treatment options include pharmacological therapies such as cholinesterase inhibitors and memantine, which provide limited benefits and often have side effects, as well as non-pharmacological approaches like cognitive rehabilitation and lifestyle modifications. However, both treatment strategies face limitations and inconsistent patient response. Emerging therapies, including immunotherapies targeting alpha-synuclein, gene therapies, and stem cell-based approaches, hold potential for modifying disease progression.

Overall, this review highlights the complexity of PDD and the limited treatment options available for managing the disease and the aim of providing a foundation for understanding the disease and highlighting debates within current research.

Introduction

Parkinson's Disease (PD) is the second most prevalent neurodegenerative disease that affects

people over the age of 65, with over 10 million people worldwide being diagnosed according to the Parkinson's Foundation (Parkinson's Foundation. "Parkinson's Disease Statistics." *Parkinson's Disease Statistics*, Parkinson's Foundation, www.parkinson.org/understanding-parkinsons/statistics.). It mostly affects one’s motor skills, which slowly decline over time (5). Of those 10 million people with a diagnosis of PD, most of them will end up developing Parkinson's Disease Dementia (PDD). These patients will additionally develop cognitive impairments that progress over time (6). Crucially, experiencing such symptoms affects not only the patients but also those around them. This is because patients often lose their independent living abilities as the disease progresses (6).

With the increasingly aging population, the 10 million figure is only expected to increase as time goes on. According to the Global Health Observatory, which is an initiative by the United Nations to provide key metrics on health data, life expectancy has increased by 6.4 years from 2000-2019 (2), with a subsequent increase in the expected number of people who will receive a neurodegenerative diagnosis (3). These statistics show two highly important reasons for further researching PDD: i) it shows our rapidly aging population and as mentioned before PDD mainly affects those over 65; ii), although people are living longer, they are not living all those years in full health.

This paper therefore aims to advance the overall understanding of PDD by providing an overview of the disease and laying the foundation for further research. It will summarize and discuss all aspects of the disease including risk factors, mechanisms, diagnostic criteria, clinical presentation, and treatment options to highlight gaps in the field. The paper will also highlight current debates within the field, particularly in the diagnosis of Lewy Body Dementia (LBD), which shares similar pathology and prognosis with PDD (4). Given the growing prevalence of PDD and its significant impact on patients and caregivers, it is critical to understand the underlying mechanisms driving the disease progression of PD.

Overview of Parkinson's Disease

PD is a progressive neurodegenerative disorder characterized by both motor and non-motor symptoms (13).

The hallmark of PD is the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), the area of the basal ganglia which produces dopamine, a neurotransmitter that is essential for motor skills (6). The basal ganglia are a group of subcortical nuclei located in the midbrain. They are responsible for coordinating fine motor control and rely heavily on dopamine produced by the neurons in the SNc (12). As the disease

progresses, there is an increased loss of dopaminergic neurons, subsequently leading to a decrease in the level of dopamine in the basal ganglia (6)(12). This trend over time leads to clinical Parkinson's symptoms such as bradykinesia, muscular rigidity, resting tremors, and postural instability (6). The cause for the loss of dopaminergic neurons can be associated with the formation of Lewy bodies (6)(9). Lewy bodies (LB) are insoluble aggregations of misfolded alpha-synuclein proteins that form and aggregate in the SNc but later spread to all parts of the central nervous system (CNS) as the disease progresses (8)(9).

Alpha-synuclein protein is a relatively small protein at 140 amino acids that is normally found in the presynaptic terminals of nerve cells in the brain (7). Although the exact function of alpha-synuclein has not been identified, multiple studies show that it is responsible for regulating the release of neurotransmitters (11). However, when alpha-synuclein aggregates in the form of LB it has been shown to cause a variety of neurotoxic events (6). One is mitochondrial dysfunction, which reduces ATP production and increases oxidative stress, leading to neuronal energy failure and apoptosis (6)(10). It also has been shown to impair the ubiquitin-proteasome system and autophagy pathways (10). These pathways are responsible for clearing damaged proteins and becoming overwhelmed by excessive alpha-synuclein accumulation, leading to further cellular stress (10). Additionally, LBs have been shown to result in the chronic release of pro-inflammatory cytokines that increase neurodegeneration (10). Finally, alpha-synuclein normally regulates synaptic vesicle recycling, but its aggregation in LB impairs synaptic transmission, reducing dopaminergic signaling and accelerating neuron loss (11). Overall, the accumulation of LB leads to a variety of motor symptoms and nonmotor symptoms that affect the patient's life.

The motor symptoms that can be observed include bradykinesia, muscular rigidity, resting tremors, and postural instability (6). These cardinal motor symptoms are visible after a 60% loss of dopaminergic neurons (9). Bradykinesia involves slowness in the initiation and

execution of voluntary movements (13); Rigidity can cause discomfort and pain, as well as limit the range of motion (13); resting tremors are one of the most recognizable symptoms of PD, often starting in one hand or fingers, and occurring at rest (13). The tremor is typically rhythmic and tends to improve as a person attempts a voluntary movement (13). Lastly, postural instability, which is a gradual loss of balance and coordination, leads to a tendency to lean forward or backward (13).

Patients often also present nonmotor symptoms after their motor ones. These can include depression and cognitive impairment and are strong indicators of PD developing into PDD (14). Cognitive impairment is a general term used to describe a range of difficulties from memory and concentration, and loss of visuospatial skills, all the way to more severe cognitive dysfunction (14). Difficulty in memory is usually a loss in short-term memory first followed by a loss in long-term memory as the disease progresses, and difficulty in concentration is described as an increased difficulty to stay on task and or a longer time to complete the task (15). The loss of visuospatial skills results in the impairment of determining spatial relationships between objects, and or problems with navigation in familiar environments (14). Cognitive dysfunction is a hallmark feature of cognitive impairment in PD that affects high-order cognitive function (15).

Risk Factors and Mechanisms of Parkinson's Disease Dementia

As outlined in the previous section, when Parkinson's disease progresses, its impact extends beyond motor dysfunction, leading to significant cognitive impairment and dementia in many patients with long-term studies showing 80% developing such cognitive problems (15). PDD arises due to a combination of risk factors, including aging, genetic susceptibility, and environmental influences (15). The underlying mechanisms involve complex neurochemical

changes, widespread alpha-synuclein pathology, and disruptions in key brain regions responsible for cognition (15).

Certain demographic factors increase the likelihood of developing PDD. Advanced age is one of the most significant risk factors, as older individuals with Parkinson's disease are more prone to cognitive decline (16). Additionally, the longer a person lives with PD, the greater the chance of developing dementia, with many cases of PDD emerging after a decade or more of disease progression (16). Lastly, studies indicate that men are at a higher risk of developing PDD than women, although the exact reasons remain unclear and debated (16).

Genetic factors also play a crucial role in the development of PDD, especially in familial forms of PDD. This is in contrast to sporadic PDD where the patient has no family history of it (18). One factor is the mutation of the GBA gene, which encodes the glucocerebrosidase enzyme (GCase), a lysosomal enzyme involved in the metabolism of glucosylceramide (19). The mutation causes GCase to misfold leading to its aggregation in the cellular compartments of dopaminergic neurons (19). Additionally, the impaired activity of GCase causes an increased accumulation of alpha-synuclein (19)(20). Similarly, mutations or duplications in the SNCA gene, responsible for encoding the alpha-synuclein protein, increase the risk of LB formation and accelerate cognitive decline in PD patients (17). Overall, these genetic influences highlight the role of protein misfolding and cellular dysfunction in the progression of PDD.

Environmental factors also contribute to the risk of developing PDD because DNA methylation can be affected by environmental factors and as stated before, some of the mutations are related to methylation (21). Exposure to polyaromatic hydrocarbons, endocrine disruptors, dioxins, persistent organic pollutants, certain types of pesticides, heavy metals, air pollution, cigarette smoking, and nanoparticles, has been associated with an increased incidence of Parkinson's disease and subsequent dementia (21). These chemicals are believed to

contribute to changes in RNA modification, worsening the neurodegenerative processes that underlie PD and PDD (21). Traumatic brain injury (TBI) is another environmental factor linked to cognitive decline in Parkinson's disease (22). Individuals with a history of repeated head trauma, such as athletes or military personnel, are at a higher risk of developing PD and experiencing more rapid disease progression (22). TBI can trigger chronic neuroinflammation and promote the aggregation of alpha-synuclein, further accelerating cognitive impairment (22).

The mechanisms driving PDD involve widespread neurochemical changes that go beyond the dopaminergic deficits typically associated with Parkinson's disease (23). While the loss of dopaminergic neurons in the substantia nigra leads to motor symptoms, PDD also involves significant disruptions in the cholinergic system (23). Acetylcholine, a neurotransmitter essential for memory and attention, is significantly reduced in

PDD due to the degeneration of cholinergic neurons in the basal forebrain (23). This cholinergic deficit contributes to cognitive dysfunction and resembles the patterns observed in Alzheimer's disease, further underscoring its role in dementia development (23). In addition to cholinergic dysfunction, PDD involves further disruption of dopamine signaling in cortical and subcortical regions, impairing executive function, working memory, and attention (23).

While Parkinson's disease primarily affects motor pathways, in PDD LB deposits extend into the limbic system and neocortex, leading to severe cognitive impairment (24). Compared to PD without dementia, PDD involves a more extensive spread of Lewy body and alpha-synuclein pathology (6)(10)(11), which correlates with the progression of cognitive decline (24).

Several key brain regions are particularly affected in PDD, contributing to the observed cognitive impairments. The hippocampus, which is critical for memory formation and spatial

navigation, undergoes atrophy and synaptic dysfunction in PDD patients, leading to memory deficits similar to those seen in Alzheimer's disease (25). The amygdala, responsible for emotional regulation and associative learning, is also affected, resulting in mood disturbances, anxiety, and impaired emotional processing (24). Additionally, the prefrontal cortex, which plays a vital role in executive function, problem-solving, and attention, shows significant dopaminergic and cholinergic deficits (24). Damage to this region further exacerbates the hallmark cognitive symptoms of PDD, including difficulties with decision-making, multitasking, and planning.

Diagnostics of Parkinson's Disease Dementia

The clinical criteria for the diagnosis of PDD were created by an MDS (Movement Disorder Society) task force in which they provide 5 criteria: i) a pre-existing diagnosis of PD; ii) PD developed at least 1 year before the PDD symptoms appeared; iii) PD is associated with decreased cognitive ability; iv) the cognitive decline is severe enough to impair daily life(28)(25); v) there is impairment in more than one cognitive domain (Attention, Executive Function, Visuospatial Skills, and Memory) (28). As discussed by Poewe et al., (2008), in PDD "dementia syndrome is defined as (i) impairment in at least two cognitive domains and (ii) cognitive deficiency severe enough to impair daily life (social, occupational or personal care) that must be independent of impairment because of PD motor symptoms" (Poewe et.al, 2008).

Neuropsychological testing plays a crucial role in diagnosing PDD. These tests are short and easy to administer while being able to detect cognitive impairment (26). The Montreal Cognitive Assessment (MoCA) is widely used in PDD populations because it is sensitive to the four domains of cognitive impairment mentioned previously: impairment in attention, executive dysfunction, visuospatial impairment, and memory loss (26)(28). Impairment in attention is seen as the inability to maintain attention that is required to complete executive functions (42).

It includes both the lack of sustained attention (the ability to maintain attention for long periods) and the lack of selective attention (the ability to maintain attention despite the presence of multiple stimuli in an environment (42). Executive dysfunction is described as the inability to complete tasks that "enable a person to engage successfully in independent, purposive, and self-serving behavior,"(Stuss, 2011) (33)(34). It is first presented through language difficulties, and patients often struggle with switching between tasks, decision-making, and abstract reasoning (25). Visuospatial impairment is another prominent feature, leading to difficulties in recognizing objects, navigating familiar environments, and judging distances (34). Patients may experience problems with facial recognition or misinterpret visual stimuli, which can contribute to confusion and disorientation (34). Memory loss is also prevalent in PDD. Memory loss in PDD is typically seen as a loss in short-term memory followed by a loss in long-term memory as the disease progresses (34). Additionally in PDD learning is also impaired along with verbal fluency compared to just PD (34). The Mini-Mental State Examination (MMSE) is also commonly used but is less sensitive to the early cognitive changes in PDD as it was originally developed to detect Alzheimer's disease (26). In addition to these general screening tools, more detailed cognitive batteries, such as the Parkinson's Disease Cognitive Rating Scale (PD-CRS) and the Mattis Dementia Rating Scale, are used to assess specific cognitive domains affected by PDD (27). These tests evaluate memory, attention, executive function, language, and visuospatial abilities to provide a comprehensive cognitive profile of the patient as a starting point for further assessments (27).

Neuropsychiatric symptoms are also common with PDD and often appear alongside cognitive decline. Hallucinations are common, with it occurring in 45% to 65% of patients, and mostly presenting in the visual domain. These may involve seeing people, animals, or objects that are not present (34). These hallucinations are often well-formed and convincing, which can contribute to significant distress for both the patient and their caregivers (34). Depression and

anxiety are also common in PDD, with 40% to 58% experiencing depressive symptoms, and 30% to 49% experiencing anxiety (34). Apathy, or a profound loss of motivation, is another frequent symptom found in 54% of patients, leading to social withdrawal, decreased interest in activities, and a general lack of emotional response (34). These neuropsychiatric features are believed to be linked to dysfunction in the limbic system and cholinergic deficits in the brain (23)(24).

Neuroimaging is an essential tool in diagnosing PDD, as it helps detect structural and functional changes in the brain (30). Magnetic resonance imaging (MRI) is commonly used to assess brain atrophy, particularly in the hippocampus and cortical regions (29). Cortical thinning in the posterior regions of the brain, including the parietal and occipital lobes, is often observed in patients with PDD, which correlates with visuospatial impairment (30). A specific type of MRI called diffusion-weighted imaging is also used to observe white matter changes (degeneration of axons and myelin damage), in which increased alterations are supposed to track increased cognitive impairment (29).

More invasive imaging techniques, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT), provide insight into the neurochemical changes associated with PDD (30). Dopamine transporter (DaT) imaging, performed using SPECT, can detect reduced dopamine activity in the striatum, which is characteristic of PD and PDD (29). PET imaging with fluorodeoxyglucose (FDG-PET) can reveal hypometabolism in the posterior cortical regions (29).

Research into biomarkers for PDD has gained significant attention in recent years, as they have the potential to improve early diagnosis. Amongst these, cerebrospinal fluid (CSF) biomarkers have shown promise in diagnosing PDD, and are a preferred choice due to the contact with the extracellular space of the brain (31). CSF is obtained via a lumbar puncture,

and this method usually results in little side effects (31). However, the procedure is still considered invasive, making CSF difficult to use in routine disease monitoring (31). In CSF, clinicians can detect levels of alpha-synuclein, the key pathological protein in PD and PDD, which are often reduced in the affected individuals due to its accumulation in Lewy bodies (31).

Finally, blood-based biomarkers are also being investigated as a less invasive alternative to CSF analysis (32). Inflammatory markers, such as C-reactive protein (CRP) and cytokines, are elevated in PD and PDD, suggesting a role for neuroinflammation in disease progression (32).

Distinction Between Lewy Body Dementia and Parkinson's Disease Dementia

PDD and Lewy body dementia (LBD) are two closely related neurodegenerative disorders that fall within the spectrum of Lewy body diseases (35). Both conditions share common pathological features, primarily the accumulation of alpha-synuclein and the formation of Lewy bodies in the brain, but vary in the timing of clinical presentation (35). Their overlapping pathology, coupled with the similarity in clinical presentation results in difficulty in diagnosing PDD from LBD (35).

Both PDD and LBD are characterized by the abnormal aggregation of alpha-synuclein, as outlined in previous sections (35). In both conditions, misfolded alpha-synuclein accumulates within neurons, forming Lewy bodies, which are the hallmark pathological features of Lewy body diseases (6). These abnormal protein aggregates are primarily found in the substantia nigra, limbic system, and cortical regions, contributing to both motor and cognitive symptoms (6)(9).

Although the presence of Lewy bodies is common to both PDD and LBD, the spatial distribution and timing of their accumulation in the patients’ brains differ slightly between the

two disorders (37). In Parkinson's disease (PD) and PDD, the pathological process typically begins in the basal ganglia, particularly in the SNc, where dopaminergic neurons are progressively lost (6). This results in the hallmark motor symptoms of Parkinson's disease outlined in the previous section (12). As the disease advances, Lewy bodies spread to the cortical regions, leading to the cognitive decline characteristic of PDD (37). In contrast, LBD involves more widespread cortical involvement from the outset, with Lewy bodies accumulating in the limbic and neocortical regions earlier in the disease course (37). This more diffuse distribution of alpha-synuclein pathology contributes to the early and prominent cognitive symptoms seen in LBD, distinguishing it from PDD (37).

While PDD and LBD share similar cognitive, neuropsychiatric, and motor symptoms, the primary distinction lies in the timing of cognitive impairment relative to motor symptoms (28). This difference is clinically established using the "one-year rule" (28). In PDD, motor symptoms precede the onset of dementia by at least one year. Patients are initially diagnosed with PD based on classic motor symptoms, and cognitive impairment gradually emerges later in the disease course (36). Although, as already discussed in detail, the cognitive deficits in PDD primarily involve executive dysfunction and, attention (33)(34), visuospatial and memory deficits are generally less severe in the early stages compared to LBD (34)(5). As PDD progresses, hallucinations, delusions, and apathy may develop, further complicating disease management (34).

In contrast, in LBD cognitive symptoms develop either before or concurrently with motor symptoms (36). In fact, unlike PDD, where motor dysfunction is well-established before dementia onset, patients with LBD often present with early cognitive impairment, attention deficits, and psychiatric symptoms from the beginning (5). One of the hallmark features of LBD is marked fluctuations in attention and alertness, where patients may experience episodes of

profound confusion followed by periods of near-normal cognition (5). This variability can make LBD difficult to diagnose, as it may resemble delirium or other cognitive disorders (37).

Another distinguishing feature of LBD is the presence of recurrent visual hallucinations, which occur earlier and more frequently than in PDD (5). Patients with LBD may also experience delusions and paranoia, i.e., odd beliefs, which can contribute to caregiver distress (5). In contrast, hallucinations in PDD generally appear later in the disease course and tend to be less frequent (5). Additionally, REM (Rapid-Eye-Movement) sleep behavior disorder (RBD) is prevalent in both conditions but is often more severe and appears earlier in LBD, sometimes preceding cognitive and motor symptoms by years (5).

In terms of neuroimaging being used to distinguish LBD and PDD, many studies found conflicting evidence (38). For example, one MRI study has shown that LBD exhibits greater cortical atrophy compared to PDD, particularly in the posterior cortical regions such as the occipital and parietal lobes using voxel-based morphology (39). In contrast, they found that PDD showed more subcortical atrophy with relatively preserved cortical structures in the early stages (39). However, another study claimed that they were unable to find any significant difference between the cortical atrophy of LBD and PDD (40). The use of functional imaging using fluorodeoxyglucose in PET/SPECT also had conflicting conclusions when trying to distinguish between PDD and LBD (38). In one study, the authors compared patients with either LBD or PDD to a healthy control group and claimed that when compared to the controls, PDD, but not LBD, presented more functional connectivity alterations in the frontal and striatal regions (41). However, in the same study, when they compared LBD patients to PDD patients directly, no statistically significant difference was found (41).

Similarly, when looking at CSF and blood biomarkers, although alpha-synuclein levels in CSF can be used to identify differences between PDD and Alzheimer's they are not able to

distinguish PDD from LBD due to alpha-synuclein levels being almost identical (39). However, the increased presence of ceramides in the CSF of patients with LBD was found to be elevated compared to PDD and Alzheimer's (39). Ceramides are a type of lipid called a sphingolipid that helps regulate neuroinflammation similarly to cytokines (39).

Overall, it is evident that the main difference in the diagnosis of PDD and LBD is the difference in the clinical presentation of the symptoms. There is still an open debate about the differences in pathology and imaging findings, with results often pointing to conflicting models. This is why experts believe these differences are not enough to distinguish the two diseases from one another.

Current Treatment Methods

Pharmacological interventions play a central role in managing the cognitive and behavioral symptoms of PDD. Inhibitors, such as cholinesterase inhibitors, are commonly prescribed to improve cognitive function (43)(45). Rivastigmine is the only cholinesterase inhibitor for PDD that is approved by the Food and Drug Administration (45). Acetylcholine is a neurotransmitter involved in memory and learning, which is often depleted in PDD due to cholinergic system dysfunction (23). Rivastigmine works by inhibiting the function of cortical acetylcholinesterase and butyrylcholinesterase, which are two enzymes that are responsible for the breakdown of acetylcholine therefore increasing its levels and improving cognition (43)(45). However, cholinesterase inhibitors are not a cure for PDD and can only offset the disease and improve the patient's quality of life during the disease progression (43). It is also important to consider and weigh the side effects of this medication when prescribing it. This is because, despite the benefit for cognition, cholinesterase inhibitors can cause gastrointestinal side effects such as nausea, vomiting, and diarrhea (43). Additionally, studies have shown that rivastigmine can exacerbate tremors by 10% (45). Other cholinesterase inhibitors exist as well,

such as Donexpil and Galantamine but are not used in PDD due to clinical trials being unable to display any statistically significant improvement results (45) (43).

Additional pharmacological treatment options have been researched, but show conflicting results (43) (45). For example, another pharmacological option includes memantine, an NMDA (N-methyl-D-aspartate) receptor antagonist, which regulates glutamate activity to prevent excitotoxicity and neuronal damage (45). Glutamate is a major excitatory neurotransmitter, however, if a neuron is overexposed to glutamate it can cause excitotoxicity - which leads to neuronal damage and death (46). This ends up exacerbating cognitive impairment symptoms shown in PDD (46). While memantine has shown benefits in treating Alzheimer's disease, its effectiveness in PDD is less consistent (43). Some studies suggest that memantine can improve cognitive and behavioral symptoms in PDD, but others report minimal or no benefits. Nevertheless, both studies showed the cholinesterase inhibitors to still be superior to memantine in improving cognitive impairment (45)(43).

In addition to the treatments that target cognitive decline, other medications are often needed for managing the psychiatric and behavioral symptoms of PDD (such as hallucinations, agitation, and sleep disturbances). For this purpose, antipsychotic medications are often required (47). Pimavanserin, a selective serotonin inverse agonist, has been approved for the treatment of the common psychotic symptoms of PDD such as hallucinations (47). Unlike traditional antipsychotics, pimavanserin does not block dopamine receptors, thus avoiding the worsening of motor symptoms that are often a consequence of other antipsychotics (47). While pimavanserin has been shown to reduce hallucinations and delusions without significant motor side effects, it can increase the risk of cardiac complications (47).

Non-pharmacological interventions are hypothesized in managing PDD as well, particularly for improving cognitive function and enhancing overall quality of life (48).

Cognitive rehabilitation programs, which focus on memory training, problem-solving, and attention exercises, have shown promise in slowing cognitive decline and maintaining mental function (48). These programs often include structured activities designed to stimulate memory and executive function, such as puzzle-solving, memory recall exercises, and strategy games (48). The benefits of cognitive rehabilitation include improved cognitive performance, increased independence, and enhanced emotional well-being (48). However, the effectiveness of these programs can vary depending on the stage of the disease, and patients with more advanced PDD may struggle to engage in or benefit from complex cognitive tasks (48). Additionally, the benefits of these programs typically do not outweigh the pharmacological treatment when solely observing cognitive improvement (48) (45).

Challenges with current treatments

Despite the availability of both pharmacological and non-pharmacological treatments, managing PDD remains challenging. One of the primary difficulties is balancing the benefits of symptom relief with the potential for side effects (13). Many medications used to treat PDD symptoms can interact with drugs prescribed for motor symptoms of Parkinson's disease, leading to complications such as increased sedation, worsened motor function, or cardiovascular problems (47). The variability in how PDD manifests among patients further complicates treatment, as cognitive, behavioral, and motor symptoms progress at different rates and require individualized approaches (28)(25).

Another challenge lies in diagnosing PDD early enough to implement effective interventions (13). Cognitive decline in PD often emerges gradually, making it difficult to distinguish early signs of PDD from normal aging or mild cognitive impairment (13). Additionally, many pharmacological treatments provide only modest benefits and are often

accompanied by significant side effects, which can deter patients from adhering to treatment plans (43)(45).

Emerging Therapies

Emerging therapies offer hope for more effective disease-modifying treatments. One example is immunotherapies that aim to clear misfolded alpha-synuclein from the brain are currently in clinical trials, with some early results suggesting reduced protein accumulation and improved cognitive function (50). Small-molecule inhibitors that prevent alpha-synuclein misfolding and propagation are also being explored as potential disease-modifying treatments (50). Gene therapy is another promising avenue for PDD treatment. Researchers are investigating ways to enhance the expression of neuroprotective factors, such as brain-derived neurotrophic factor (BDNF), to support neuronal health and synaptic function (51). Gene-editing technologies, such as CRISPR-Cas9, are also being studied to correct mutations in genes like GBA and SNCA that are linked to increased PDD risk (49). Additionally, stem cell therapies offer another potential strategy by replacing lost dopaminergic neurons and restoring normal neurotransmitter activity (49). Early-phase trials have shown that stem cell-derived dopaminergic neurons can integrate into brain circuitry and improve motor function, though their long-term effects on cognitive decline remain uncertain (49). Despite these promising developments, the heterogeneity of PDD and the overlap of motor and cognitive symptoms present ongoing challenges in treatment development.

Conclusion

In summary, PDD represents a complex and debilitating extension of PD that significantly impacts patients and caregivers. Diagnosis of this disorder requires a careful evaluation of cognitive decline that is independent of motor impairments. Furthermore, understanding the risk factors and mechanisms underlying PDD is essential for improving

diagnosis, treatment, and patient outcomes. Despite the significant clinical challenges and the limited treatment options, taking a comprehensive approach that integrates pharmacological and non-pharmacological strategies, alongside emerging therapies, holds the most promise for improving patient outcomes and enhancing the quality of life for those affected by PDD.

Methods

For this literature review, PubMed was used as the main search database. The key research words used were as follows: "(Parkinson's Disease Dementia) AND (Risk factors), (Parkinson's Disease Dementia) AND (Diagnostic Criteria), (Parkinson's Disease Dementia) AND (Lewy Body Dementia), (Parkinson's Disease Dementia) AND (Pharmacological Treatment Methods), (Parkinson's Disease Dementia) AND (Clinical Criteria)". Exclusion criteria included: books, pre-prints, non-human studies, and articles in a language other than English. Inclusion criteria included: review articles, original research papers, case studies, clinical trials, and clinical reports. Screening of 51 articles was done by reading abstracts and discussions/conclusions sections of the literature to find patterns within PD, risk factors and mechanisms of PDD, diagnostics of PDD, and treatment methods of PDD.

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