



## A Review of Parkinson's Disease Dementia & Parkinson's Disease; An Overview & Comparison with other Neurodegenerative Conditions

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### Abstract

Parkinson's Disease Dementia (PDD) is a neurodegenerative disease that often occurs later in the disease process of Parkinson's Disease (PD). When PDD is present, the cognitive impairment symptoms outweigh the severity of the motor symptoms associated with Parkinson's Disease. While similar to Alzheimer's disease (AD) and Dementia with Lewy Bodies (DLB), PDD differs based on certain cognitive symptoms and the timing of the onset of symptoms. Pharmacological management of PDD is similar to AD and DLB. Parkinson's Disease Dementia patients must be monitored for their safety and provided simple and routine schedules. This article will provide an overview of the disease, identification and management, and contrasts with AD and DLB

**Keywords:** Parkinson's Disease Dementia, Cognitive Impairment, Dementia With Lewy Bodies, Alzheimer's Disease, Parkinson's Disease

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### Introduction

Parkinson's Disease (PD) is the second most common neurodegenerative disease and is present in 0.3% of people worldwide, approximately 5 million people.<sup>1</sup> The cardinal symptoms associated with PD are asymmetrical resting tremor, bradykinesia and rigidity often with postural changes. Often the first sign of PD noticed is the pill rolling motion of the hands at rest (tremor), which often increases with ambulation. Many people associate PD with the motor symptoms such as the hand pill rolling, tremors, rigidity, kyphosis, and bradykinesia.<sup>2</sup> The pathologic hallmark of PD is Lewy bodies and Lewy neurites.<sup>3</sup> This hallmark is also present in Dementia with Lewy Bodies, and similar to Parkinson's Disease Dementia (PDD). The neurodegeneration seen in PD is caused by aggregation of the protein,  $\alpha$ -synuclein, in the central and peripheral autonomic networks. Parkinson's Disease results from the widespread depletion of dopamine in the substantia nigra and the nigrostriatal pathways to the caudate and putamen regions.

The results of dopamine depletion are inhibition of the thalamus and reduced excitatory input to the motor cortex. The biomarkers identified through the reduced shape volumes of the caudate and thalamus, due to insufficient dopamine levels, increase the likelihood of a person diagnosed with PD to also develop cognitive impairment. Cognitive changes can occur in patients with PD due to its effect on dopamine as well as acetylcholine, norepinephrine and serotonin. These chemicals in the brain support cognition, attention and mood.<sup>4</sup> The neurodegeneration in PD is thought to be due to genetic and environmental factors. A person's risk for acquiring PD will double if a first degree relative is diagnosed with PD. Genetic markers that have been identified to predict cognitive impairment in PD are apolipoprotein E (APOE) and catechol-o-methyltransferase (COMT) genotypes, microtubule-associated protein-tau (MAPT) haplotypes, and the presence of genetic mutations. The APOE genotype does give the strongest prediction of future cognitive impairment in PD patients.<sup>5</sup>

### Diagnosing Parkinson's Disease (PD)

There are biological markers to diagnosis of PD.<sup>6</sup> Thus, the diagnosis is based on the patient's clinical presentation and physical examination. The patient must display 2 of the 3 cardinal manifestations, which are resting tremor, bradykinesia, and rigidity.<sup>7</sup> The "gold standard" for diagnosing PD is a post mortem study of the brain, which will show Lewy bodies in multiple areas of the brain.<sup>8</sup> Part of the diagnosing process to determine the presence of PD is differentiating the abnormal findings and symptoms from other diseases, such as Dementia with Lewy Bodies (DLB), Alzheimer's Disease (AD), and Vascular Dementia (VD). Both AD and VD can coexist with PD, but continued research is linking dementia to PD. Special neuroimaging can be performed to assist in differentiating PD from the other neurodegenerative disorders.<sup>9</sup> Magnetic resonance imaging studies can detect white matter hyperintensities in the parietal-occipital areas of the brain found in many PDD cases. However, these white matter hyper-intensities were more severe in the temporal lobe in DLB.<sup>10</sup>

### Diagnosing Parkinson's Disease Dementia (PDD)

The diagnosis of PDD on average occurs almost 10 years after diagnosis of PD, but can be as long as 20 years.<sup>11</sup> Patient's diagnosed with PDD may be referred for further testing to determine cognitive involvement. A comprehensive neuropsychological evaluation may be performed; this test requires both oral and written answers from the patient to assess different cognitive domains. Abnormalities in testing provide a range of diagnoses from mild cognitive impairment (MCI) to actual dementia.<sup>12</sup> There is also a PDD specific MCI criteria that involves an assessment based upon attention/working memory, executive function, episodic memory, visuospatial and language.<sup>13</sup> The patient is able to carry out activities of daily living with MCI, but if dementia is suspected the patient experiences deficits in more than one cognitive area and everyday functioning is impaired. While 25% of Parkinson's Disease patients will be diagnosed with MCI, only 40% will develop dementia over the long term.<sup>14</sup> If dementia develops early in PD (within a year), a diagnosis of DLB should be considered rather than PDD.<sup>15</sup> One test used to determine visuospatial impairments, which gives increased consideration for PDD, is the Benton's judgement of line orientation testing.<sup>16</sup>

One study found great efficacy with using the clock-drawing test (CDT) to screen for cognitive decline. The test can be completed in less than 1 minute and involves giving the patient instructions to draw a clock with all the numbers and set the hands of the clock to the time of ten after eleven. Each drawing was scored based on the size of the clock, precision, overall accuracy, presence and sequencing of the numbers, and placement of the hands. Patient's with early stage PDD often drew the clock face very small due to interference in the basal ganglia and demonstrated poor fine motor skills. Patient's with known PDD have great difficulty with drawing of the spatial layout.<sup>17</sup>

#### Susceptibility to Parkinson's Disease Dementia (PDD)

Approximately 75% of PD patients who have been diagnosed for more than ten years will also develop PDD.<sup>18</sup> However, the rate of PDD increases to 83% of patients diagnosed for more than 20 years.<sup>19</sup> The longer a patient has the disease, the more susceptible they are to having cognitive symptoms, but not all PD patients develop PDD. Patients diagnosed initially with PD at age 60 or older are at increased risk of also developing PDD. Declining episodic memory and MCI can occur early in PD, but it also serves as a risk factor for progression to PDD. Parkinson's Disease is 50% more common in males than females and males are at greater risk than females for developing PDD.<sup>20</sup> Additionally, patients with PD experiencing hallucinations and/or thought disorders are at increased risk for PDD.<sup>21</sup>

#### Parkinson's Disease (PD) & Parkinson's Disease Dementia (PDD) Symptoms

Cognitive changes are common in PD and can start early in disease process and progressively deteriorate. As PD progresses the non-motor symptoms become more severe than the motor symptoms and can greatly decrease quality of life. The attributes of cognition mostly affected by PD are attention, working memory, short-term memory, executive function, language and visual reasoning. Patients with PDD often have difficulty concentrating on conversations, reading books, multitasking, planning, organizing, solving problems, and remembering where items are placed. Most patients do not have impairment in their long-term memory, but they have difficulty retrieving information from short-term memory.<sup>21</sup>

Many PDD patients experience "tip of the tongue syndrome", which means they have trouble finding the right words.<sup>22</sup> These patients often use simple speech and make short sentences due to cognitive decline. Those with PDD often speak in a low tone that is difficult to understand at times and have pauses in their speech that are

inappropriate. PDD patients also have great difficulty with naming objects. Patients with PDD often have difficulty shifting their attention from one subject to another and often become fixated on one subject for longer than usual. These patients also have difficulty conveying their emotions, their expression may be flat mostly even if they want to be happy or sad.<sup>23</sup> Psychosis is often seen in approximately 40% of patients in advanced stages of PDD. These patients may experience visual hallucinations, delusions, and are often paranoid due to the hallucinations. Most patients with PDD also have an impaired sense of direction or spatial maps. Unfortunately, PDD is associated with high mortality and often decreases the patient's life span by 4 years.<sup>24</sup>

#### Parkinson's Disease Dementia (PDD) Vs. Alzheimer's Disease (AD)

Parkinson's Disease and Alzheimer's Disease are neurodegenerative diseases that can be hereditary, but mostly are sporadic. Changes in the brain caused by PD are very similar to changes seen in AD and Cerebrovascular disease. In fact, AD and Vascular Dementia can coexist with PD, but recently the cognitive symptoms associated with a patient diagnosed with PD is termed PDD. In comparison to PD, AD presents with more pronounced memory loss and confusion and lacks the motor symptoms found in PD. Decline in memory is much greater and faster in AD compared to PDD. In AD, the onset of dementia is early in disease process, but dementia in PD usually occurs at least 1 year after motor symptoms. Patients with AD do not display the parkinsonism symptoms that are present in PD. Even though AD and PDD have differences, the medications used to treat each disease are similar; donepezil, rivastigmine, and galantamine.<sup>25</sup>

#### Parkinson's Disease Dementia (PDD) Vs. Dementia with Lewy Bodies (DLB)

Similar to Alzheimer's Disease, DLB is also a neurodegenerative disease, but DLB shares more similarities to PDD than AD. The internal morphological process of  $\alpha$ -synuclein related neurodegeneration within the brain causes most of the cognitive impairment seen in both PDD and DLB. Up to 75% of patients diagnosed with DLB will develop Parkinsonism (motor symptoms in PD), but the resting tremors are less frequent than those with PD or PDD.<sup>26</sup> Patients with PD and DLB often present with the same cognitive impairment symptoms; attention decline, executive function and visuospatial function decline. If dementia develops within 1 year of the initial diagnosis of PD, a diagnosis of DLB rather than PDD should be considered.<sup>27</sup>

There has been much debate whether PDD and DLB are the same disease. However, PDD and DLB are listed as two separate entities in the DSM-5 and differentiated by time of onset of motor and cognitive symptoms. One of the more appropriate ways to classify DLB is as an atypical form of Parkinsonism. Dementia with Lewy Bodies present with more cognitive impairment symptoms and a faster rate of cognitive decline than PDD. Rapid Eye Movement (REM) sleep behavior disorder is more commonly experienced in DLB than PD or AD, and often precedes cognitive decline. Hallucinations and mood disorders occur spontaneously and more frequently in DLB than PDD. Patient's with PDD often develop visual hallucinations after initiating L-dopa therapy rather than spontaneously. Language impairments are much milder in patients with DLB than PDD. Patient's with DLB often walk at a slower pace and have more difficulties with balance than those with PDD. Orthostatic hypotension is also a common finding with DLB that is not frequently noted in PDD.<sup>29</sup>

Enhanced medical technology, such as the voxel-based morphometric MRI, has allowed researchers to identify greater loss of grey matter in the frontotemporal, occipital and parietal areas of the brain in patients with DLB compared to PDD. This loss explains the increased occurrences of visual hallucinations in DLB. Postmortem research has shown that patients with DLB did have a greater amount of damage to

the brain than patients with PDD. The faster pace of cognitive decline and death from time of diagnosis for patients with DLB is much shorter than the patients with PDD.<sup>30</sup>

### Pharmacologic Therapy for Parkinson's Disease Dementia (PDD)

Current medications used for PDD only treat the symptoms, but do not slow the progression of the disease. Negative side effects from medications is present in many of the medications used to treat PD and PDD. Levodopa derived medications, which are dopamine agonists, are often used for initial treatment for symptoms of PD due to their ability to increase dopamine supplies, but these drugs can also worsen some symptoms which are not dopamine dependent. The dopamine agonists and anticholinergic drugs used to treat the motor symptoms in PD may increase the risk for hallucinations and confusion especially in patients diagnosed with PDD.<sup>31</sup> Levodopa medications treat symptoms including tremors, rigidity, verbal memory, and spatial working memory.<sup>32</sup>

Donepezil, rivastigmine, and galantamine can cause negative side effects, which may decrease medication compliance. These side effects include nausea, vomiting, diarrhea, decreased appetite and weight loss, as well as worsening tremors. Rivastigmine is the only drug that is Food & Drug Administration (FDA) approved specifically for the treatment of mild to moderate PDD.<sup>33</sup> There are two medications that are currently being studied for treatment of PDD; SYN-120 and nilotinib.<sup>34,35</sup>

### Non-Pharmacologic Therapy for Parkinson's Disease Dementia (PDD)

Due the lack of pharmacological treatments specific for PDD, alternative approaches have recently been implemented, including deep brain stimulation and cognitive rehabilitation. Deep brain stimulation (DBS) is sometimes performed on patients with PDD to improve motor functions including tremors, rigidity and slowness. Deep brain stimulation can be safely performed in patients with PDD. While the procedure may not improve cognition, it does appear to have benefits on other Parkinson's symptoms.<sup>36</sup>

Cognitive rehabilitation is feasible in PDD and may either improve or preserve cognitive performance over time. Advances in this area depend on selection of patients with a homogeneous cognitive phenotype as well as definition of appropriate timing of intervention and clinical variables. A single-blind pilot randomized control trial was performed to determine if cognitive rehabilitation produced positive results for patients with PDD or DLB. In collaboration, the patient and a therapist identified goals of care. The most popular goals were self-care, appropriate self-administration of medications, ability to learn new skills and maintain social and enjoyable activities. The therapist worked with each patient to develop a plan to achieve the goals using compensatory and/or restorative strategies. Outcomes of the intervention were measured at two months and 6 months. The patients and the caregivers reported better quality of life and health status, and decreased stress levels than those patients who did not receive the cognitive rehabilitation.<sup>37</sup>

### Caring for Patients with Parkinson's Disease Dementia (PDD)

Patient's with PDD often require frequent and constant supervision due to the motor and cognitive symptoms effecting safety. Regular routines allow the patient to anticipate daily activities. Smaller, simplified activities with frequent cues provided may be necessary. For example, tell the patient "walk to the bathroom" (allow the patient to complete this step before further instructions), "turn the water on", and then "wash your hands". Label household items and keep things in the same organizational place. Mental and physical exercises are important. Provide puzzles of any sort for the patient to

complete to stimulate the brain. Include patients with PDD in family and social events to maintain interactions and help them feel loved and important.

Patient's with PDD may have trouble comprehending what another person is saying to them. Always make eye contact with the patient, speak slowly and clearly using simple language to increase that patient's opportunity to understand and interact. Be specific if statements and questions using one subject at a time. When questioning a patient with PDD, give choices for answers rather using open ended questions. Providers need to be patient and persistent when caring for those with PDD.

### Conclusion

A diagnosis of PDD can occur approximately 10 years after diagnosis of PD, but can be as long as 20 years. Patients with PDD often have difficulty concentrating on conversations, reading books, multitasking, planning, organizing, solving problems, remembering where items are placed, and speaking. If dementia develops within a year of PD onset, consideration of Dementia with Lewy Body disease is warranted. Similar medications used to treat cognitive impairment in AD and DLB are used for patients with PDD as well, but rivastigmine is the only drug FDA approved for PDD.

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