How do Environmental Factors Affect the Development of Parkinson's Disease?

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Abstract

Parkinson's disease (PD) is a neurodegenerative disease that greatly impacts the lives of millions all over the world. The exact cause and origin of PD is unknown, but as neurologists research about the disease, they learn and discover previously unknown aspects of the disease. Through research, scientists have started to uncover that environmental factors, including toxicant exposure, head injury, and regular behavioral habits can all contribute to the development and/or progression of the disease both negatively and positively. Currently, there are several existing treatment options for PD patients, with each working in different ways and treating a few of the many symptoms of PD. Most of these treatment methods are relatively temporary and do not provide much long-term comfort. Additionally, none of them are without substantial side effects and do not fully cure the symptoms or the disease. To understand these symptoms on a deeper level and potentially discover new cures, extensive research and sharing of knowledge is required.

Key Terms: Parkinson's Disease, Neurodegenerative Diseases, Environmental Factors

How do Environmental Factors Affect the Development of Parkinson's Disease?

Parkinson's Disease (PD) is the second-most common neurological disease, preceded only by Alzheimer's (Tolosa et al., 2021). It affects "1–2 per 1000 of the population at any time," and "1% of the population above 60 years" (Tysnes & Storstein, 2017). It is a chronic and lifelong disease, with no working cure in place. Although mainly affecting people above age 60, it can also occasionally present itself in younger populations.

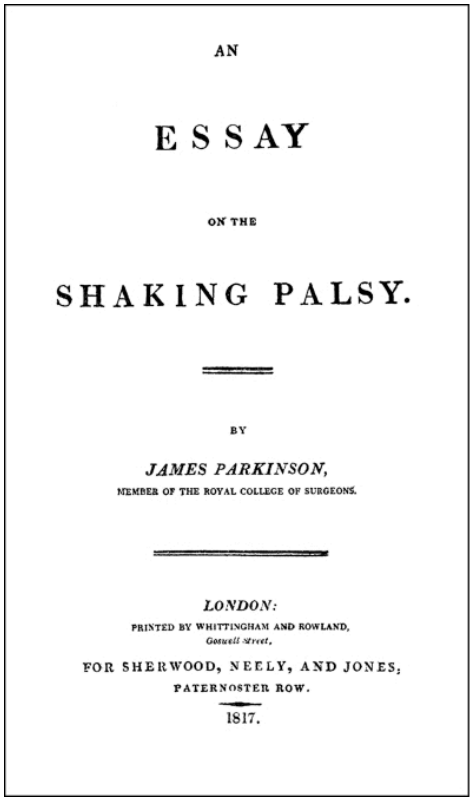
Although the exact cause of PD is not yet known, research suggests that it may be linked to environmental factors that instigate and/or speed up the development of the disease. Some of these factors include exposure to toxic chemicals and head injury. Additionally, "[g]enetic susceptibility factors may modify the effects of environmental exposures" (Simon et al., 2020). Although genetic components can play a factor in the development of the disease, most often it is related to behavioral and environmental factors. A study testing "concordance rates in monozygotic and dizygotic twins estimated the heritability of PD to be only 30%," a number much smaller than ideal to claim that PD is mostly hereditary.

In addition to chemicals and head injury, lifestyle can also influence the development of the disease. Cigarette smokers have shown lower risks of developing the disease, possibly due to the levels of nicotine consumed regularly. Additionally, regular caffeine consumers, especially men, have shown lower risk as well. High consumers of dairy have been associated with a higher development risk, due to the number of toxicants present in dairy and dairy products.

Definitions and Literature Review

Parkinson's disease is a neurological disease, most commonly presenting itself in people over 60 years old. It affects the central nervous system, causing "rest tremor, rigidity, bradykinesia, and stooping posture" (Beitz, 2014). Although affecting many throughout history,

the disease was first formally observed and documented in 1817 by English surgeon and physician James Parkinson, from which the disease's name is derived. Although Parkinson originally named the disease "Shaking palsy" because of its most telltale symptom, French neurologist Jean-Martin Charcot later noted that not all patients experienced the tremor symptom. So, he coined the term Parkinson's Disease, which is what it is known as today. James Parkinson documented his research and findings in his monograph "An Essay on the Shaking Palsy," in 1817 (see Fig. 1 – Parkinson's *Essay on the Shaking Palsy*). This was known to be "the first clear medical document dealing with Parkinson's disease" (Goetz, 2011). Later, Jean-Martin Charcot conducted more extensive research, noted his findings in clearer detail, and solidified research and information about the disease.



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

Goswell-street,

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.

Figure 1- Parkinson's Essay on the Shaking Palsy (Goetz, 2011)

Research on existing papers about Parkinson's disease and its environmental factors mainly results in papers all focusing on similar topics. Almost all of them were structured around the following three key aspects: what PD is, symptoms of the disease, and current methods of treatment. There is not much existing information about the effects environment can have on a patient and their experience with PD. In light of that, this review paper is not only written about the three main aspects of Parkinson's disease, but also how environmental factors affect the disease itself.

Some of James Parkinson's initial observations of PD included patients having difficulty performing activities even without tremor, and a slowness in movement rather than weakness. He also noted a considerable time delay "[b]etween the thought and the action," known as bradykinesia (Goetz, 2011). Charcot later noticed that patients with PD could be distinguished into two categories: the "tremorous and the rigid/akinetic form." Patients with tremors had uncontrollable shaking limbs, especially their arms and hands, while the rigid/akinetic form had trouble with mobility. With his detailed research and findings, PD had started to become more well-known and relevant to the medical community as the knowledge of his findings spread.

The most obvious body part affected by Parkinson's Disease is the brain. As it is a neurodegenerative disease, it stems within the brain and results in neurological and motor deficits. One additional distinguishable symptom of Parkinson's disease is the stooping posture. Charcot's findings especially noted this symptom, as well as "facial bradykinesia and contracted forehead muscles," which he noted resulted in a "perpetual look of surprise" on the patient's face (see Fig. 2 – Charcot's Patient Observations) (Goetz, 2011).

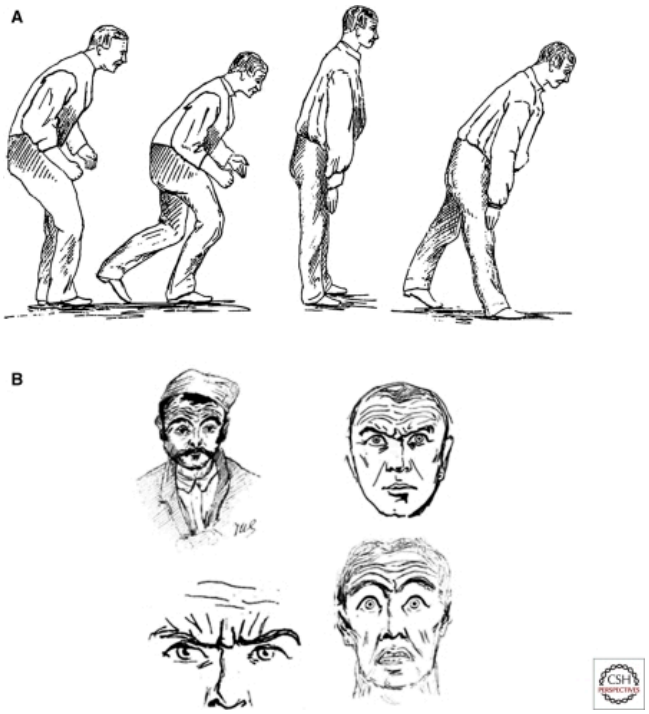


Figure 2 – Charcot's Patient Observations (Goetz, 2011)

One of the hallmarks in the development of Parkinson's disease is "loss or degeneration of the dopaminergic (dopamine-producing) neurons in the *substantia nigra* and development of Lewy Bodies" in these dopaminergic neurons (Beitz, 2014). Lewy bodies are misfolded proteins created by the body. The misfolded proteins do not function as they are supposed to, and therefore do not have a designated location to work at. They become unusable and unbreakable by the body and end up in the brain. Dopaminergic neurons are special neurons in the brain that release or are involved in the release of dopamine as a neurotransmitter, sending signals to various parts of the body to complete their respective tasks. They are in the *substantia nigra* (SN), a region in the center of the brain responsible for much of motor control and emotional response (see Fig. 3 – Substantia Nigra). Dopamine is a crucial hormone to the human body, responsible for the "feel-good" and pleasuring feelings. It acts as a reward system for the body and is essential for good physical and mental health.

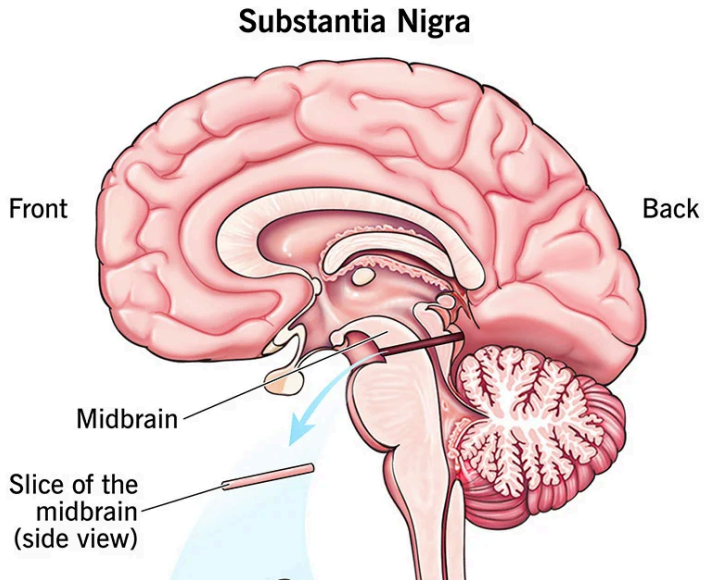


Figure 3 - Substantia Nigra (SN) ("Substantia Nigra (SN)," n.d.)

When the neurons responsible for this hormone degenerate or die off, motor control substantially decreases in the patient. Lewy bodies, which are "abnormal intracellular

aggregates" containing proteins such as synuclein and ubiquitin, interact with dopaminergic neurons to significantly impair the neuron function and make proper dopamine production and motor movement difficult (Beitz, 2014). These aggregates are mostly made of cytoplasm and are insoluble by the body. The telltale symptoms of PD begin to openly show once "50% or more of the dopamine neurons in the midbrain are lost" ("Parkinson's Disease," n.d.-a). Although PD's pathology is generalized as stemming in the *substantia nigra* and involving only dopaminergic neurons, the disease involves non-dopaminergic neurons outside the SN as well. Initial clinical diagnosis of PD is based on the motor deficits such as stooping posture, bradykinesia, and resting tremor, but there are non-motor deficits as well. These include "anosmia, constipation, depression and REM sleep behavior disorder," which can all begin to develop years before the motor deficits develop or are medically discovered (Simon et al., 2020).

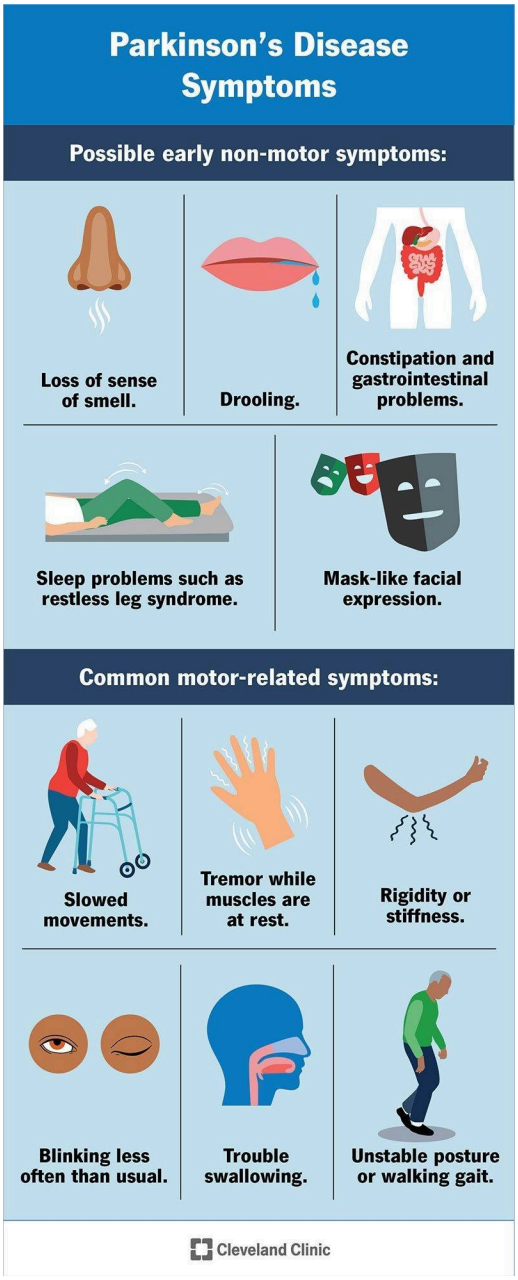


Figure 4 - Symptoms of PD ("Parkinson's Disease," n.d.-b)

Contextualizing the Research

Parkinson's disease stands a very significant disease in the world, "with a global prevalence of more than 6 million individuals" today (Tolosa et al., 2021). The most significant risk factor for the development of Parkinson's disease is age, as most patients are aged 60 and older. Expert neurologists estimate that PD affects "at least 1% of people over age 60

worldwide" ("Parkinson's Disease," n.d.-b). Additionally, "men are more susceptible than women with a prevalence ratio of approximately 3:2" (Tolosa et al., 2021). Although the definitive cause of the disease is not yet known, there are several factors that have been tested and show probable ties to the development of the disease.

Environmental factors play a very significant role in the development of Parkinson's disease. Some of these factors include exposure to toxic chemicals, head injury, and lifestyle. All three of these factors can combine with genetics to alter the outcome of the development of the disease. Interestingly, some factors increase the risk of developing Parkinson's disease, while others lower the risk.

Exposure to toxic chemicals such as pesticides has shown association with an increased risk for developing Parkinson's disease. Farm workers and residents of rural areas have been shown to be at a higher risk of developing the disease. Direct exposure, as well as passive/second-hand exposure both contribute to toxicity and risk. The specific pesticides that have been lab-tested to display signs of parkinsonism are "paraquat, rotenone, 2,4-D and several dithiocarbamates and organochlorines," which have led to theories of their link to the development of PD (Simon et al., 2020). Extreme head injury can also increase the risk of PD. Trauma to the head can cause permanent neural defects, which can lead to the misfolding of proteins and the formation of more Lewy bodies. Additionally, behavioral factors can also affect the diagnosis of Parkinson's disease. Some of these factors include daily lifestyle (such as eating habits), and daily activity routines.

Research suggests that regular cigarette-smokers are at a lower risk for developing PD. There is preliminary evidence suggesting genetic modification through intense tobacco and nicotine consumption, which may be preventing the development of Lewy bodies. The same

applies for regular coffee-drinkers and caffeine-consumers, especially in men. The men who drank the most amount of coffee seemed to have the most benefits when it came to preventing or "curing" PD. On the other hand, dairy consumption seems to be related to higher risk of developing PD, due to the naturally occurring toxins in dairy and dairy products. Research has also shown that maintaining a healthier diet, such as eating lots of fruits, vegetables, and grains aids with lowering the risk of the disease (Simon et al., 2020).

Lastly, exercising regularly has shown to reduce the risk of PD, especially in men. The figure below shows the current number of people with PD in blue, the estimated number of patients if people increased their amount of regular physical activity by 20% in red and by 80% in green (Simon et al., 2020). Increased physical activity also helps with muscle stiffness and rigidity, flexibility and balance, as well as mental wellbeing, by improving depression or anxiety.

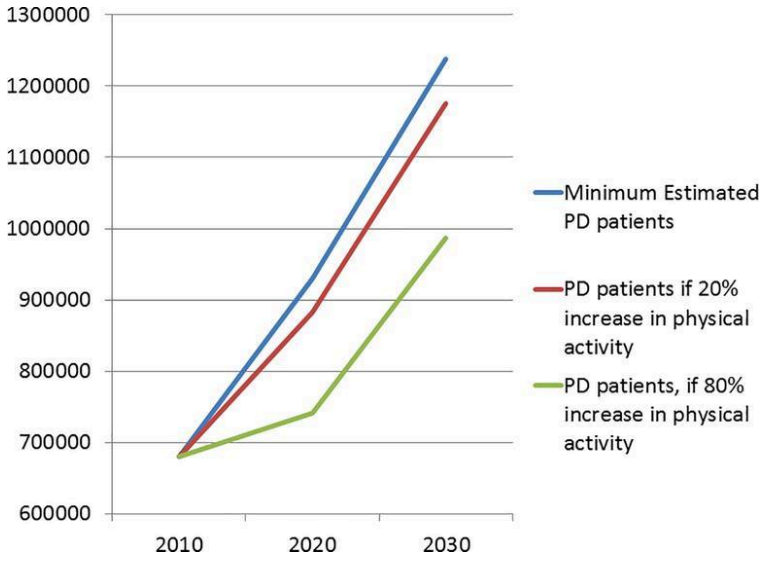


Figure 5 (Simon et al., 2020)

Although there is no working cure for Parkinson's disease, there are existing medicines to reduce the effects of the disease. The most common treatment option is medication, especially that to reestablish dopamine levels in the body. A popular prescription medication is carbidopa-levodopa. Levodopa is currently the most effective on the market and is a "natural

chemical that passes into the brain and is converted into dopamine" ("Parkinson's Disease," n.d.-c). It is mixed with carbidopa to prevent premature dopamine production outside the brain, reducing overall side effects, including "nausea or lightheadedness" ("Parkinson's Disease," n.d.-c). This artificial "production" of dopamine allows the body to achieve tasks it was not able to do because of the disease, including wider range of motion, fewer non-motor symptoms, and even increased happiness and better mental health. However, after long periods of using this medication, its effectiveness begins to deteriorate, and the medicine begins to fluctuate effectiveness in a waxing and waning manner, and eventually "'[wear] off'" ("Parkinson's Disease," n.d.-c). Additionally, after taking higher doses of the medication, patients may experience involuntary motor movements, called dyskinesia.

Another type of existing medications are dopamine agonists, which, unlike levodopa, do not change into dopamine once they reach the brain. Instead, they "mimic dopamine effects" in the brain, tricking it into believing sufficient dopamine production is still occurring. This also allows everyday tasks to be completed with much more ease and comfort. However, dopamine agonists "aren't as effective as levodopa in treating symptoms," even though they do last longer and can sometimes be used in combination with levodopa to treat the waxing and waning effects of it. Dopamine agonists share similar side effects with levodopa, but also encompass more, such as "hallucinations, sleepiness and compulsive behaviors such as hypersexuality, gambling, and eating" ("Parkinson's Disease," n.d.-c).

Monoamine oxidase B (MAO B) inhibitors are a type of medicine that, instead of replacing or mimicking dopamine in the brain, preserve the little amounts that are naturally being produced. These medicines include selegiline, rasagiline, and safinamide, which "help prevent

the breakdown of brain dopamine by inhibiting the brain enzyme monoamine oxidase B (MAO B),” which is the unwanted enzyme that breaks down the dopamine created by the brain.

The last three main types of medication are Catechol O-methyltransferase (COMT) inhibitors, which work with levodopa and prolong its effects by blocking one of the enzymes that breaks down dopamine, anticholinergics, which help control the trademark PD tremor, and amantadine, which provides short-term relief of the early-symptoms of Parkinson’s disease (“Parkinson’s Disease,” n.d.-c). Each medicine works in different ways and treats different symptoms that come with PD, but they all also have their own side effects that alter and impact the patient. However, if one medicine were to be chosen, levodopa is currently the most effective and widely used of these few.

The last type of treatment currently available is a surgical procedure called deep brain stimulation (DBS). In this procedure, surgeons “implant electrodes into a specific part of the brain. These electrodes are connected to a generator, which is attached to the chest near the collarbone. Like a pacemaker, the generator “sends electrical pulses to the brain and may reduce Parkinson's disease symptoms” (“Parkinson’s Disease,” n.d.-c). This treatment method is most often used for patients who have very advanced Parkinson’s disease, to the point where medications such as levodopa have no effect or unpredictable effect on the body.

Although these treatment options do help reduce the effects of Parkinson’s disease, none of them are 100% effective and without side effects. The most probable option for the comfort of patients is diagnosing the disease early and treating earlier stages later than late. Recent research from scientists at Duke University shows a possible blood test detecting a key indicator of Parkinson’s disease, well before motor symptoms become apparent (“New Blood Test Detects a

Key Indicator of Parkinson's Disease," n.d.). Detecting the disease this early would help begin treatment immediately, before neurological damage can get to the point of no return.

Currently, the only method to diagnose Parkinson's disease is through the physical symptoms exerted by the disease. By this point, neurological damage is too extensive, and the disease has advanced too much for treatment to significantly impact anything. Additionally, even though many patients currently exhibit Parkinson's disease symptoms, there is no surety that they have Parkinson's disease. All of these could be the result of another disease or disorder, unknown to physicians and medical researchers alike. A way to definitively diagnose a patient with Parkinson's disease means they can participate in clinical trials, medical studies, etc. with hopes of the development of medical advancements and possible cures to the disease.

The research conducted by senior author and scientist Laurie Sanders and her team at Duke University was based around DNA testing and damage in the mitochondria, which are commonly known as the "powerhouses" of cells and are responsible for the bulk of cellular respiration. As mitochondria contain their own DNA that is separate from the DNA inside the cell's nucleus, it can be damaged without affecting the entire cell. Sanders and her team used evidence from previous studies, which related "mitochondrial DNA damage with an increased risk of Parkinson's disease," and used reports of "an accumulation of mitochondrial DNA damage specifically in the brain tissue of deceased Parkinson's patients" ("New Blood Test Detects a Key Indicator of Parkinson's Disease," n.d.). In the study, Sanders and her team studied the genetic material inside the mitochondria of cells of Parkinson's disease patients and healthy people to compare the two and note genetic differences. Using Polymerase Chain Reaction (PCR) technology, the team was able to replicate their collected DNA samples and examine them much easier. Through this study, the researchers were not only able to examine parkinsonian and

healthy blood cells, but also the "high levels of the damaged DNA in the blood samples of people who harbor the genetic mutation LRRK2, which has been associated with an increased risk of the disease" ("New Blood Test Detects a Key Indicator of Parkinson's Disease," n.d.). Their researched was able to detect Parkinson's disease in patients both with and without the LRRK2 mutation. In total, this study is an extremely important contribution to the world of Parkinson's disease research and medical innovation.

Discussion and Conclusion

Parkinson's disease is an extremely significant and relevant topic in the medical community, as it affects millions globally. Being one of the most common neurodegenerative diseases, it is constantly being researched and tests are regularly being conducted to develop cures. As it is being researched more, neurologists are learning more about the cause and etiology of the disease, and what external factors can influence the development and progression of the disease. Some of these external factors are environmental and others are genetic or behavioral. Environmental and behavioral factors can affect the development of Parkinson's disease both negatively and positively. For example, some behavioral habits including consumption of caffeine and regular smoking surprisingly seem to reduce the risk of developing Parkinson's disease. Exposure to toxic chemicals, regular consumption of dairy, and head injury, on the other hand, increase risk of developing PD.

Parkinson's disease is not a topic that should be taken lightly. It affects large populations of the world, greatly impacting their daily lives. It is important to take measures of action and do whatever is possible to prevent the development of this disease. There is no present cause or cure for Parkinson's disease, which makes it hard to determine what can be done to prevent it. However, living a healthy lifestyle can't hurt. Exercising regularly can improve mental and

physical health, and for current PD patients, it can help reduce the rigidity/bradykinesia symptoms. Additionally, maintaining a healthy diet by eating several kinds of fruits, vegetables, grains and protein with substantial variety can improve body function and performance.

Parkinson's disease is not a new generation disease and is not purely attributed as a lifestyle disorder. We can positively conclude that environmental factors and lifestyle contribute to the aggression of the chances of being impacted. However, for generations early sufferers were treated with varying results, as the name of the disease had an evolution as well.

A successful management of the PD has been made possible with the discovery of dopamine in the 1950s and the subsequent developments in PD research has presented varying concluding results and effects.

Despite the increased attention on PD there is still no definite diagnostic tests that can medically confirming the presence of the disease. Instead, diagnosis and treatments are administered based on prior knowledge and observable symptoms of the patient.

Research has concluded that PD is more than just a motor disorder, as an intense focus on non-motor aspects focusing on environmental factors are under way today. While research into the genetic basis of PD continues, rehabilitation therapy is showing promising results. Despite many advances, the medical management of PD is complex. As PD progresses to the advanced stage, care becomes increasingly complicated. Considering these challenges, research into varying therapies is occurring simultaneously. For now, healthcare providers continue to educate themselves about available treatments, management and look forward for better alternatives in the near future.

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