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# Alternative Treatment Options to Levodopa and Carbidopa for Parkinson's Disease Patients

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## ABSTRACT

The most commonly used treatment for Parkinson's Disease (PD) is levodopa used in conjunction with carbidopa. Despite being able to alleviate the motor symptoms of PD, it is unable to slow down the progression of the disease or give neuroprotective effects. There is no effective cure for PD or any treatment that is able to prevent the advancement of Parkinson's pathology. The purpose of this research was to examine different combinations of treatments and medications that provide best results for patients and investigate novel research that is conducted in order to target the causes of PD, rather than its effects and symptoms. Interviews of doctors were conducted in order to determine the most commonly used treatments and what they have had success with when treating patients. The results revealed that levodopa still remains the most effective treatment, but its effects can be improved by adjunctive medications or therapies. Recent research also suggests that drugs that target other factors of PD pathology separate from dopaminergic neurons provide more neuroprotective effects and may be able to prevent the progression of the disease.

## Introduction

According to the Parkinson's Foundation, around 60,000 people are diagnosed with Parkinson's disease (PD) each year just in the US (*Statistics | Parkinson's Foundation*, n.d.). Despite being the second most common neurodegenerative disease, the most common treatments of Parkinson's disease are not cures and are unable to stop progressive cell death in the brain. Current treatments of PD are focused on improving the dopamine levels in the brain and are able to alleviate the motor deficits of tremor, bradykinesia, rigidity, and impaired posture, but are unable to stop the progression of the disease or treat causes of PD. The most prescribed medicine, levodopa, has shown to have unwanted side effects, one being levodopa-induced dyskinesia (LID) that has been shown to decrease when used along with other treatments. Treatments that focus on other parts of the brain than dopaminergic neurons may have better PD neuroprotective effects, or the ability to prevent neuronal death and slow down. Some of these targets include the expression of lymphocyte activation gene-3 (LAG-3) proteins, α-Syn, glial cells, and mitochondrial function. Glial cells in particular have shown to be effective in terms of stopping the death of dopaminergic cells. All of these alternatives can be better treatment targets for PD than levodopa because they affect the pathology of the disease more directly by targeting areas other than dopaminergic cells and will be effective for longer without compromising the alleviation of motor symptoms. The purpose of this paper is to describe the mechanisms of current available treatments, explain the side effects of levodopa, namely LID, and introduce novel treatment and research that targets other parts of the brain than dopaminergic pathways to achieve better neuroprotective effects for PD patients.

Parkinson's disease was first described in 1817 by James Parkinson, an English physician, as a "shaking palsy" because of tremors and other motor symptoms displayed in the disease (*History of PD,* n.d.). Now, the disease is defined as an incurable, progressive neurodegenerative disorder characterized by motor symptoms, including tremors, stiffness of movement, bradykinesia, and postural instability (Panicker et al., 2021). Loss of dopaminergic cells in the substantia nigra in the brain, which is involved in the regulation of movement in the body, is the main mechanism

of PD. Dopaminergic cell death can be caused by the accumulation of alpha-synuclein (α-Syn), Lewy bodies, and increased neurotoxicity observed in PD.

## Review of Literature

### Current Treatment for Parkinson's Disease

The current available PD treatments focus on the lack of dopamine and are unable to stop the progression of the disease. The most common and effective treatment for PD is levodopa, which is usually prescribed with carbidopa in order to help the body absorb the levodopa before breaking it down in the stomach (*Levodopa and Carbidopa: MedlinePlus Drug Information*, 2022). The levodopa is absorbed through the gastrointestinal tract and converted into dopamine, which helps provide extra dopamine in place of the loss of dopamine in PD (Cerri & Blandini, 2020). To combat the lack of dopamine in the brain in PD, levodopa is administered, since it is a precursor to dopamine and the body is able to metabolize it in order to provide dopaminergic function in the brain. Since dopamine-dependent function is essential in the substantia nigra, which is related to movement, levodopa administration allows the brain to continue to use the exogenous dopamine and continue a relatively normal regulation of the body's movement.

Although levodopa remains the most popular treatment, its effectiveness may eventually fade as the severity of the PD progresses and L-DOPA-induced dyskinesia (LID) will set in (Parker et al., 2018). LID is characterized by different types of spontaneous and uncontrollable motor abnormalities that are a reverse of the symptoms of Parkinson's disease. Eventually, levodopa is unable to properly alleviate the motor deficits in PD, perhaps due to continuous dopaminergic cell death in PD. However, if the PD is not treated with levodopa, the motor symptoms of PD include an increased amount of tremor and stiffness that can be debilitating (*Stages of Parkinson's | Parkinson's Foundation*, n.d.).

On the other hand, if the patient has been receiving regular prescriptions of levodopa, opposite symptoms will also be observed in the long run, including involuntary movements in the neck, face, jaw, tongue, shoulders, or limbs (Calabresi et al., 2010). Dopamine agonists and other formulations of levodopa are able to treat PD by lowering the occurrence of parkinsonian movement, but both still lead to the inevitable onset of LID. In addition to deep brain stimulation (DBS), all treatments used for PD are unable to stop or slow down the progression of the disease (Dawson & Johns Hopkins Medicine, 2019). While current treatments alleviate the motor symptoms for a short period of time, they do not alter the way the brain functions in the disease. Another drawback is that LID sets in after extended use of levodopa in late stage PD. In the early stages of PD, remaining dopaminergic neurons store the excess exogenous dopamine from the levodopa doses, decreasing the variation of dopamine levels in the brain (Brooks, 2008). In later stages, so many dopaminergic neurons have perished and this storage ability diminishes, contributing to the excess involuntary movement, as opposed to the slowness and tremors in PD. However, in spite of the temporary effects and possible severe long term side effects, levodopa is still the most commonly prescribed medicine for the disease. In fact, almost all PD patients will take it at some point during their treatment ("Approved Medications | American Parkinson Disease Assoc.," n.d.). The ingestion of levodopa will almost always lead to LID and other alternative treatments could provide better long-term results.

### Side Effects of Levodopa

Levodopa also has many unwanted side effects, ranging from mild to severe, that decrease when used alongside other treatments. There are a wide variety of treatments, including drugs such as dopamine agonists and amantadine, surgical options like deep brain stimulation, and other options such as physical therapy, focused ultrasound thalamotomy, and different prescription timelines that may be able to prevent side effects and improve quality of life. Levodopa is currently the most effective prescribed treatment for PD, but it comes with many side effects, including levodopa-

induced dyskinesia (LID) (Olanow et al., 2017). Experienced in almost all patients who take levodopa, LID is an inevitable part of the course of treatment. LID is characterized by "chorea, ballism, dystonia, [and] myoclonus" which can occur in the "neck, facial muscles, jaw, tongue, hip, shoulder, trunk, and limb" of the patient (Pandey & Srivanitchapoom, 2017) which are all different types of movement disorders that involve involuntary, unpredictable, and abrupt muscle movements in the listed parts of the body. This can lower quality of life of patients and limit the treatment options because the levodopa dosage will often be curbed in order to try and stop the LID. Other than LID, levodopa has other side effects: dizziness, loss of appetite, nausea, constipation, muscle pain, insomnia, and REM sleep behavior disorder (*Side Effects of Sinemet (Carbidopa-Levodopa), Warnings, Uses*, n.d.).

Dopamine agonists are a popular alternative and sometimes prescribed alongside levodopa to decrease motor fluctuations and other negative side effects. In a 2020 study, it was found that apomorphine treatment, a type of non-ergot dopamine D2 agonist, was able to reduce the "off" time of levodopa, decreasing the severity of the dyskinesia (Cerri & Blandini, 2020). The off time refers to the period of time where the motor and non-motor symptoms begin to start up again between medication doses. By decreasing this period of time, the patient is able to have a more stable behavior throughout the day and not have periods of time where their body is moving in unusual ways. When levodopa is used with dopamine agonists, the dosage can often be decreased, which lowers the risk and severity of LID, which is a common strategy that PD and motor disorder specialists take in order to reduce LID. Another effective drug option is amantadine, a medicine originally used to prevent influenza, but also found to be beneficial as an antidyskinetic drug. It is one of the "only medicines that can be used alongside levodopa that does not worsen the LID" (Von Coelln, 2021) because many drugs combined with levodopa tend to make the LID worse, since they work similarly to the mechanisms of levodopa by providing synthetic dopamine to the brain. However, amantadine has shown to decrease the effects of levodopa quite effectively; although, there are some unwanted side effects to be cautious of, including decreased appetite, depression, and swollen legs (*Amantadine,* n.d.).

Another popular option is to combine the levodopa prescription with surgeries such as deep brain stimulation (DBS), focused ultrasound thalamotomy (FUS-T), and light-activated optogenetic surgeries. DBS is a surgical treatment for PD that targets the subthalamic nucleus (STN) and reduces the effects of LID because the dosage of levodopa can be lowered after the surgery (Von Coelln, 2021). The DBS provides electrical stimulation in the brain to create an action potential for dopaminergic neurons, which means that the dopamine neurons are able to fire without receiving stimulation from actual dopamine. Levodopa dosage can be reduced following the surgery because not as much is needed to stimulate previous dopamine-dependent neurons (Vijayakumar & Jankovic, 2016); lower dosage means the brain is not flooded with dopamine, diminishing the severity of LID. However, the levodopa prescription cannot be completely eradicated as some of the motor symptoms of PD will come back even with the electrical stimulation from the DBS. Some patients also do not like this option because DBS is an invasive surgery and can be bothersome to have the battery connected to the electrode in the brain constantly on hand. Focused ultrasound thalamotomy (FUS-T), on the other hand, is a noninvasive treatment with no surgical incision. Instead, doctors use MRI to see where the target areas of PD are in the brain and guide the ultrasound rays to that one point to destroy small amounts of cells in the brain. The patient can be awake for this treatment, and there is no pain, hardware, or surgical incision. This therapy option provides similar results to DBS; it eases the "off" time of levodopa and decreases the severity of dyskinesia, but cannot produce good enough results to completely stop the prescription of levodopa. FUS-T is a good option for those who cannot or do not want to have the DBS surgery because it is less expensive, less invasive, and uses less batteries. Unfortunately, FUS-T is currently only approved for procedure on one side of the brain and may not have satisfactory results as this means only one side of the body's motor movements will improve (Von Coelln, 2022). A clinical trial for approval to be used on both sides is currently underway. If FUS-T becomes approved for use on both sides of the brain, it may be more of a viable treatment to a wider range of PD patients.

Another option that can be used alongside the prescription of levodopa is physical therapy. Various exercises and physical therapies have shown to be able to decrease the dosage of levodopa. In recent studies, the Unified Parkinson's Disease Rating Scale (UPDRS) scores were used to measure the level of various non-motor and motor experiences of daily life of PD patients. In these studies, physical training has shown to improve UPDRS-II and UPDRS-

III scores in PD patients and decrease the levodopa dose (Mak et al., 2017). Quality of life of PD patients was improved when exercise was regularly incorporated into their daily life. Their motor skills were also improved, and the results showed to be possibly neuroprotective, since the amount of levodopa prescribed could be decreased. Decreasing levodopa could also, in turn, decrease the severity of dyskinesia as there is less levodopa being prescribed.

Timing of levodopa intake can also vary the outcome and symptoms of PD treatment through different prescription methods of levodopa. In a 2017 review by Pandey and Srivanitchapoom, different ways of prescribing levodopa were outlined. More frequent and smaller doses of levodopa can help decrease the peak-dose dyskinesia effects (Pandey & Srivanitchapoom, 2017). Longer-acting levodopa capsules can also help patients with off-period dyskinesia. However, these different schedules of treatment can be bothersome for the patient to keep remembering to take and may not completely rid the LID.

The use of different types of treatments along with levodopa can be beneficial because it allows the dosage of levodopa to be decreased to make the effects of LID less jarring or obvious. However, the need for a levodopa prescription cannot be eradicated because it is still the most effective drug for PD. If levodopa is entirely unused, the motor symptoms of PD may not diminish even if patients are on other medication or have received surgery.

## Novel Targets for Parkinson's Treatment

More recent approaches to treating PD target other areas of the brain. Instead of focusing on the dopamine and dopaminergic cells, some researchers focus on other causes of the disease, such as the α-Syn aggregation, brain toxicity, fragmented mitochondria, and LAG3 proteins. These drugs have shown to have much better neuroprotective effects in MPTP-induced models of mice and in cell cultures from mice with PD. These studies are outlined in the following paragraphs.

One approach researchers have been investigating is targeting the α-Syn aggregation and inside the brain because they are known to be the inherent cause of PD and loss of dopamine cells. α-Syn aggregation begins in the gastrointestinal tract and spreads through the nervous system to the brain, causing neurons to die in PD patients (Kim et al., 2019). Increasing interest in this area has led to drug research that tries to prevent α-Syn from accumulating. One such example is Anle138b, an α-Syn aggregation inhibitor, that produced neuroprotective results (Valera et al., 2016). Anle138b was able to block the neuronal degeneration and disease progression in animal models of PD. This means that it was more effective than levodopa in decreasing the amount of dopaminergic cell death in the brain. α-Syn has shown to be a better target for treatment because it was able to actually slow down the rate of neurodegeneration. However, if the treatment is paused, the α-Syn begins to accumulate again and the neurodegeneration continues to occur.

Other researchers have targeted other aspects that are caused by the α-Syn aggregation. α-Syn accumulation causes glial cells in the brain to become neurotoxic, which may be what causes dopaminergic cells to die (Valera et al., 2016). When the α-Syn was inhibited, it bore positive results of reduced neurotoxicity and slowed progression of PD. More extensive research exists to target α-Syn levels or find other ways of slowing disease progression, such as decreasing neurotoxicity in hopes of producing neuroprotective results. NLY01, a GLP1R agonist, reduced the α-Syn and the level of cell death. The agonist also resulted in a decrease of astrocyte conversion to their neurotoxic A1 forms (Yun et al., 2018). This drug works by inhibiting the release of cytokines from microglia. Since the neurotoxic cytokines were unable to reach the astrocytes, another type of glial cell, the astrocytes remained healthy and were prevented from turning into their A1 toxic forms. Because the toxicity was inhibited, the dopaminergic neurons in the brain survived, showing that the progression of the disease was also slowed down by changing the pathology of the disease, providing better neuroprotective effects than levodopa, which is unable to stop or slow down cell death. However, α-Syn continues to aggregate in the brain, so the root cause is not completely gone, but they are rendered less harmful because the microglia are still unable to release neurotoxins.

Another target in the brain to slow down PD is the mitochondrial function in glial cells. The P110 drug inhibited the fragmentation of mitochondria and resulted in neuroprotection of the dopaminergic cells. P110 works

through two different mechanisms: decreasing the amount of fragmented and dysfunctional mitochondria and increasing the ratio of healthy mitochondria compared to the fragmented mitochondria (Joshi et al., 2019). Neuroprotective results were produced because there was less activation of A1 astrocytes from the fragmented mitochondria and the healthy mitochondria was able to prevent more neurotoxicity, showing that mitochondria play a significant role in PD and can be another target for medicine. Drugs that target mitochondrial function may become better alternatives to levodopa in the future because they can better prevent neurotoxicity and slow down the progression of the disease.

All these targets have shown promising results and there are many other drugs that target these parts of the pathology of PD or novel targets. However, most of the research of these targets is relatively new, so there are no treatments currently available to the public for prescription. Some of the drugs are in their clinical trials, but still have a minimum of two years before they are released to the general public (Seo, 2022). The new field of glia research will likely be an integral part of how PD research progresses in the future. Many researchers are shifting from targeting dopamine loss and replenishing it to creating drugs that can actually change the disease's pathology and aim at more of the causes of PD rather than its effects.

Parkinson's disease afflicts many people all around the world, causing problems with movement, mood disorders, and decreased quality of life. The rates of diagnosis are increasing, and more and more elderly people suffer from the effects of PD. Although there are treatments that can curb these symptoms, there is no current cure for PD, and nothing is prescribed to prevent the progression of the disease. These temporary treatments also have mild to severe side effects; the most prescribed medicine for PD, levodopa, has the severe side effect of LID that almost no patient can escape from in late-stage PD treatment. Better treatment alternatives for this exist, whether it is combining different medicines to postpone the LID that sets in, or new treatment targets. The exploration of new treatments show promising experimental evidence that a treatment that better slows down the progression of the disease can be created with the new targets. In particular, the glial research community has high hopes for stopping dopaminergic cell death and has a drug (NLY01) in its second phase of clinical trials. Patients and doctors should consider these alternatives and combination therapies when deciding the best treatment process for the patient.

## Methods

Primary data was collected to answer the research question: Are there better alternative treatments than levodopa and carbidopa for PD in terms of how it affects the pathophysiology of Parkinson's Disease? The hypothesis was that better alternatives for the treatment of Parkinson's Disease that affect the cause of the disease more directly and be effective for 10% longer without compromising the alleviation of motor symptoms do exist. The primary data collection involved interviews of five researchers and a comparison of the treatments they use and which ones they have had the most success within terms of motor function improvement and severity or prevention of side effects.

During the data collection process, five doctors were interviewed: Dr. Stephen E. Grill, Dr. Debra Ehrlich, Dr. Friedrich Rainer von Coelln, Dr. Lisa Shulman, and Dr. Stephen Reich. Google Meet meetings were set up with each of the doctors throughout March and April. The doctors were asked an assortment of similar questions, with adjustment for the flow of conversation and time restrictions of the interviewees (Appendix A). The questions were mostly about what treatments the doctors usually prescribe and how they alter the treatment in the occasion of certain side effects or different combinations of symptoms. Patterns were analyzed from the five interviews in order to form conclusions.

## Results

The results of the data collection partially supported the hypothesis that better alternatives to levodopa exist, based on the level of motor function improvement and level of side effects. The interviews showed how formulations of levodopa and carbidopa remain the most popular and effective treatment for PD since it was approved for prescription,

but there are ways to use it in combination with other therapies or medicines in order to improve its efficiency or reduce side effects. Across the five doctors, there were several consistencies in the way they treat their patients in a variety of ways, including their initial treatment, reaction to short term side effects, reaction to long term long term side effects, and surgical options (Appendix C).

For all the doctors, the initial, go-to treatment is levodopa. They all agree that levodopa and carbidopa together are prescribed to every single one of their Parkinson's patients and remains the most effective treatment to this day. It allows patients to regain a mostly normal life for several years longer. However, one doctor stated that although it is the most effective drug therapy, it may not treat all active symptoms of Parkinson's disease, such as balance or cognitive problems. Most of the doctors also agreed that there are certain short term side effects of levodopa that are common, namely nausea, orthostatic hypotension, and sleepiness. For nausea, most of the doctors recommended taking medication on a full stomach or taking anti-nausea medication. Some responses stated that nausea is usually not an issue after a while because the body becomes more used to the medication and tolerates it better. As for orthostatic hypotension, hydration can help decrease the dizziness. Altogether, the conclusion that the benefits of levodopa outweigh the relatively minor side effects was prevalent throughout the responses.

When prompted about the dyskinesia that arises in long term prescription of levodopa, all of the doctors still stuck to levodopa as the best treatment. The reasoning was that LID is much milder than the symptoms of Parkinson's and can be treated with other strategies. Three of the doctors initially try to either cut back on levodopa or spread out the doses over more time points in order to manage the fluctuations of levodopa in the blood and brain. Most of the doctors try prescribing COMT inhibitors or MAO-B inhibitors if this approach does not work, as these medications are able to slow down the breakdown of levodopa into dopamine and decrease the plasma level fluctuations of levodopa. Another popular drug was amantadine, an antiviral medication that can be used with levodopa. Two of the doctors also believe that often, the dyskinesia may be so mild that the patients themselves do not realize it and have no decrease in quality of life from it. In these cases, the doctors do not treat dyskinesia unless it becomes more severe. Most of the doctors agree that LID should not be a deterrent for prescribing levodopa and can be dealt with in other ways without avoiding levodopa prescription.

Dopamine agonists also used to be a popular treatment for LID, but most of the doctors were opposed to prescribing them. Three of the doctors are against prescribing them at all, and if they do, they are very cautious with selecting which patients to prescribe it to. This is due to their side effects of impulse control disorder and withdrawal effects. The impulse control issues can create a steep increase in compulsive behavior, including gambling, excessive spending, intake of pornography, or hypersexuality. The withdrawal effects also cause patients to develop anxiety, dysphoria, and cravings for dopamine agonists when patients are taken off of it. These two side effects cause most of the doctors to be weary of prescribing it. One doctor also explained that it has all the same side effects as levodopa, but more severe. However, another doctor did not agree with the rest of the responses and regularly prescribes dopamine agonists and said that clinical trials show that it is effective in delaying dyskinesia and motor fluctuations. Most of the doctors disagree with this view and believe that the research supporting this is outdated; dopamine agonists actually do not delay dyskinesia.

The surgical options that were most recommended were deep brain stimulation and the Duodopa intestinal gel pump. The DBS is the most popular surgical option because it is more adaptable than the focused ultrasound thalamotomy or pallidotomy procedures. Its position can be changed by around a centimeter and its intensity can be varied as well. Focused ultrasound thalamotomy can also only be used on one side of the brain, which does not provide as much benefit for PD patients who have symptoms on both sides of the body. The doctors agree that DBS is able to provide the most improvement in motor symptoms without too high of a risk of side effects. The other option, the intestinal gel pump is recommended by two doctors, but is not as popular among the patients. By allowing a finer titration of levodopa into the body, the doctors believe that the pump would decrease dyskinesia or motor fluctuations by giving more constant levodopa in the body, but have found that their patients are not as interested when they hear that the pump needs to be installed like a feeding tube. The overarching opinion that the two surgeries provide high patient satisfaction with the resulting effects is present.

As for non-medication therapies, all the doctors recommend lifestyle changes, including more aerobic exercise and physical therapy as needed. Two doctors included that aerobic exercise can have major benefits, including a potential neuroprotective effect, which medication is still unable to provide. Most of the doctors recommend physical therapy more for those who are unable to exercise by themselves or need help with balance or more specific issues surrounding movement. Two of the doctors also recommend that the patients have regular social interaction as well, either by joining patient support groups or meeting with their friends. Another doctor also explained that some patients may be recommended therapists if they have high anxiety or depression resulting from Parkinson's.

## Discussion

These conclusions and responses partially support the hypothesis that levodopa is not the best treatment. All of the doctors still depend on levodopa as the best treatment and have not found an alternative that provides better results than it. However, part of the previous research was supported in that levodopa is often not the best treatment on its own. Many doctors prescribe adjunctive medications, including COMT inhibitors, MAO-B inhibitors, anti-nausea medication, and amantadine in order to handle the side effects of levodopa. This leads to the conclusion that although levodopa is still the best treatment, it needs to be managed with other medications alongside it. Regarding dopamine agonists, the mixed results raise the question of when the shift away from dopamine agonists occurred and whether this could lead to more research on why dopamine agonists increase symptoms of issues with impulse control. Another question is whether patients would be able to find greater benefits from the intestinal gel pump rather than pill formulations of levodopa because it allows for finer titrations of medication and would prevent LID by ridding the high level of fluctuation in the body. Further research would need to be done to answer either of these questions.

An interest in more neuroprotective medication was also expressed throughout the doctors, but most were not knowledgeable on the currently ongoing clinical trials, but remain aware of new medications that come out. Since there has been a major shift in targeting dopaminergic neurons in the brain to research on other aspects of PD, including α-Syn, LAG-3 proteins, glial cells, and mitochondrial function, there may be an increase of these medications in patient treatment in the future. Because these medications have more neuroprotective effects and directly impact the mechanisms underlying PD, they may be more effective than levodopa in the long run. However, research of these novel targets have not progressed to the point where they are available for prescription, so it may take several years before their effects are seen in PD patients.

Despite the valuable information that was collected from the interviews, there were limitations to this research. Five doctors were interviewed during this process, but all of them were from the Maryland/DC region. If more doctors were interviewed throughout the nations, the results may differ. There were also time constraints that differed for each interview. Interviews 4 and 5 were both less than 30 minutes due to the interviewees' busy schedule while the others were able to speak for longer and elaborate more on their opinions.

In order to maximize patients' quality of life, doctors and researchers work together in order to determine the best route of action. At the moment, levodopa remains the most effective treatment for levodopa, in conjunction with other medicines or therapies, including surgeries and regular exercise. However, as research of other targets progresses, neuroprotective medicines may emerge as the most efficacious treatment and allow dopaminergic neurons in the brain to survive for longer.

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