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The Fallouts and Downsides of the use of Dopaminergic Drugs to treat Motor Symptoms in
Parkinson's Disease and Non-Dopaminergic Treatments Being Developed to treat Both
Motor and Non-Motor Symptoms: A Literature Review

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Abstract

Parkinson's disease is the second most common neurodegenerative disease in the world and yet has no effective treatments that treat all symptoms to date. The most common form of treatment is levodopa, a dopaminergic medication designed to compensate for the lack of dopamine in the brain. However, L-dopa has proven to cause more side-effects than it does provide solutions. These side effects are in the form of both motor and non-motor symptoms. L-dopa commonly causes dyskinesia, a symptom that increases difficulty for voluntary movement, and sleep problems in patients who suffer from Parkinson's Disease. Moves to research in non-motor symptoms and treatment through non-dopaminergic means have begun due to the ineffectiveness of L-dopa. Unfortunately, no promising results have been brought to the forefront, suggesting the need for even more research in the field and in the non-dopaminergic route of treating patients.

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Introduction

Parkinson's disease, medically defined as a chronic progressive neurological disease that is linked to decreased dopamine production, was originally documented as such in 1817, and is now the second most common neurodegenerative disease in the world, right under Alzheimer's; one in every 100 people over the age of sixty are affected by the disease (Simuni et al., 2009).

Neurodegenerative diseases affect the neurons in the brain, which can cause a wide array of issues throughout the body's natural ecosystem. When different neurons begin to deteriorate and eventually die off, they cannot be repaired or regrown. In Parkinson's, the neurons that deteriorate are associated with the production of dopamine. Dopamine is a neurotransmitter that controls reward and pleasure centers, as well as regulates movement and emotional responses. When this neurotransmitter dies off, the break in connection begins to cause both motor and non-motor

symptoms to occur.

Motor symptoms are any symptoms that involve movement, such as: rigidity (stiff or inflexible muscles); resting tremor (uncontrollable movement or shaking when muscles are at rest); bradykinesia (slowness of movement); and postural instability (difficulty in maintaining the body in a stable and balanced position (Sumini et al., 2009). Non-motor symptoms involve all the other symptoms that do not involve movement, such as olfactory dysfunction (one of the first signs of Parkinson's disease yet the hardest to detect), sleep disorders, and neuropsychiatric symptoms, such as depression (Zhang et al., 2016). Motor-symptoms are the most obvious symptoms in a Parkinson's disease patient and, therefore, are more commonly treated by physicians. There are different forms of treatment for Parkinson's disease, such as pharmaceuticals and physical therapy. The most widely used treatment is L-dopa, a dopaminergic drug that aims to compensate for the low dopamine levels in the brain.

Dopamine, L-dopa, and the Brain

Before attempting to understand Levodopa, or L-dopa, it is important to understand how the brain functions with proper levels of dopamine. The part of the brain that is directly affected by the loss of neurons and increase in dopamine from the dose of L-dopa is the basal ganglia. The basal ganglia are a group of sub-cortical nuclei in the midbrain that

include: the striatum, a small group of subcortical structures that receives the primary input from the cerebral cortex; the globus pallidus, another small group of subcortical structures that control the inputs sent from the striatum and oversees voluntary movement; the subthalamic nucleus, a receiver of inputs from the striatum that works to regulate

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motor behavior; and the substantia nigra, the most important component of the basal ganglia with respect to Parkinson's disease (Sharma et al., 2015). The substantia nigra is a pigmented nucleus consisted of two components, the substantia nigra pars reticulata and the substantia nigra pars compacta, that receive inputs from the striatum (Sharma et al., 2015). The substantia nigra pars compacta has the highest concentration of dopaminergic neurons than any other part of the basal ganglia. These dopaminergic neurons create a dopamine pathway, known as the nigrostriatal dopamine pathway, which completes the signal pathway and acts as a feedback loop to the striatum (Sharma et al., 2015). This pathway is crucial to facilitating movement and the entire function of the basal ganglia, as each structure is inter-reliant on the relay of inputs and outputs. If the pathway is disrupted by denervation or disconnection between structures, the entire balance of this feedback loop to the rest of the brain is interrupted, causing issues with motor and non-motor functions requiring dopamine.

With Parkinson's disease, the dopamine neurons in the substantia nigra

pars compacta begin to die off due to the neurodegenerative disease, which results in decreased levels of dopamine in the striatum and leads to the deterioration of motor and non-motor functions (Hung & Schwarzschild, 2013). Those problems consist of all the motor symptoms physicians know to date, like tremors, rigidity, slowness of movement, and postural instability. Although the lack of dopamine neurons are located in the substantia nigra, it is the dopamine deficiency in the striatal region of the brain that led to L-dopa therapy (Sharma et al., 2015). L-dopa was then developed to try and alleviate these symptoms by compensating for the lack of dopamine reaching the striatum (Sharma et al., 2015). L-dopa was first tested on Parkinson's disease patients in 1961, and for the first six years the results were inconsistent and the treatment was heavily questioned (Sharma et al., 2015). It was not until 1967, when L-dopa was administered to twenty-eight individuals for a time frame of two years, that solid results began to surface (Cotzias et al., 1969). This discovery led to the use of L-dopa as the top treatment of choice today, even though it has been proven that the use of the drug chronically can induce side effects that make Parkinson's disease worse.

Problems with L-dopa affecting both motor and non-motor symptoms

As of now, it is uncertain how L-dopa induces side effects that make Parkinson's disease worse, only that it does over a prolonged use of the drug over time. Dyskinesia, the most

notorious of the side effects that is caused by L-dopa, is increased difficulty of making voluntary movements, causing fluctuations in movement that appear to be intentional to some degree but is not.

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While on L-dopa, thirty-five to forty percent of Parkinson's disease patients reported to have developed dyskinesia by four to six years of treatment, with the number increasing to ninety percent with up to a decade of treatment (Hung, 2013). According to Sharma et al., in "Neurobiology of l-DOPA induced dyskinesia and the novel therapeutic strategies" the dopamine denervation of the striatum plus hyper-responsiveness of medium spiny neurons to dopaminergic treatment and over expression of specific components in the signal transduction pathway all play some role in dyskinesia. In early Parkinson's disease patients, L-dopa can yield better results due to the few healthy neurons that are present that are able to properly convert levodopa into usable dopamine (Sharma et al., 2015). However, when the dopaminergic denervation is severe, as observed in advanced Parkinson's disease patients, the L-dopa is more difficult to convert properly into dopamine, instead being decarboxylated at other non-dopaminergic sites that cause fluctuation in intrasynaptic levels of dopamine (Sharma et al., 2015). This kind of fluctuation is hypothesized to cause dyskinesia to some degree, since the dopamine needed for the brain to properly function is too inconsistent to be useful.

Research in non-dopaminergic treatments

Research has now found itself looking towards new methods of treatment in hopes of finding something effective that has less side effects than L-dopa.

L-dopa spurs just as many issues with different non-motor symptoms as with motor symptoms. Use of L-dopa has also proven to affect nocturnal sleep cycles in multiple studies according to Chahine and Li (2013 and 2017). Sleep deprivation is a common non-motor symptom in Parkinson's disease patients, and research points to L-dopa aggravating an already existing symptom. It was reported on multiple occasions that the administration of L-dopa at later times of the day caused sleep problems throughout the night (Li et al., 2017). The higher the dose, the more L-dopa inhibits the patient's ability to sleep. A higher dose effects the D1 dopamine receptor rather than the D2 receptor, which is the receptor closely related to adenosine. These doses of L-dopa are given to patients who have either suffered from the disease for a long time or have a more severe version of the disease. The problem that stems from that is the need no way to treat both the sleep deprivation that occurs naturally due to the disease and the sleep problems that occur by use of L-dopa. Since most physicians know L-dopa works for motor symptom ailment, even though they are unsure how to treat the sleep troubles that come with it, the use of L-dopa is still prominent.

Neuroplasticity, or the brain's ability to reorganize itself by forming new neural pathways to compensate for injury or disease, has been a new field of study

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stemming from cognitive sciences. This concept of the brain is being applied to a brain with Parkinson's disease, and one of the most effective treatments that researchers have found involving neuroplasticity is forced exercise. Forced exercise is exercise for a certain interval of time at a rate of speed greater than the patient's preferred pace. A study done by Ridgel in 2009, titled "Forced, not voluntary, exercise improves motor function in Parkinson's disease patients. Neurorehabilitation and Neural Repair", that has been widely reported on over the years, had Parkinson's disease patients riding stationary tandem bicycles for one hour three times a week over an eight-week period. The group was split into voluntary and forced exercise, where forced exercise patients had to pedal at eighty to ninety RPM and voluntary exercise patients could pedal at whatever pace was comfortable for them. After the study finished, the forced exercise group had a thirty percent improvement with their symptoms compared to the voluntary group, and a twenty percent improvement even two weeks after the trial ended (Ridgel et al., 2009). Today, that practice is still heavily tested on and is now sparking different businesses to have stationary bike classes specifically for Parkinson's disease patients.

Another angle for non-dopaminergic treatments stems from how other neurotransmitters in the brain are just as affected by Parkinson's disease and have just as much of a role in the signal pathways in the brain as dopamine (Hung & Schwarzschild, 2013). One of

these neurotransmitters is adenosine, and certain adenosine receptors, such as A_{2A} , can oppose any inhibitory effects controlled by a dopamine receptor, such as D2, by activating striatopallidal neurons (Hung & Schwarzschild, 2013). Over-activity in the indirect nigrostriatal pathway used by adenosine receptors have also been found to agitate dyskinesia (Sharma et al., 2015). According to recent trials, when A_{2A} is blocked the excessive activity found in the indirect pathway that emerges from dopamine depletion, due to the lack of a dopamine pathway, is inhibited (Hung & Schwarzschild, 2013). It is speculated that blocking A_{2A} may alleviate problems with motor functions and dyskinesia due to the reduction in motor fluctuations, and it was found that in rodent and non-human primate models, the use of A_{2A} antagonists reversed parkinsonian deficits without development of tolerance consistently (Hung & Schwarzschild, 2013). Research in this area is still new, but it points to the importance of other neurotransmitters in motor symptoms, and the same can be said for all the other neurotransmitters in the brain and their target functions. The interconnectivity of the brain makes the understanding of Parkinson's disease more difficult, as there are more components to what is directly and indirectly affected by the lack of dopamine. Using other neurotransmitters to treat both non-motor and motor symptoms may prove to be more effective than using dopaminergic pharmaceuticals as further studies in this area continue.

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Bridging the gaps

Unfortunately, most of the research that is happening on Parkinson's disease is new and still too inconsistent to provide any solid solutions. Other areas of research involve stem-cell therapy; however, no promising treatments have evolved past the rat-testing phase. The real problem stems from how and when Parkinson's disease is diagnosed in a patient. Currently, there are no effective ways of diagnosing Parkinson's disease early enough to take preventive measures (Simuni et al., 2009). Even eight years after the Simuni publication, that statement continues to remain true. Most patients are not

diagnosed with Parkinson's disease until motor symptoms are apparent, but by that point the disease has progressed to where too many dopamine neurons have perished. After losing a certain amount of dopamine neurons, the brain can only try to compensate for what is lost, but the damage extends to the signal pathways that are disrupted all throughout the brain, thus making the damage more difficult to repair. Treatments treat side-effects of a disease that are most prominent instead of treating the root of the issue, which is almost impossible with how and when Parkinson's is being diagnosed.

Conclusion

Parkinson's disease is still a major unknown in the medical field due to the complex interconnectivity of the brain, which makes the origin and outreach of the disease far more difficult to pinpoint. Although the disease has now been documented and tested on for 100 years, there is still much to learn. One consensus from every source provided is that dopamine is no longer the only neurotransmitter in the brain that is affected or affects a brain diagnosed with Parkinson's. The complex network of neurons within the brain rely too heavily on one another for only one damaged good to be treated for. Almost all the treatments found thus far treat symptoms but do not treat the root of the problem. However, that in and of itself may be the root of the problem: the unknown. Too many variables and too many complexities have been uncovered since

the disease was first discovered. And as the growing number of elder people around the world grows since more people are living longer lives, the risk of more people developing Parkinson's disease is inevitable. Effective diagnostics and treatment have yet to be developed, and the disparity of what is unknown and what is known will begin to appear as more people are diagnosed with the disease. More research needs to be conducted in this area, along with the potential methods in using other neurotransmitters and receptors to treat the lack of dopamine, as well as methods that concentrate on using the neuroplasticity of the brain to help alleviate symptoms. Sadly, research in possible cures in promising areas are less likely to be funded due to the higher possibility of finding concrete solutions that may or may not require

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pharmaceuticals, another obstacle that, although indirectly, can inhibit the progress of finding better ways to treat

Parkinson's disease.

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