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Dopamine Agonists and their Optimality in Treating Parkinson's Disease Compared to Other Treatments

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ABSTRACT

Parkinson's Disease (PD) is a neurodegenerative disorder that has been plaguing tens of thousands of people each year, and as a result, there has been lots of research to find a drug or compound which, if used correctly, will allow for a decrease in the symptoms of the disorder. One idea that is of question is whether dopamine agonists might be able to help reduce the effects that the disease has upon a person. As a result, the question of how useful dopamine agonists are in the treatment of or minimization of the effects of Parkinson's Disease rises. This paper focuses heavily on the topic of the optimality of dopamine agonists in the treatment of Parkinson's disease and relies upon past research on the subject of PD treatments/therapies. Although an agonist, in scientific terms, is known as a chemical substance capable of combining with a specific receptor on a cell and initiating the same reaction or activity typically produced by the original substance itself, these dopamine agonists have not proven to be as effective as can be assumed. These agonists, even with the ability to imitate the reaction of dopamine agonists, are not as useful as other treatments to PD, such as Levodopa. In this paper, comparisons were conducted between the two largest categories of PD therapy to derive a conclusion. The findings indicate some rather surprising results, and prove that dopamine agonists might not be as useful in the treatment of Parkinson's Disease as one might assume.

Introduction

Everyday life is filled with moments of great joy and stimulation, and although these feelings are very common, no one appears to try to find out what causes them. The reason for these moments is because the brain dopamine, which rushes its way around and causes one to feel good, pleasured, and/or satisfied. Dopamine, a neurotransmitter, plays an integral part in the lives of many people due to it swarming around our brain consistently. However, some people lack dopamine greatly, maybe due to stress, anxiety, alcoholism, or drug use. This lack of dopamine affects many people, causing their lives to disappear right before their eyes as a disease starts to develop. This disease is known as Parkinson's disease, and it takes control of the people that lack dopamine. Parkinson's Disease has not had a cure found for it yet, but that brings up a question: can we reduce the effects of the disease since we cannot cure it yet? Agonists are drugs or other chemical agents that bind to a particular receptor to replicate the role of the thing that should actually bind to that receptor. The idea of agonists has gotten many people thinking in respect of Parkinson's, given the impact it has, plaguing over 10 million people worldwide. This idea has got people thinking if dopamine agonists can be used to help combat Parkinson's, and that is a question that could change the lives of many. People have done lots of research on topics about Dopamine's relationship to the brain. One thing that has been found out is that dopamine is central for learning from rewards and punishments. Data has also proven to the world that dopamine levels and cognitive performance show an inverse U-shape relationship. However, even though dopamine causes or plays a role in those things and that is proven by data, it is more important to note the role of dopamine on Parkinson's disease, which is caused by a lack of dopamine in the brain. Parkinson's disease causes a combination of symptoms related to one's motor abilities, mainly due to the degeneration of dopamine neurons in a part of the substantia nigra, known as the pars compacta, which is a part of the brain. Research has proven that dopamine degradation, whether the cause of it

be catechol ortho-methyltransferase, monoamine oxidase, or any other potentially dopamine-harming substance, leads to the rise of Parkinson's disease in one's brain. It is proven that 5,6-indolequinone, which is said to be one of the most reactive species under dopamine oxidation, can form a biomolecule with alpha-synuclein, leading to the generation of neurotoxic protofibrils that most likely will play a major role in the development of Parkinson′s disease, bridging a connection between Parkinson's disease and dopamine (Bisaglia et al. 2007). It has clearly been established that a lack of dopamine, or the degeneration of dopamine, is a leading cause of Parkinson's disease. Even with countless trials being completed, there has been no cure found for Parkinson's disease. This research will potentially fill in the gap of the lack of a cure for Parkinson's by giving an idea of what a cure could be like, and if not that at the very least it could help create a treatment to help relieve the symptoms and maintain quality of life. This research not only helps show a potential cure for Parkinson's disease but can help create a necessity for furthering knowledge on the topic of dopamine agonists and ways to use them for other things. It is clear that Parkinson's is a big issue, and we need to resolve it. As of now, there must be some efforts made in the area of dopamine, given that a lack of it leads to Parkinson's disease, to negate the effects of Parkinson's disease on many people. That brings up one question based on the data mentioned before and the pounds of research done on the topic: is the use of dopamine agonists in treating, or reducing the effects of, Parkinson's Disease more optimal when compared to other treatments.

Dopamine

Dopamine has played a role in the function of the brain for an extended period, affecting emotional states and feelings amongst other things. However, with these neurotransmitters there comes issues, such as the emergence of Parkinson’s disease if the quantity of dopamine begins to decrease noticeably. Dopamine requires receptors, specifically called dopamine receptors, to attach to locations of the brain and stimulate certain feelings. Based on the functions of the dopamine receptors, they can be divided into D1-like receptors and D2-like receptors. Each of the receptor families has a variety of roles. D1-like receptors can induce the production of cyclic adenosine monophosphate (cAMP) and activate PKA, while D2-like receptors can reduce the accumulation of cAMP by interacting with either G1 or G0 proteins. (Liu et al. 2019) D1-like receptors and D2-like receptors are involved in multiple signal transduction pathways. D1-like receptors have been found to be involved in signal transduction pathways that are linked to various neuropsychiatric disorders, doing so by activating phospholipase C and by causing a calcium release. D1-like receptors not only participate in signal transduction pathways, but also play a major role in the regulation of the electrochemical gradient formed by the sodium/potassium pump (Na^+K^+-ATPase).

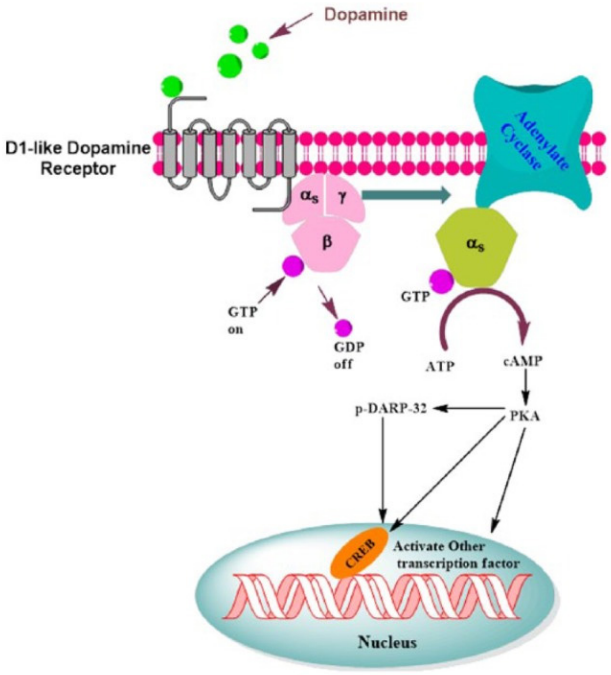


Figure 1. Potential D1-like receptor-mediated signal transduction[3]

D2-like receptors, differently from D1-like receptors, activate pathways related to cell proliferation, with one such example being the mitogen-activated protein kinase (MAPK). D2 receptors, on top of their use in pathways, play a role in behavior and extrapyramidal activity controlled by the postsynaptic receptor. (Mishra et al. 2018) Continuing the contrast between the two forms of receptors, the activation of D2 receptors can lead to the inhibition of PRL secretion by decreasing cell calcium levels. However, some D1 receptors stimulate PRL secretion by stimulating vasoactive intestinal peptide secretion.

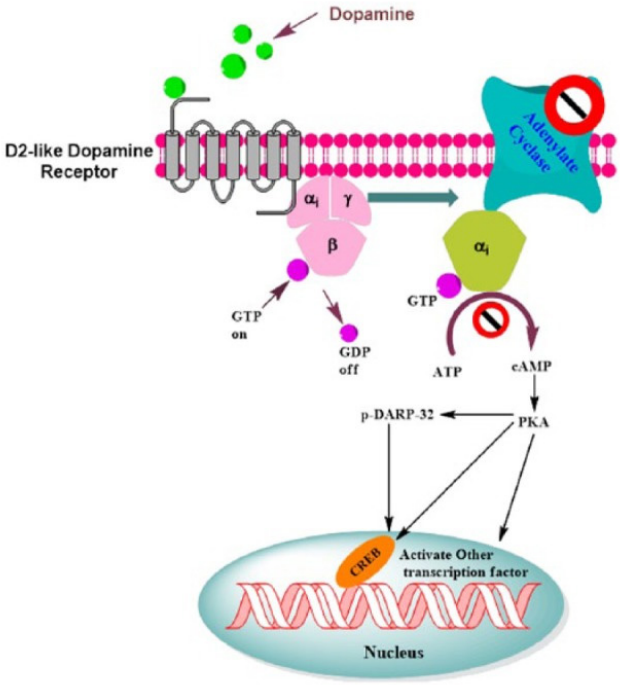


Figure 2. Potential D2-like receptor-mediated signal transduction[3]

Through the process of alternative splicing, there are two isoforms of D2R that are produced. These isoforms are known as D2S and D2L, representing a short form and long form respectively. The component that sets the D2S isoform and D2L isoform apart is the encoding of the third intracellular loop of the receptor in D2L. The two isoforms are hypothesized to have major roles in the mitogen-activated protein kinase pathways. In an experiment testing the previously mentioned hypothesis, the observations showed that the pituitary size and PRL levels of mice were found to be reduced in those who expressed D2S in comparison to wild-type or D2L. (Liu et al. 2019) Another theory that has been discussed and tested for accuracy is that the decrease of D2S expression potentially plays a role in D2R resistant prolactinomas. In the pituitary gland, D2L has a lower expression level than D2S. Not only do Dopamine receptors have unique names and functions, but the dopamine agonists, which are compounds or chemicals that mimic dopamine, have many names and functions as well. Most commonly known due to their use as first-line treatments for prolactinomas, BRC and CAB are the two main dopamine agonists that are used. (Liu et al. 2019) These two agonists can inhibit prolactin inhibitor secretion and impact health conditions such as brain tumors. Among the two, BRC was the first dopamine agonist used for clinical purposes, being helpful towards the successes of clinical trials due to it being a D2 receptor agonist and a D1 receptor antagonist. (Liu et al. 2019) The simulation of the four molecules and enzymes listed prior not only decreases PRL but also further inhibits the production of cAMP.

Current Treatments and Medications to Parkinson's Disease

Over the years, there have been many treatments that have been made to combat the effects of Parkinson's disease. However, the majority of these treatments cannot be considered "successful." Treatments range from things such as therapy, physical activities, and medications, with the latter being proven to be the most impactful in the category of treatments. Some of the medications include Entacapone, Tolcapone, and Opicapone. There have also been lots of investigations done, like the fact that there is evidence for neuroprotection with the monoamine oxidase B inhibitor is known as rasagiline being effective against Parkinson's disease, but this has not been followed through because it is not covered in most areas and could require other external factors that are unnecessary. As a result of these investigations/experiments and other external factors, up until the present day, there has been no medication that can be deemed as successful in the treatment of Parkinson's disease as has L-DOPA, more well known in the medical community as Levodopa or l-3, 4-dihydroxyphenylalanine. Levodopa is an amino acid that is made through the biosynthesis of l-tyrosine, another well-known amino acid. Levodopa was first discovered in the 1960s and was found to be the first symptomatic treatment to combat Parkinson's disease. Levodopa led to the increased usage of both dopamine agonists and monoamine oxidase B inhibitors. No medication is recommended for the treatment of Parkinson's disease, but many factors are taken into account when deciding which medication should be prescribed. If symptoms are very mild, the patient may choose not to begin levodopa therapy to treat Parkinson's disease. Since patients who develop Parkinson's disease between the ages of 21 and 50 are more likely to develop levodopa-induced abnormal movements, also known as dyskinesia, dopamine agonists were introduced as the initial treatment. However, the advantage of dopamine agonists addressed prior diminishes over roughly 10 years, giving levodopa an advantage for the long-term, where the impact of the treatment is more important. (Rizek et al. 2016) Levodopa is usually started first in those who develop Parkinson's disease after the age of 50 due to the increased risk of neuropsychiatric adverse effects, which are caused by dopamine agonists. Levodopa allows the patient to have better control of the motor symptoms caused by Parkinson's disease when put in comparison to dopamine agonists and monoamine oxidase B inhibitors(MAOBIs). However, levodopa also leads to the development of dyskinesias and motor fluctuations after either long-term use or high-dose treatment. (Rizek et al. 2016) Patients will likely have to adjust their treatment plans, and will most likely need to prescribe themselves levodopa two to five years after the levodopa treatment finishes. L-Dopa, as stated multiple times before, has been the most effective treatment for Parkinson's disease thus far, even more than using solely dopamine agonists in therapy.

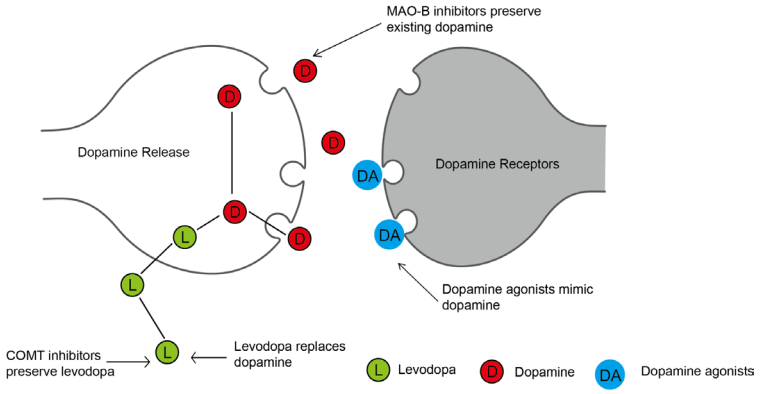


Figure 3. How levodopa and dopamine agonists help increase dopamine quantities[14]

The way that L-Dopa connects itself to dopamine to be so successful in its actions is by traveling to the Central Nervous System (CNS) first. After the bound pair travels into the CNS, the l-dopa is converted into more dopamine by an enzyme known as aromatic amino-acid decarboxylase(AADC). This enzyme is not specific to dopamine neurons, however, it is found in many different cells including glia and endothelia, including that of 5-HTergic neurons. (Stansley et al. 2015) Upon delving into Stansley's research it can be found that 5-HT neurons have been responsible for the majority of l-dopa induced dopamine release within extrastriatal brain regions such as the substantia nigra pars reticulata, hippocampus, and prefrontal cortex. L-dopa's ability to convert from its natural structure to dopamine allows for it to be the most effective medication thus far, and has shown to be connected to dopamine and raising dopamine levels.

Use of Dopamine Agonists

Although Dopamine agonists have been proven to be a medication towards the minimizing of the effects of Parkinson's Disease, there have been a few side effects of a dopamine agonist therapy for Parkinson's disease. The dopamine agonist drug family has become associated with specific side effects that can diminish the quality of life among PD patients, proving that dopamine agonists might not be as effective as medication towards minimizing the effects of Parkinson's disease due to the long-term downfalls. Therapy with dopamine agonists leads to many side effects in patients with Parkinson's disease, usually among patients age 65 and older. Those side effects could be mild and frequent, but could also be serious and debilitating. Some side effects include constipation, nausea, headaches, and hallucinations (both visual, tactile, and auditory). Some other side effects include fibrosis, peripheral edema, heart failure, and valvular heart disease." (Borovac et al. 2016)

Table 1. Common Dopamine Agonists for Therapy and Side Effects created by Samarth K

Drug	Maintenance/Dose Range	Side Effects
Bromocriptine [D2 class primarily] D2>D3>D4]	Oral, 2.5-40 mg/day	Common side effects: constipation, nausea, vomiting, asthenia, dizziness, headache, rhinitis Serious side effects: pericardial/pleural effusion, myocardial in-

		farction, heart valve disorder, retroperitoneal and pulmonary fibrosis, gastrointestinal ulcers, hallucinations, psychosis
Cabergoline [D2 >> D1]	Oral, 0.125-1 mg 2 x/week	Common side effects: constipation, nausea, dizziness, headache, fatigue Serious side effects: congestive heart failure, heart valve disorder, pericardial disease, retroperitoneal fibrosis, pleural effusion, pulmonary fibrosis, pleural fibrosis, peripheral edema
Lisuride [D2 class primarily]	Oral, 0.2-4.5 mg/day Subcutaneous, 0.035 mg/kg IV, 0.002 mg/kg	Common side effects: orthostatic hypotension, nausea, headache, tiredness, dizziness, dyskinesia, vertigo, Erytrhomelalgia, Dyspnoea, peripheral edema, sweating Serious side effects: Somnolence, sleep disorders, impulse control disorders, cardiac fibrosis, pulmonary fibrosis, pleural fibrosis, pleural effusion, retroperitoneal fibrosis
Pergolide [D2 >> D1]	Oral, 0.05 mg/day Usual response up to 0.1 mg per day	Common side effects: constipation, diarrhea, nausea, sedation, orthostatic hypotension, dizziness, tachycardia, dyspnoea, hallucinations, confusion, psychosis, visual disorders Serious side effects: cardiac valvulopathy, pleural fibrosis, cardiac failure, impulse control disorders
Pramipexole [D3 > D2, D4] Use for depression subtypes in PD	Oral, 0.125 mg 3x/day (IR) Oral, 0.375 mg/day (ER)	Common side effects: orthostatic hypotension (IR), constipation, nausea, asthenia (IR), confusion, dizziness, dyskinesia, extrapyramidal movement, headache, insomnia, hallucinations, edema of the lower extremities Serious side effects: heart failure, Melanoma, Somnolence, psychosis,

		neuroleptic malignant syndrome, impulse control disorders
Ropinirole [D2 >> D3, D4]	Oral, 0.25 mg 3x/day (IR) Oral, 2 mg/day (ER)	Common side effects: hypotension, orthostatic hypotension, nausea, vomiting, constipation, edema of the lower extremities, impulse control disorders, dizziness, dyskinesia, somnolence, fatigue Serious side effects: sinus node dysfunction, Syncope, sleep attacks, hallucinations
Rotigotine [D1, D2, D3 > D4, D5]	Transdermal, 2 - 4 mg/day	Common side effects: orthostatic hypotension, application site reaction, diaphoresis, nausea, vomiting, dizziness, dyskinesia, headache, sleep disturbances, somnolence, fatigue, edema of lower extremities Serious side effects: first-degree AV block, syncope, sleep attacks, compulsive behavior, hallucinations, impulse control disorders
Apomorphine [D2, D3, D4 >> D1]	Subcutaneous, 0.2 to 0.6 mL (2-6 mg) for “off” episodes	Common side effects: peripheral edema, contusion, injection site reactions, nausea and vomiting, confusion, dizziness, dyskinesia, somnolence, hallucinations, nasal discharge, yawning Serious side effects: angina pectoris, cardiac arrest, hypotension, prolonged QT interval, syncope
Piribedil [D2, D3]	Orally 150-250 mg/day (3-5 divided doses)	Common side effects: nausea, vomiting, confusion, agitation, dizziness, hypotension, orthostatic hypotension, Syncope Serious side effects: impulse control disorders, Somnolence

The table above is a list of common dopamine agonists that are used by doctors, scientists, and other people in similar careers for Parkinson's disease therapy, and shows both the common and serious side effects of each of the agonists used.

It can be concluded (Table 1) that the use of Dopamine Agonist therapy might not be as effective in reducing the effects of Parkinson's Disease due to all of the common and serious side effects of the most common dopamine agonists, helping point towards a negative answer in response to the research question proposed on the effectiveness of dopamine agonists in minimizing the effects of Parkinson's disease. The fact that dopamine agonist therapy affects people above the age of 65 is not a good sign either, mainly because those who are diagnosed begin to develop Parkinson's around age 60 and older, putting them right in the range of where the side effects become prominent. However, the use of dopamine agonist therapy has also proven to be beneficial towards the minimization of the effects of Parkinson's disease, as motor complications were reduced with dopamine agonists compared with levodopa. (PD MED Collaborative Group et al. 2014) However, the consistent trend that continues with the use of dopamine agonist therapy is that the other side effects of the process were increased, and also led to poorer short-term symptom control. (PD MED Collaborative Group et al. 2014)

Limitations of Dopamine Agonists

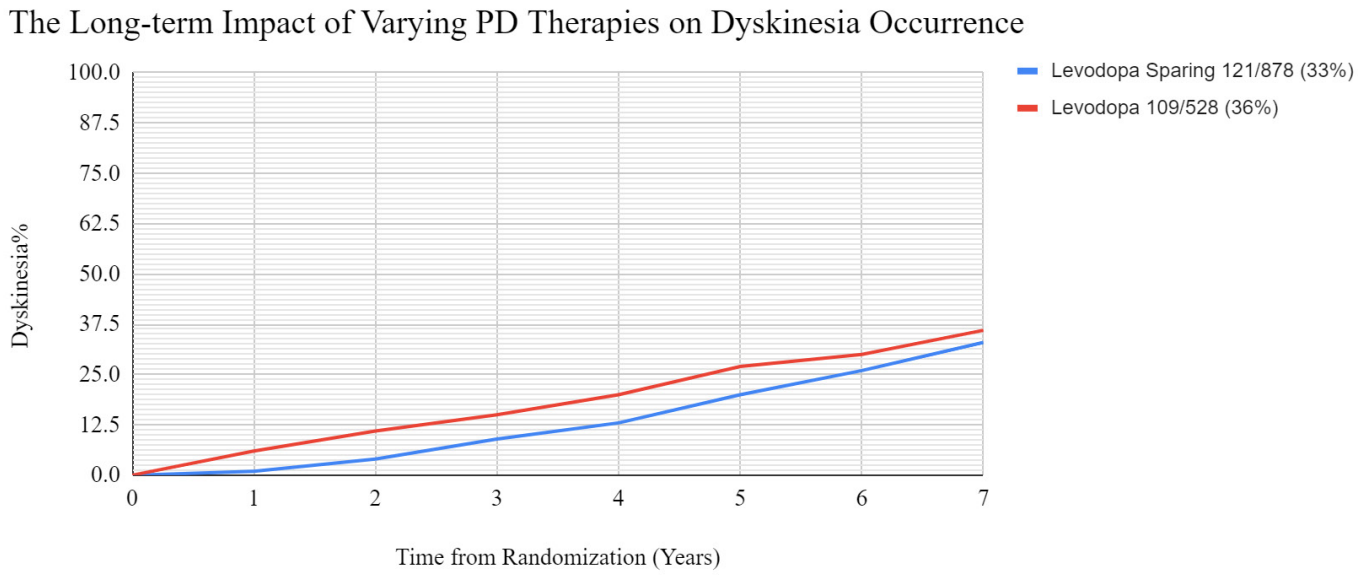
As clearly shown earlier (Table 1), Dopamine Agonists have their fair shares of limitations to their name. The form of therapy for Parkinson's Disease that requires the use of dopamine agonists causes lots of side effects, both serious and common. It has been proven that the role of dopamine agonists might go on a decline in the future, mainly because these drugs have a shorter half-life and have to be taken multiple times a day, which can seriously affect patient compliance. (Borovac et al. 2016) Due to the inability to find the correct combination of dopamine agonists or just a single one by itself, to treat Parkinson's Disease, further research efforts are necessary to produce long-lasting agonistic effects, with an optimal safety profile. However, it is important to note that dopamine agonists that are successful in displaying prolonged effect, as well as extends the duration of a half-life can be seen as a road to take in the future. Additionally, it has been seen that over the past few years or so, dopamine agonists have shown a trend of continuous improvement. To summarize, through the countless research papers established, the biggest limitations of dopamine agonists in their use for therapy is the fact that they have many side effects, and that they have a shorter life span, but if there is a way to increase the life span and/or reduce side-effects, then dopamine agonists might become just as, if not more, resourceful than Levodopa.

A Comparison of Levodopa to Dopamine Agonists

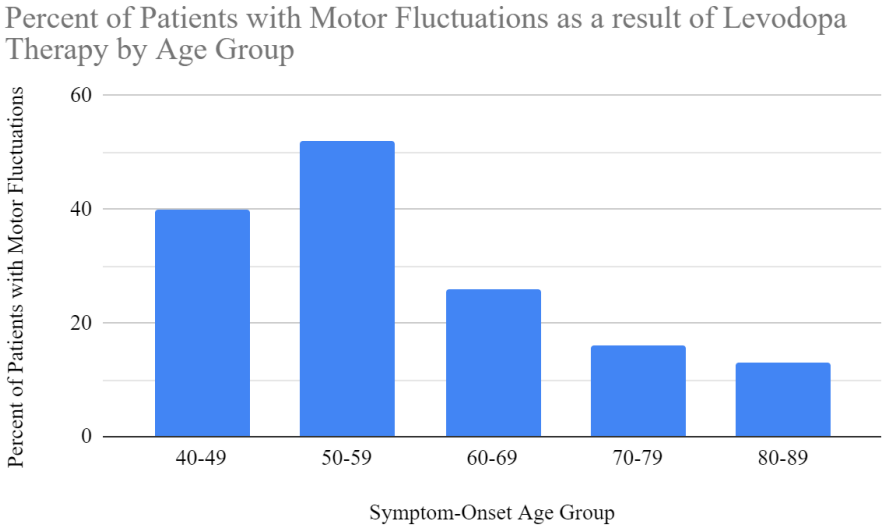
As addressed, levodopa and dopamine agonists have been two of the most common treatments used to manage and counteract the effects of Parkinson's Disease upon an individual. However, these two treatments have proven to be different from each other. Published on November 9, 2020, an experiment comparing the use of levodopa and dopamine agonists after subthalamic stimulation in Parkinson's disease. In this experiment, the patients involved were enrolled in pairs; After the procedure was completed, one of the patients in the pair was randomly assigned to levodopa monotherapy, while the other was assigned to dopamine agonist monotherapy. (Picillo et al. 2020) After administering the experiment, a set of interesting results was obtained.

It was found that DA monotherapy is not more effective in improving NMS (Non-Motor Symptoms) compared to LD monotherapy after STN DBS (Deep brain stimulation of the subthalamic nucleus). A variety of other interesting conclusions were formed, with those being that monotherapy after surgery is safe in more than half of patients, particularly those on LD, LD monotherapy is feasible only in a minority of patients (34.2%) in the long term, and that DA monotherapy is not tolerated and is associated with the development of impulse control disorders in a

significant proportion of patients. (Picillo et al. 2020) These conclusions show that levodopa therapy was more effective than dopamine agonist therapy, shown by the fact that dopamine agonists did not improve non-motor-symptoms after the experiment, and led to impulse control disorders.



Graph 1. Impact of using Levodopa Therapy and Therapy without Levodopa on Dyskinesia Percentage created by Samarth K



Graph 2. Percentage of Patients facing Motor Fluctuation due to Levodopa Therapy created by Samarth K

The graphs above display some of the downfalls of the use of Levodopa Therapy in the treatment of Parkinson's disease. It can be seen that one of the biggest limitations to Levodopa therapy is an impairment in voluntary movement and motor abilities.

Another trial, published on June 10, 2014, aimed to establish which of these three classes of drug, [dopamine agonists, levodopa, and monoamine oxidase B inhibitors] as initial treatment, provided those diagnosed with Parkinson's disease with the most effective control of symptoms. It also aimed to find out which drug gave the same group

of people the best quality of life. (PD Med Collaborative Group et al. 2014) In this trial, a variety of tests were performed and data was observed, as shown below, and these helped yield important results to the question established. Some data found that levodopa required the least quantity (mg/day) to be effective amongst the three, but also caused the highest rate, by three percent, of dyskinesia amongst patients throughout long-term usage (Graph 1). It was found that levodopa provides better short-term control of the motor symptoms of people who were recently diagnosed with Parkinson's disease. It was also found that levodopa in treatment or medication yields fewer side effects than dopamine agonists or MAOBIs when used for the same purpose. However, the drug leads to more motor complications and causes poor symptom control (Graph 2). (PD Med Collaborative Group et al. 2014)

This trial resulted in similar conclusions to that of the one analyzed prior. This trial concluded that no short-term or long-term benefit was seen from initiation of treatment of patients with early Parkinson's disease with levodopa-sparing therapy—dopamine agonists or MAOBI—rather than levodopa, meaning that levodopa has proven to be the best option in the management and treatment of Parkinson's Disease. (PD Med Collaborative Group et al. 2014) The conclusion derived from the results of the trial diminishes the optimality of the other options, dopamine agonists and MAOBIs, studied, proving that dopamine agonists, the central focus of this paper, lacks in aspects when compared to those of levodopa.

Conclusion

After an in-depth review of past research papers about the topic of whether dopamine agonists can be the optimal option in the treatment of management of Parkinson's disease, a conclusion can be reached. Through the research performed, it can be concluded that dopamine agonists can be effective in the reduction of the effects of Parkinson's Disease, however, there are better options than the extensive list of Dopamine Agonists. To answer the question proposed in the introduction, dopamine agonists can not be, and are not, the optimal option in the treatment and management of Parkinson's disease. As found through an analysis of the use of levodopa, it can be seen that this dopamine precursor has been very successful in the management of Parkinson's disease, and minimizing the effects of the disease on a person. Also, as found through an analysis of the dopamine agonists used to manage Parkinson's disease, and a study of the side effects, both lethal and non-lethal, that the use of dopamine agonists in therapy leads to, it can be seen that dopamine agonists might be too great of a risk to health to use as a form of therapy for Parkinson's disease management. When comparing both of the analyses performed, it can be seen that levodopa has proven to be more helpful than dopamine agonists, mainly due to the reasoning that when using levodopa in Parkinson's Disease therapy, there are minimal side effects, whereas, as stated previously, dopamine agonists in therapy will cause a vast amount of side effects. Also, after an in-depth comparison between dopamine agonist therapy and levodopa therapy, as well as a discussion on the limitations that the use of dopamine agonists therapy, it can yet again conclude the answer, as stated above, to the question proposed at the start. To summarize, although dopamine agonist therapy does help resolve some of the side effects caused by Parkinson's Disease, the costs and lack of benefits of using this therapy greatly outweigh the positives, leading to the conclusion that we can use dopamine agonists to reduce the effects of Parkinson's disease, but they are not optimal in treating Parkinson's disease when compared to other treatments.

Acknowledgments

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