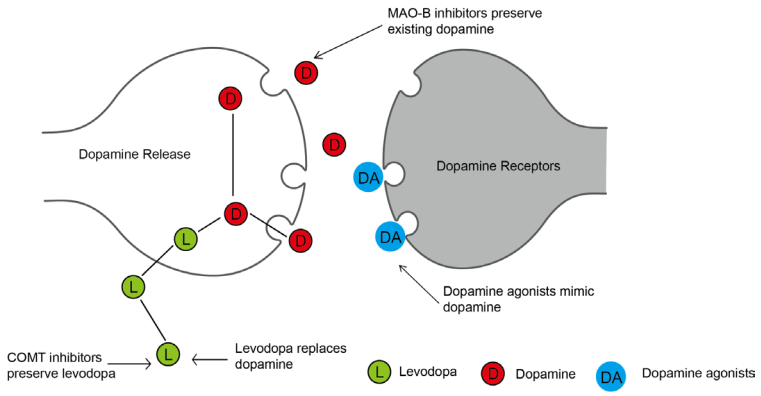


Figure 3. How levodopa and dopamine agonists help increase dopamine quantities[14]

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

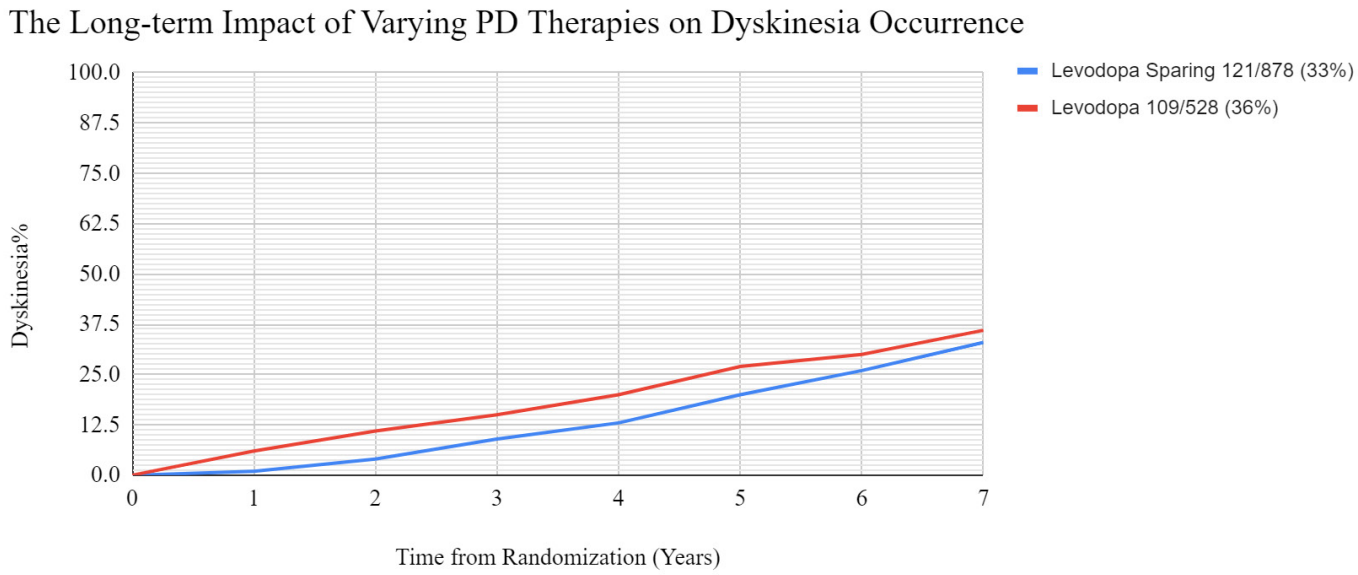
As clearly shown earlier (Table 1), Dopamine Agonists have their fair shares of limitations to their name. The form of therapy for Parkinson's Disease that requires the use of dopamine agonists causes lots of side effects, both serious and common. It has been proven that the role of dopamine agonists 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

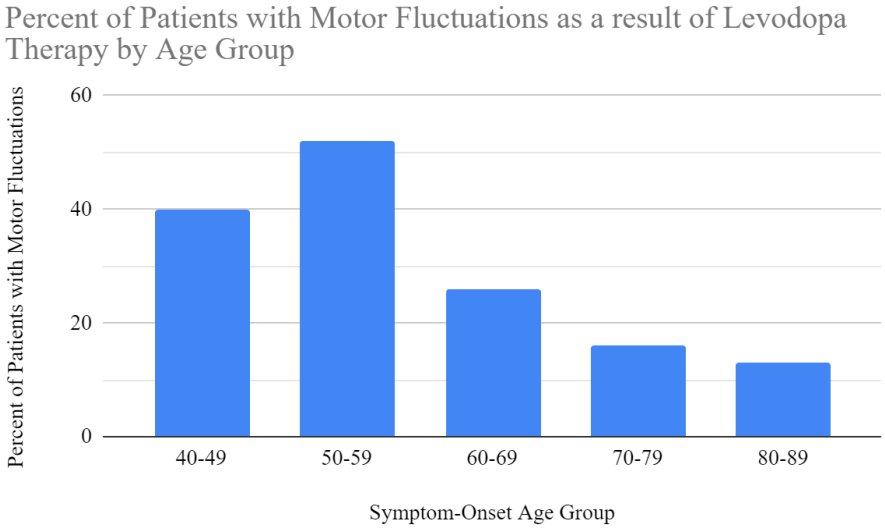
As addressed, levodopa and dopamine agonists have been two of the most common treatments used to manage and counteract the effects of Parkinson's Disease upon an individual. However, these two treatments have proven to be different from each other. Published on November 9, 2020, an experiment comparing 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.

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