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Novel Therapies in the Treatment of Parkinson's Disease

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Abstract

Parkinson's Disease (PD) is the second most common neurodegenerative disease, caused by the degenerative progression of dopaminergic neurons located in the substantia nigra pars compacta, which results in the decreased production of dopamine — a necessary neurotransmitter to maintain homeostasis. However, the ultimate cause of damage done to these neurotransmitters is unknown, as it has been found that the development of Lewy Bodies, overproduction of calcium ions, and other protein mutations can all cause dopaminergic neurons to be deficient. The development of PD causes deteriorating symptoms such as bradykinesia, motor tremors, muscle stiffness, and impaired balance. No cure for Parkinson's disease has been developed, in which researchers have instead developed therapies to combat the degenerative symptoms that result from PD. Recently, there has been an amplification in research and generation of medical pharmacologic therapies and invasive surgical therapies, such as Deep Brain Stimulation, to alleviate symptoms. Although current pharmacologic therapies function to a certain degree, they are not effective over long periods, which is how PD becomes increasingly damaging. Similarly, there is a lack of definitive disease-modifying therapies such as alpha-synuclein antibodies, LRRK2 antibodies, exenatide, and isradipine. These disease-modifying pharmaceuticals, surgical therapies, and future treatments must continue to be researched for safety, longevity, and effectiveness to promote optimal quality of PD patients.

Keywords: Parkinson's Disease, Therapy, Agents, Mutation, Neuroscience, Neurodegenerative Disease

1. Introduction

Parkinson's Disease (PD) is a progressive neurodegenerative disorder that is caused by the loss of specific neurons within the substantia nigra pars compacta, which are responsible for the production of dopamine. Dopamine is extremely important to the well-being of an individual, as it serves as a chemical messenger between various parts of the brain and nervous system to coordinate bodily movement (Kaila & Lang, 2015). As dopamine production decreases, the ability of an individual to control and coordinate bodily movements with ease progressively deteriorates. PD has been around for a long period but was first discovered by an English physician named James Parkinson, who the disease is named after. Today, PD is considered the second most common neurodegenerative disease after Alzheimer's Disease, affecting more than 10 million people worldwide. Although PD affects all cultures and races equally, it is approximately 2 times more prevalent in males than in females (Cerri et al. 2019).

James Parkinson first described the disease as "shaking palsy" after observing the tremors that could occur in someone with the disease. In addition to these tremors, people with PD may encounter coordination trouble, slow movement, deteriorating posture and balance, and stiffness in their legs, arms, or neck. Because of these degenerative symptoms that are almost guaranteed to develop in an individual

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with PD, many people want to treat the disease. Unfortunately, not only are there no specific prevention techniques for PD, but there are no definitive treatment plans that can eradicate the neurodegenerative disease from the body. Instead, various types of intensive therapies have been developed to combat the grueling symptoms that come with PD that normally result from a mutation in specific genes, ultimately making certain proteins dysfunctional and harmful towards dopaminergic neurotransmitters. Currently, the therapies that exist are somewhat effective, but have many problems that leave a lot to be wanted by researchers, neurologists, and patients. In this literature review, we will discuss the effectiveness and problems with current treatments, as well as the effectiveness, extended benefits, and problems with upcoming disease-modifying therapies, mainly including surgical and neural pathway targeting agents. Although PD might be a disease with no cure at present, it is important for researchers exploring these current therapies of PD to understand the problems with these therapies, as well as what upcoming benefits and problems disease-modifying therapies can offer in order for further advances in PD therapies to be developed.

2. Materials and Methods

This paper was created through a literature review, an exploration of academic papers and clinical trials. We methodically searched PubMed and Google Scholar to identify literature reviews, clinical trials, and randomized control trials examining baseline information on different protein mutations that cause PD, as well as associations between disease-modifying therapies and PD. No date or language restrictions were used, although most papers that were used are from the 21st century. The search strategy for these papers included keywords “Parkinson’s” AND “Disease modifying therapies (Alpha-synuclein, LRRK2, Levodopa, COMT-Inhibitor, MAO Inhibitor, Exenatide, Insulin, Isradipine, L-type calcium, or DBS)” OR “Epidemiology”. When more than one clinical trial on the same therapeutic was eligible, the clinical trial with the most participants was used for statistically significant reasoning.

3. Results and Discussion

3.1 Current Therapies

Levodopa

Levodopa is a central nervous system agent that is effective as a dopamine-replacement therapy. The main use of Levodopa is to relieve bradykinetic symptoms of idiopathic PD as well as be utilized as a baseline drug to which other potential drug therapies for PD are compared. With oral inhalation and infusion via nasojejunal tube being the exclusive methods of intake, Levodopa can enter the body and bypass the blood-brain-barrier, unlike neural-produced dopamine, and is converted into dopamine by the aromatic amino-acid decarboxylase enzyme in the central and peripheral nervous system (Figure 1) (Fahn et al., 2004). In a clinical trial determined on evaluating the effectiveness of Levodopa against worsening symptoms in patients with PD, it was found that the progression of PD in patients who received Levodopa treatment rather than the placebo treatment had significantly slowed based on the Unified Parkinsons’ Disease Rating Scale (UPDRS) (Fahn et al., 2004). Although this study constructively evaluated the effectiveness of Levodopa, it failed to evaluate the effectiveness of the drug against significantly long periods. To address this limitation, a prospective study over a mean treatment duration of 11.1 years focused on evaluating the effectiveness of Levodopa on motor control in patients with idiopathic PD determined that motor response improved over the course of the first 5 years of treatment. Subsequently, the motor response of the patients fluctuated in parallel with the conservation of motor response (Alty et al., 2019). This means that compared to the immediate improvement of symptoms caused by the intake of Levodopa, the drug is not as effective in the long run. This may occur because of the progressively deteriorating neurological functionality that PD causes, ultimately leading to gradually worsening symptoms over time. However, based on our observations and examination, we suggest that currently, Levodopa is likely the most reliable and effective treatment for Parkinson’s Disease especially

with the assistance of enzymatic materials. In the future, however, technological advancements may cause Levodopa to become less frequently used.

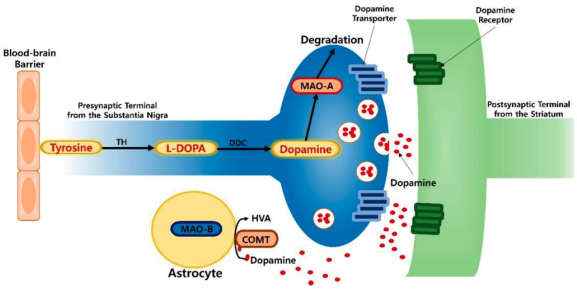

Figure 1. Levodopa's function within individual neurons. Levodopa bypasses the blood-brain barrier and interacts with the synaptic cleft with the assistance of enzymes such as COMT and MAO-B to be converted to dopamine (Jung et al. 2019).

COMT-Inhibitors

Catechol-O-methyltransferase (COMT) inhibitors are a class of drugs used alongside Levodopa to alleviate the worsening motor symptoms associated with PD. Although Levodopa is considered the most effective medication therapy for PD, it loses its effectiveness over time. COMT-Inhibitors can be useful in this sense as they are not only able to extend the effectiveness of Levodopa when used, but they can also allow for lower doses of Levodopa which can have medical and financial benefits for patients (Connolly & Lang, 2014). COMT-Inhibitors function by blocking the further activity of COMT, which is an enzyme that destroys neurotransmitters such as dopamine, the main cause of PD (Finberg, 2019). The most common COMT-Inhibitors used for PD therapy are entacapone, tolcapone, and opicapone, which all slow down the breaking down of Levodopa, allowing more of it to bypass the blood-brain-barrier and reach the brain, leading to the alleviation of PD symptoms. A clinical trial attempted to test how effective COMT-Inhibitors are in combination with Levodopa for PD therapy and found that the use of entacapone — a type of COMT-Inhibitor — was significantly more effective than using Levodopa exclusively in treating motor malfunctions (Merello et al., 1994). The problem with COMT-Inhibitors, however, is that they are not effective as a therapeutic when acting alone (PD Med Collaborative Group et al., 2022). This may ultimately cause patients to have to purchase more medication and experience more side effects that come with consuming them.

MAO-Inhibitors

Similar to COMT-Inhibitors, Monoamine Oxidase B (MAO-B) Inhibitors are a class of drugs to help treat the symptoms of PD that are usually used alongside Levodopa. However, MAO-B Inhibitors may be used exclusively in the early stages of PD, in which they have moderate effectiveness against PD symptoms. Monoamine Oxidase is an enzyme found in cells and can be classified as either type A or type B. MAO-B is typically found in the brain in which it plays a role in the breakdown of neurotransmitters such as dopamine, ultimately causing the loss of dopamine activity and the appearance of PD symptoms. The goal of MAO-B Inhibitors is to block the activity of this enzyme so these neurotransmitters are lost to a lesser extent (Finberg, 2019). MAO-B Inhibitors have also been found to slow the breakdown of Levodopa after it passes through the blood-brain barrier, which may boost the effectiveness and sustainability of the medication (Finberg, 2019). Typically, MAO-B Inhibitors come in the form of orally consumed tablets, making the effects of the drug easy to obtain. A clinical trial was conducted to test the effectiveness of MAO-B Inhibitors in patients with PD, in which it was found that there were very small yet persistent alleviating effects found in patient mobility scores when MAO-B Inhibitors were used in combination with Levodopa, which is the most common method of use (PD Med Collaborative Group et al., 2022). The study, however, also found that MAO-B inhibitors were not effective in alleviating PD symptoms when used alone, which is the main issue in the utilization of the drug (PD Med Collaborative Group et al., 2022). Ultimately, this causes financial and medical complications, which is why MAO-B Inhibitors aren't the most common nor effective medication in PD symptom relief.

3.2 Molecular Pathway Targeting Agents

Alpha-Synuclein

Alpha-Synuclein is a neural transmitter whose normal function has not been established, but has been suggested to be a cause of familial PD. Mutated alpha-synuclein proteins are thought to cause PD by abnormally aggregating into the form of Lewy Bodies and Lewy Neurites. As a result, the

accumulated alpha-synuclein proteins can spread by binding their fibrils to neuronal cell surfaces to gain entry into the cytoplasm until the entire cell surface of neurons is bound by alpha-synuclein fibrils in which the proteins can overtake the cells (Hijaz et al., 2020). As the proteins spread among neuronal cell pathways, they will eventually overexpress themselves in which they will be able to inhibit and slow neurotransmitter releases, specifically dopamine ultimately leading to neurodegeneration. To combat the spread of alpha-synuclein in cellular pathways and host cells, advances in therapies have been developed to produce disease-modifying effects by targeting the spread, production, aggregation, and degradation of alpha-synuclein. We suggest that it is important for scientists to examine therapy alpha-synuclien further, as it is a mutation that a significant amount of people have, risking these individuals for PD. An example of these therapies can be found in a clinical trial investigating the tolerability and safety of alpha- synuclein antibody PRX002 over 2 years, where it was determined that repeated treatment of PRX002 was generally safe and tolerable for patients with PD while inducing reductions in free serum alpha-synuclein (target engagement) (Jankovic et al., 2018). Unfortunately, little is known about the holistic effectiveness of these antibodies and therapies against the aggregation of alpha-synuclein in molecular pathways, so more experimental research is needed to determine whether they are realistic approaches to combat PD symptoms.

Leucine-Rich Repeat Kinase 2

Leucine-Rich Repeat Kinase 2 (LRRK2) is a large protein that has many different functions but has also been suggested to account for 5-13% of familial PD and 1-5% of sporadic PD when mutated (Qin et al., 2018). When the LRRK2 protein mutates, it causes the protein's enzymatic activity to uncontrollably increase kinase activity in the kinase domain or through the GTPase domain by intentionally weakening and damaging the GTP hydrolysis process (Nguyen et al., 2020). With this, neuronal toxicity is induced in cultured cells which has been suggested to impair dopaminergic activity, ultimately leading to the development of PD over time. It has also been determined that mutated LRRK2 may influence the aggregation of alpha-synuclein, ultimately invading cell structures and molecular pathways through increased kinase activity (Zimprich et al., 2004). To combat these imminent mutative threats, certain therapeutic interventions have been developed to prevent neurodegenerative effects. One of these developments are LRRK2 inhibitors, which were tested in preclinical trials and were suggested to prevent some aspects of neurodegeneration by potentially using autophagy to replace deteriorating cells (Lee et al., 2012). Although this trial was mostly successful, it was limited by lung toxicity which could cause other harms when given, which is why more research needs to be conducted on this treatment type. In fact, treatment of LRRK2 mutation is very much incomplete and dangerous as it can have detrimental effects on its victims.

3.3 Deep Brain Stimulation

Deep Brain Stimulation (DBS) is a minimally invasive procedure that has the potential for symptom alleviation in those with neurodegenerative diseases, most commonly, Parkinson's Disease. To start DBS, a thin wire covered in electrodes is implanted to induce high-frequency electrical stimulation in specific regions of the brain. The location where the electrodes are placed depends on what area of the brain is creating abnormal signals which are causing the patient to experience symptoms. To power the signal-inducing electrodes, a battery-powered operator is connected to the thin wire, and placed into the chest wall. The battery-powered operator is regulated by a computer, which contains instructions for when the electrodes should send electrical impulses. When properly functioning, the electrodes send pulses of electrical signals to normalize the occurring abnormal electrical activity in which the defective signals coming from likely damaged neurons are blocked (Fariba & Gupta, 2021). To test the effectiveness of DBS in alleviating the motor deficiency symptoms of PD, a clinical trial was conducted where it was found that neurostimulation of the subthalamic nucleus was significantly more effective than solely medication where UPDRS scores had mean improvements of 9.5-19.6 points

(Deuschl et al., 2006). Although DBS offers some beneficial effects for those with neurodegenerative symptoms, there is a significant risk for extremely damaging adverse events. Examples of such adverse events include fatal internal brain hemorrhages, device malfunctions, marginal paralysis, reduced coordination, and deteriorating emotional and mental status (Topp et al., 2021). With the potential for patients to undergo these adverse events, more research and testing must be conducted to reduce the limitations associated with DBS. This is mainly because of the beneficial effects that DBS offers when successful in which it can alleviate PD symptoms more effectively than most medications. After examining the effectiveness of DBS, we may suggest that in present day, DBS is not the safest nor reliable treatment for Parkinson's Disease. It is likely that this may not be the case in the future due to technological advancements in this field.

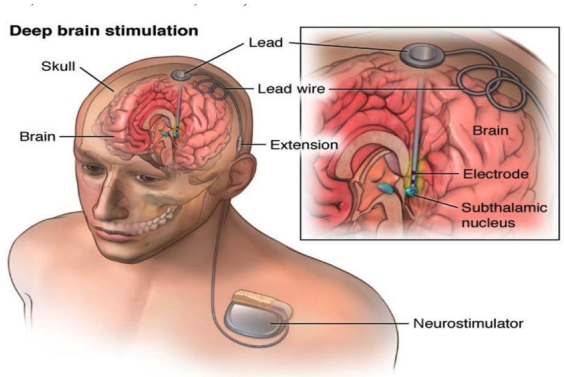

Figure 1 Anatomical illustration of DBS STN

Figure 2. Diagram showing how Deep Brain Stimulation functions as a treatment, as well as materials used in their specific locations. Electrodes placed in the brain are connected to a neurostimulator, which sends electrical signals to stimulate electrical activity within the brain (Mayo Foundation, 2021).

3.4 Neuronal Rescue Pathway Targeting Agents

Exenatide

Glucagon-like peptide-1 (GLP-1) receptor agonists are medications that mimic a naturally occurring hormone that can have neuroprotective effects against PD while typically being used as a medication to treat Type-2 diabetes. The most tested form of these agents is Exenatide, which is typically used to help an individual's pancreas produce insulin more efficiently to control blood sugar levels better. However, in a recent clinical trial investigating the effectiveness of Exenatide against motor PD, it was determined that Exenatide had beneficial effects on motor scores that sustained beyond the period of exposure to the medication (Athauda et al., 2017). Not only this, but in an open-label Phase II study, it was determined that not only did deteriorating symptomatic ataxia improve, but cognitive-behavior improved as well (Aviles-Olmos et al., 2013), making Exenatide an extremely beneficial impermanent medication for PD. Exenatide and other GLP-1 receptor agonists are so effective because they have been shown to be beneficial to mechanisms regulating reduced inflammation that appears after the development of PD as well as combative to continued aggregation of alpha-synuclein as seen in animal models (Wang et al., 2021). Although these medications are effective, more research must be conducted to determine if Exenatide can be used as a long-term medication for deteriorating developments that occur during progressional PD.

L-Type Calcium Channel Blockers/Isradipine

Recent studies have suggested that dihydropyridine calcium-channel blockers, which are typically used to treat hypertension and angina, may be associated with a reduced risk of developing deteriorating symptoms in PD. This is because certain neuronal areas with spontaneous peacemaking cells, such as substantia nigra pars compacta, rely on L-type calcium channels that allow increased calcium entry into cells. With increased calcium entry, the body is more at risk for increased oxidative stress, mitochondrial damage, and increased cell death (Chan et al., 2007). To continuously combat this issue, Isradipine is typically used as a calcium-blocking medication. To test the effectiveness of Isradipine, a clinical study was conducted in which results determined that short-term treatment of PD using Isradipine may be effective, but long-term usage does not slow the progression of PD which acts as a limiting factor for this medication (Parkinson Study Group STEADY-PD III Investigators, 2020). Contrastingly, in a statistical analysis assessing the effectiveness of non-specific L-type calcium channel blockers on PD, it was found that these medications had a 27% risk reduction in developing ataxic and bradykinetic symptoms (Ritz

et al., 2010). This may suggest that Isradipine, the most common form of L-type calcium channel blocker, may not be as effective as other L-type calcium channel blocker medications.

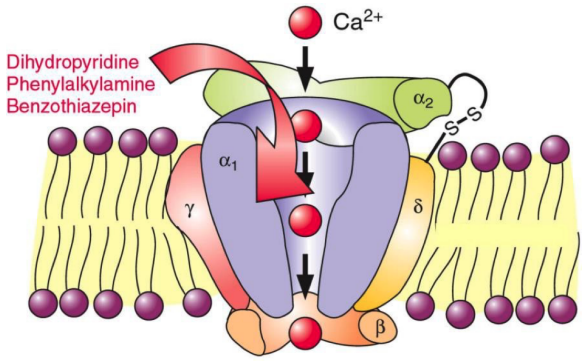

Figure 3. Diagram showing the anatomy of a L-Type Calcium Channel, as well as dihydropyridine calcium-channel blockers entering the channel as inhibitors (Wikipedia 2022).

4. Conclusion

It appears that PD is associated with a plethora of pathophysiological causes, ranging from the aggregation of alpha-synuclein, mitochondrial dysfunction, increased calcium production, and neuroinflammation. All of these causes, however, cause the impairment of dopaminergic activity, which is something that most therapies for PD attempt to fix. Although we haven't developed strategies to completely restore the neurotransmitters producing a lack of dopamine, we have developed therapies that can at least alleviate the symptoms and suffering that patients with PD undergo. To improve these therapeutics and use them to their full potential, we suggest that it will be necessary to advance methods that are used to quantify the extent to which a patient with PD responds to a certain disease- modifying approach, whether that's through molecular pathway targeting agents, levodopa, surgical methods, or neuronal rescue pathway targeting agents. By being able to measure the extent to which these therapeutics are effective, researchers and neurologists may be able to make a better prediction of how people will respond to therapeutics through the alleviation or pursuit of deteriorating motor and gait symptoms. With advances in technology and research, it will be necessary to not only consider the therapies mentioned in this review, but also to consider the restoration of neurotransmitters using microscopic technology as a potential cure for PD. Finally, based on our examinations while researching this topic, we have come to the conclusion that it would be the effective for people suffering with PD to continue to take Levodopa in combination with MAO-B or COMT Inhibitors. This combination of therapies is not only the most effective treatment for PD in the present day, but it is also the most cost-effective. Overall, although current and upcoming therapies for PD are somewhat effective, we heavily suggest it will be necessary for more developmental changes to occur in the attempt to find a terminal cure for PD.

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References

Alty, J., et al. (2009). Longitudinal study of the levodopa motor response in Parkinson's disease: relationship between cognitive decline and motor function. Movement disorders : official journal of the Movement Disorder Society, 24(16), 2337–2343. https://doi.org/10.1002/mds.22800

Athauda D., et al. (2017). Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double- blind, placebo-controlled trial. Lancet (London, England), 390(10103), 1664–1675. https://doi.org/10.1016/ S0140-6736(17)31585-4.

Aviles-Olmos I., et al. (2013). Exenatide and the treatment of patients with Parkinson's disease. The Journal of clinical investigation, 123(6), 2730–2736. https://doi.org/10.1172/JCI68295

Cerri, S., Mus, L., & Blandini, F. (2019). Parkinson's Disease in Women and Men: What's the Difference?. Journal of Parkinson's disease, 9(3), 501–515. https://doi.org/10.3233/JPD-191683

Chan, C., et al. (2007). 'Rejuvenation' protects

neurons in mouse models of Parkinson's disease. Nature, 447(7148), 1081–1086. https://doi.org/10.1038/nature05865
Connolly, B. S., & Lang, A. E. (2014). Pharmacological treatment of Parkinson disease: a review. *JAMA*, 311(16), 1670–1683. https://doi.org/10.1001/jama.2014.3654

Deuschl, G., et al. (2006). A randomized trial of deep-brain stimulation for Parkinson's disease. *The New England journal of medicine*, 355(9), 896–908. https://doi.org/10.1056/NEJMoa06028.

Fahn, S., et al. (2004). Levodopa and the progression of Parkinson's disease. *The New England journal of medicine*, 351(24), 2498–2508. https://doi.org/10.1056/NEJMoa033447
Fariba, K. A., & Gupta, V. (2021). Deep Brain Stimulation. In StatPearls. StatPearls Publishing.

Finberg J. (2019). Inhibitors of MAO-B and COMT: their effects on brain dopamine levels and uses in Parkinson's disease. J*ournal of neural transmission (Vienna, Austria : 1996)*, 126(4), 433–448. https://doi.org/10.1007/ s00702-018-1952-7

Hijaz, B. A., & Volpicelli-Daley, L. A. (2020). Initiation and propagation of α-synuclein aggregation in the nervous system. *Molecular neurodegeneration*, 15(1), 19. https://doi.org/10.1186/s13024-020-00368-6.

Jankovic, J., et al. (2018). Safety and Tolerability of Multiple Ascending Doses of PRX002/RG7935, an Anti-α- Synuclein Monoclonal Antibody, in Patients With Parkinson Disease: A Randomized Clinical Trial. *JAMA neurology,* 75(10), 1206–1214. https://doi.org/10.1001/jamaneurol.2018.1487.

Jung, H. A et al. (2019). Novel Diels-Alder Type Adducts from *Morus alba* Root Bark Targeting Human Monoamine Oxidase and Dopaminergic Receptors for the Management of Neurodegenerative Diseases. *International journal of molecular sciences*, *20*(24), 6232. https://doi.org/10.3390/ijms20246232

Kalia, L. V., & Lang, A. E. (2015). Parkinson's disease. Lancet (London, England), 386(9996), 896–912. https:// doi.org/10.1016/S0140-6736(14)61393-3

Lee, B. D., Dawson, V. L., & Dawson, T. M. (2012). Leucine-rich repeat kinase 2 (LRRK2) as a potential therapeutic target in Parkinson's disease. *Trends in pharmacological sciences*, 33(7), 365–373. https://doi.org/ 10.1016/j.tips.2012.04.001.

Mayo Foundation for Medical Education and Research. (2021). *Deep Brain stimulation.* Mayo Clinic. https://www.mayoclinic.org/tests-procedures/deep-brain-stimulation/about/pac-20384562

Merello, M., et al. (1994). Effect of entacapone, a peripherally acting catechol-O-methyltransferase inhibitor, on the motor response to acute treatment with levodopa in patients with Parkinson's disease. *Journal of neurology, neurosurgery, and psychiatry*, 57(2), 186–189. https://doi.org/10.1136/jnnp.57.2.186

Nguyen, A., et al. (2020). Dopaminergic neurodegeneration induced by Parkinson's disease-linked G2019S LRRK2 is dependent on kinase and GTPase activity. Proceedings of the National Academy of Sciences of the United States of America, 117(29), 17296–17307. https://doi.org/10.1073/pnas.1922184117.

Parkinson Study Group STEADY-PD III Investigators (2020). Isradipine Versus Placebo in Early Parkinson Disease: A Randomized Trial. *Annals of internal medicine*, 172(9), 591–598. https://doi.org/10.7326/M19-2534.

PD MED Collaborative Group, et al. (2022). Long-term Effectiveness of Adjuvant Treatment With Catechol-O- Methyltransferase or Monoamine Oxidase B Inhibitors Compared With Dopamine Agonists Among Patients With Parkinson Disease Uncontrolled by Levodopa Therapy: The PD MED Randomized Clinical Trial. *JAMA neurology*, 79(2), 131–140. https://doi.org/10.1001/jamaneurol.2021.4736.

Ritz, B., et al. (2010). L-type calcium channel blockers and Parkinson disease in Denmark. *Annals of neurology*, 67(5), 600–606. https://doi.org/10.1002/ana.21937

Rui, Q., et al. (2018). The Role of LRRK2 in Neurodegeneration of Parkinson Disease. *Current neuropharmacology*, 16(9), 1348–1357. https://doi.org/10.2174/1570159X16666180222165418.

Topp, G., et al. (2021). Safety of Deep Brain

Stimulation Lead Placement on Patients Requiring Anticlotting Therapies. *World neurosurgery*, 145, e320–e325. https://doi.org/10.1016/j.wneu.2020.10.047

Wang, V., et al. (2021). Sustained Release GLP-1 Agonist PT320 Delays Disease Progression in a Mouse Model of Parkinson's Disease. *ACS pharmacology & translational science,* 4(2), 858–869. https://doi.org/10.1021/acsptsci.1c00013.

Wikipedia. (2022). *L-type Calcium Channel*. https://en.wikipedia.org/wiki/L-type_calcium_channel

Zimprich, A., et al. (2004). Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. *Neuron*, 44(4), 601–607. https://doi.org/10.1016/j.neuron.2004.11.005