HIGH SCHOOL EDITION
Journal of Student Research
Volume 11 Issue 4 (2022)

Dopamine and the Causes, Prevention, and Advanced Treatments of Parkinson's Disease

Jeremy Nashid[1], Rajagopal Appavu[#], and Jothsna Kethar[#]

[1] McNarr Academic High School, USA
[#]Advisor

ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder with a wide range of motor and non-motor symptoms. Despite optimal medical management, PD still results in a high disability rate and secondary complications, and many patients lead a sedentary lifestyle, which in turn is also associated with a higher co-morbidity and mortality.

Dopamine is a type of monoamine neurotransmitter. It is made in your brain and acts as a chemical messenger, communicating messages between nerve cells in your brain and the rest of your body. Dopamine is what motivates us to do something. Dopamine is a large factor in many of our day-to-day actions: it decides our mood, what we remember, and even how we move and act.

This Dopamine and PD study is anticipated to inform those with PD of treatments that work better than others. Strong elements of this research paper include treatments such as MR-Guided focused Ultrasound, Gene Therapy, Park-in-Shape, and the rise of a PD Vaccine. This research paper's secondary goal is to inform those looking to avoid PD or who already have PD and wish to avoid the symptoms on how to avoid the symptoms of the disease. This Dopamine and PD study aims to explain what dopamine is, how it works, how it affects the body, and the effects of unhealthy levels of dopamine.

Introduction

Dopamine is one of the driving chemicals in our brain. Interacting with the pleasure and reward center of the brain, dopamine plays a vital role in how happy we feel. In addition to our mood, dopamine also affects movement, memory, and focus. Healthy levels of dopamine drive us to do activities that we find enjoyable, while low levels can have adverse physical and psychological impacts.

As shown in **Figure 1,** the chemical structure of dopamine is a type of monoamine neurotransmitter. It is made in your brain and acts as a chemical messenger, communicating messages between nerve cells in your brain and the rest of your body.

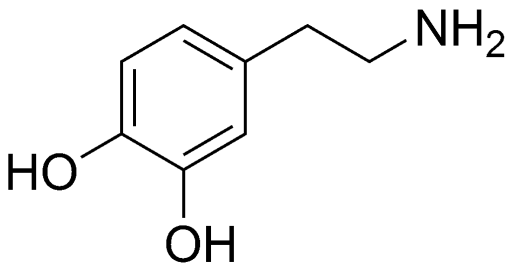

Figure 1. The chemical structure of dopamine has two Hydroxyl groups and an amine group[1].

How is Dopamine Synthesized in the Body?

Dopamine is a monoamine catecholamine neurotransmitter belonging to the 7 transmembrane G protein-coupled receptors (GPCRs), which play an important role in the regulation of not only motor functions but also non-motor functions such as motivation, cognition, emotion, and neuroendocrine secretion [2].
Dopamine is first synthesized in the adrenal gland, which is located above the kidney. The creation of dopamine is a long process. It first begins with tyrosine, an amino acid, which comes from the food that we eat. Next, an enzyme, L-dopa, is created by adding a hydroxyl group to the tyrosine. Dopamine's precursor L-dopa leaves the adrenal gland and travels through the bloodstream to the brain. Dopamine is not made directly in the brain because synthetic/manufactured dopamine can't break through the brain barrier.
Only water and other gasses like oxygen and soluble substances are able to travel through the blood-brain barrier (BBB).

What Pathways Does Dopamine Use in The Brain?

Dopamine pathways are neuronal connections in which dopamine travels to areas of the brain and body to convey important information such as executive thinking, cognition, feelings of reward and pleasure, and voluntary motor movements.

The major dopaminergic pathways in the brain include the nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular systems that play vital roles in the regulation of many physiological functions such as conveying important information, executive thinking, cognition, feelings of reward and pleasure, and voluntary motor movements. Dopamine deficiency and dopaminergic neuron death in the nigrostriatal pathway lead to the development of PD in patients. Nigrostriatal pathway death in PD is due to excessive oxidation of dopaminergic neurons[3].

Dopamine binds to dopamine receptors on neighboring dendrites to alter membrane currents. After dopamine binds to dopamine receptors, it comes off, and can then bind to proteins called transporters on the releasing neuron to be taken back up into the terminal[4].

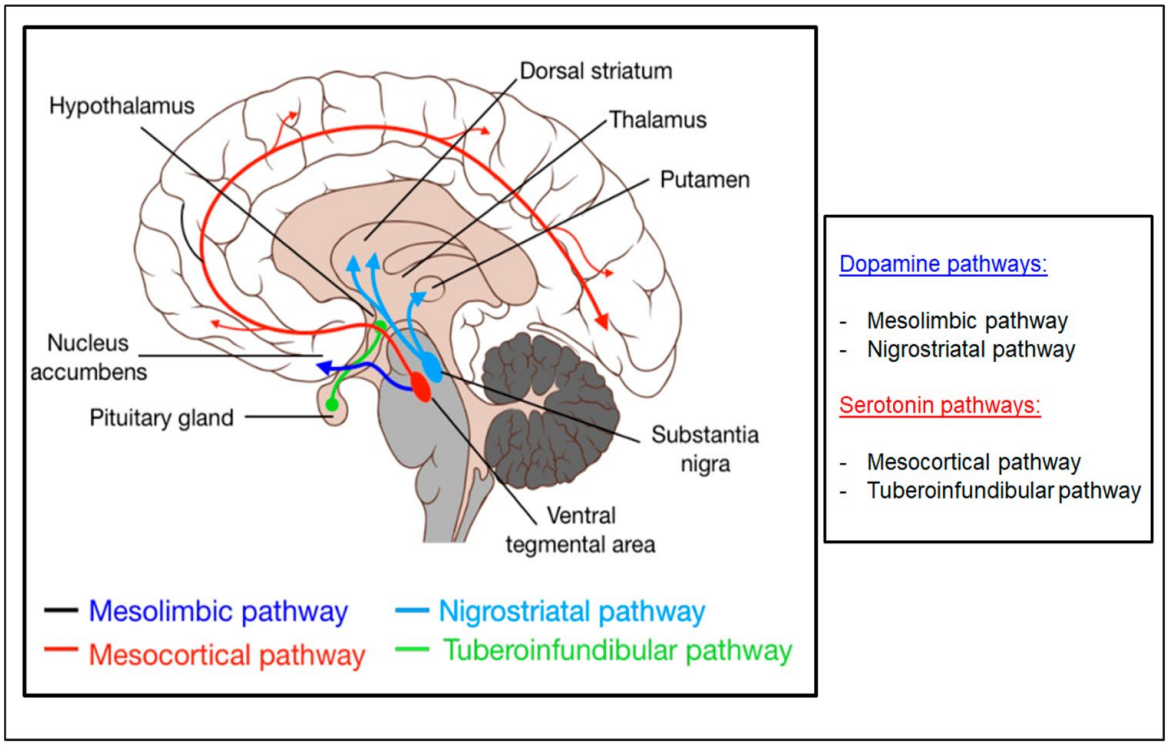

Figure 2. The above figure depicts pathways in which dopamine travels through the brain. (Mesolimbic, Mesocortical, Nigrostriatal, and Tuberoinfundibular)[5]

Parkinson's Pathology

Role of Dopamine

PD occurs due to the loss of neurotransmitters in the substantia nigra particularly in the input area known as the pars compacta (a portion of the substantia nigra, located in the midbrain) projects to the dorsal striatum, which plays a primary role in the control of motor function and learning motor skills. It is a chronic neurodegenerative disorder that progressively gets worse. These dying neurons are responsible for producing dopamine. Once those neurons die, a person will begin to experience movement problems. This is because the substantia nigra plays a critical role in controlling movement. Thus, the symptoms of PD begin to experience movement-related problems, such as tremors, rigidity, slowness of movement, and poor balance, as well as problems with memory and impairment to the cognitive and neuropsychological systems[6].

Progressive Loss of Dopamine

Although the rate of dopamine cell loss can not be measured directly, measurements in neurologically normal people show a slowly progressive loss of dopamine with age. But in PD, the loss happens at a much greater rate, an accelerated version of cell death than what is seen with normal aging[7].
The depletion of dopamine leads to alter function of glutamate, GABA, and serotonin neurotransmitter[8].

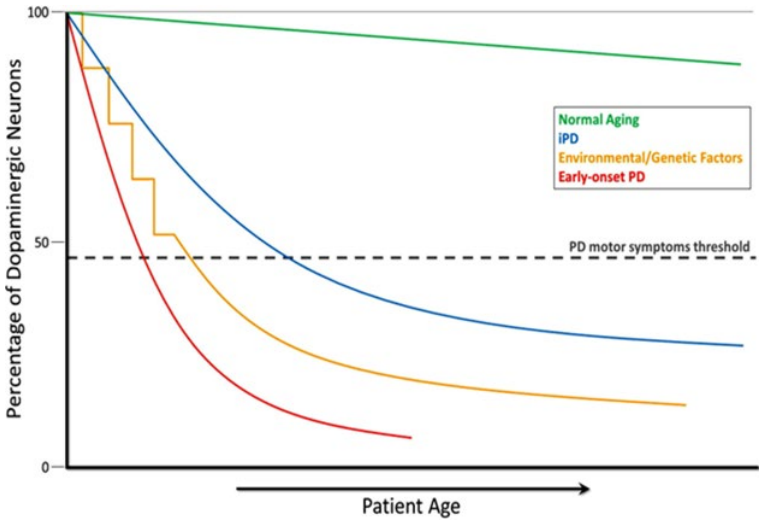

Figure 3. Percentage of dopaminergic neurons in a PD patient as opposed to a normal aging person[9].

Lewy Bodies and Alpha-Synuclein

Alpha-synuclein is a key protein involved in PD pathology. The abnormal accumulation and aggregation of alpha-synuclein in the form of Lewy bodies and neurites, more precisely, the aggregation of alpha-synuclein is associated with the dysfunctionality and degeneration of neurons in PD. Moreover, mutations in the SNCA gene, which encodes alpha-synuclein, cause early onset of PD and are the basis of sporadic PD risk[10].

Causes of PD

Environmental Health Effects Leading to PD

Pesticides have been found to cause neurodegenerative disorders like PD and Alzheimer's. Pesticides such as rotenone and paraquat could disrupt mitochondrial bioenergetic function, reactive oxygen metabolism, and re-dox function, and promote alpha-synuclein aggregation, primary factors leading to PD[11].

Alcohol and Drug Use

Alcohol acts as a reward factor for the brain, as when someone drinks for the first time the brain increases the amount of dopamine in the body. However, over time, as a person continues to drink, the brain begins to produce less of the chemical, and as the amount of dopamine plummets, so does their mood. Similarly, drugs affect your mood and the amount of dopamine in your body. Dopamine comes from the pleasure center of the brain; drugs act as substitutes for natural rewards. As in Figure 4, alcohol has a devastating effect: it decreases the amount of dopamine in your body[12].

Lower levels of dopamine cause people with addictions to drugs to be more susceptible to diseases such as PD, Restless Legs Syndrome, Depression, ADHD, Schizophrenia, and Chronic Constipation because of damaged dopamine receptors and decreased dopamine release.

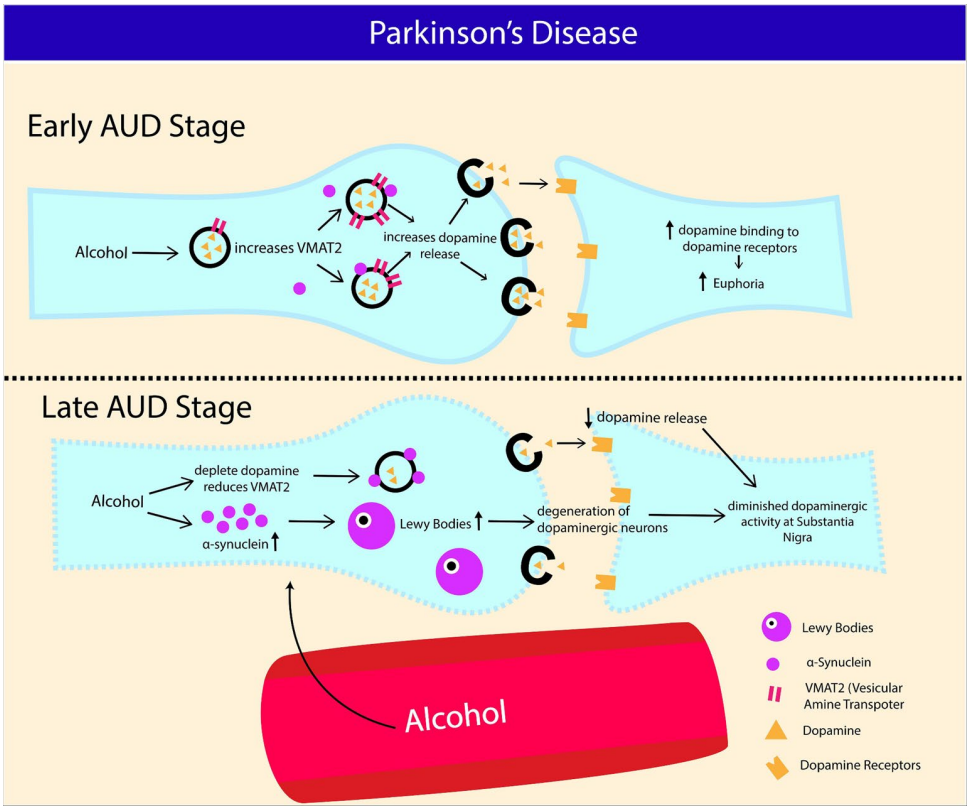

Figure 4. Alcohol's effect on dopaminergic receptors[13].

Genetic Factors Building up to PD[14].

Gene mutation is responsible for the onset of PD. Eighteen chromosomal locus (termed PARK to exemplify their relationship to PD).

a. **SNCA (PARK1 - 4):** Patients with SNCA mutations have early-onset PD. This gene is generally attributed to those of the age less than or equal to the age of 50 yrs). Provides instructions for making alpha-synuclein.
b. **LRRK2 (PARK8):** The LRRK2 gene is more active at the age of 75 yrs.
c. **Parkin (PARK2):** The Parkin gene is the most frequent cause of juvenile PD. This gene is generally attributed to those younger than or are 21 yrs of age.
d. **PINK1 (PARK6):** The PINK1 gene is a loss-of-function mutation.
e. **DJ-1 (PARK7):** DJ-1 is so uncommon, that there is not enough data to draw any conclusion about the effects of the gene.
f. **ATP13A2 (PARK9):** ATP13A2 was found to cause a form of PD named Kufor-Rakeb syndrome.

Mitochondrial Dysfunction in PD.

The mitochondria is the powerhouse of the cell. Mitochondrial dysfunction plays a major role in the pathogenesis of PD, and in particular, defects of mitochondrial complex-I of the respiratory chain may be the most appropriate cause of degeneration of neurons in PD by reducing the synthesis of ATP[15].

A. Therapeutic Approaches include:

a. Recovering physiological ATP production by targeting the electron transport chain (ETC) and antioxidative treatment strategies
b. Exercise
c. Improving mitochondrial biogenesis
d. Gene therapies targeting mitochondrial dysfunction
e. Protein-based therapies targeting mitochondrial dysfunction

Preventing the Early Onset of PD

Medicinal Plants' Effectiveness on PD

Table 1. Describing certain plants that increase dopamine level retainment[16].

Plant Name	Effect on PD
Tinospora cordifolia **(Giloy, Guduchi)**	**1.** Increased the dopamine levels **2.** Decreased iron asymmetry ratio **3.** Decreased MDA levels **4.** Increased mitochondrial complex I activity **5.** Improved locomotor activity
Sesame seed oil (SO)	**1.** Increased glutathione reductase (GR), glutathione-S-transferase (GST), glutathione peroxidase (GPx), catalase (CAT) and content of glutathione (GSH) and thiobarbituric acid reactive substance (TBARS) **2.** Inhibit the activation of Nox2 and Cox2 **3.** Restored MnSOD expression
Carthamus tinctorius **L. (Safflower)**	**1.** Improve behavioral performances **2.** Suppression of α-synuclein overexpression or aggregation **3.** Suppression of reactive astrogliosis
Chaenomeles speciosa **(Flowering Quince)**	**1.** Increased tyrosine hydroxylase-positive neurons in the substantia nigra **2.** Increased D8 cell viability **3.** Time-dependently reduced abnormal turns in apomorphine-induced rotational turning
Portulaca oleracea **(Purslane)**	**1.** Increase in crossings and rearing in open field test
Paeonia suffruticosa **(Tree Peony)**	**1.** Increased movement distance in the open field test **2.** Increased total striatal dopamine **3.** Attenuated the loss of dopaminergic neurons **4.** Reversed down regulation Akt and the mitochondrial OXPHOS subunits
Mucuna pruriens **(Velvet Bean Seeds)**	**1.** Reduced risk for drug-induced dyskinesias **2.** Increased nigrostriatal catecholamine content
Hyoscyamus niger **seeds (Black Henbane)**	**1.** Attenuated motor disabilities **2.** Increased level of GSH content and GPX, SOD and CAT activities
Hibiscus asper **leaves**	**1.** Increased SOD, GPX and CAT activities, total GSH content

(Bush Roselle)	**2.** Reduced MDA level
***Gynostemma pentaphyllum* (Jiaogulan)**	**1.** Recovered the levels of dopamine, 3,4 dihydroxyphenylacetic acid, homovanillic acid and norepinephrine in striatum **2.** Ameliorated the loss of TH-immunopositive neurons in substantia nigra

Mediterranean Diets

The population that follows Mediterranean diets has a 50% lower chance of getting PD. A Mediterranean diet consists of fruits and vegetables, which contain vitamins A (beta-carotene), C and E, Magnesium, zinc, phosphorus, and folic acid. The combination of these vitamins and dairy products, eggs, and fish (Omega 3 fatty acids, calcium, riboflavin, phosphorous, potassium, magnesium, zinc, iodine, vitamin D, vitamin E, vitamin K, and vitamin B6) allows for an increased lifespan, preventions of cardiovascular disease, and most of all prevention against PD[17]. The Mediterranean diet protects against neurodegeneration. In several studies higher adherence to a Mediterranean diet in middle age was associated with lower risk for PD.

Current PD Treatment Through Dopamine Agonists and their Disadvantages

When patients use the synthesized form of levodopa drug, it temporarily restores dopamine levels. These levels constantly rise and fall, and because of these fluctuating levels and the continuing loss of producing brain cells, it is impossible to keep a steady level of dopamine, which contributes to dyskinesia.

Recent Advances in PD Treatments

MR-Guided Focused Ultrasound for Treatment of Tremor. (MRgFUS)

MRgFUS (MR-Guided Focused Ultrasound) is a treatment to eliminate the tremor-related symptoms of PD. In the brain, MRgFUS targets the thalamus using sonication energy, the device directs thousands of beams to the VIM (ventral intermediate) nucleus of the thalamus and creates a lesion[18]. The thalamus is a key target because it generates PD tremors by generating and consolidating the bursting activity of neurons within its nuclei [19].

Pros of MRgFUS.

MRgFUS is a non-invasive procedure, meaning that there is no risk of infection or bleeding. Medical practitioners could view if the treatment is working in real time and MRgFUS provides quick recovery times.

Cons of MRgFUS.

Tremor could return months or years after the treatment, and the tremor may not improve at all. The treatment leaves the patient with long term side effects or permanent muscle weakness, unsteadiness, sensory loss, or numbness or tingling in fingers or other areas of the body.

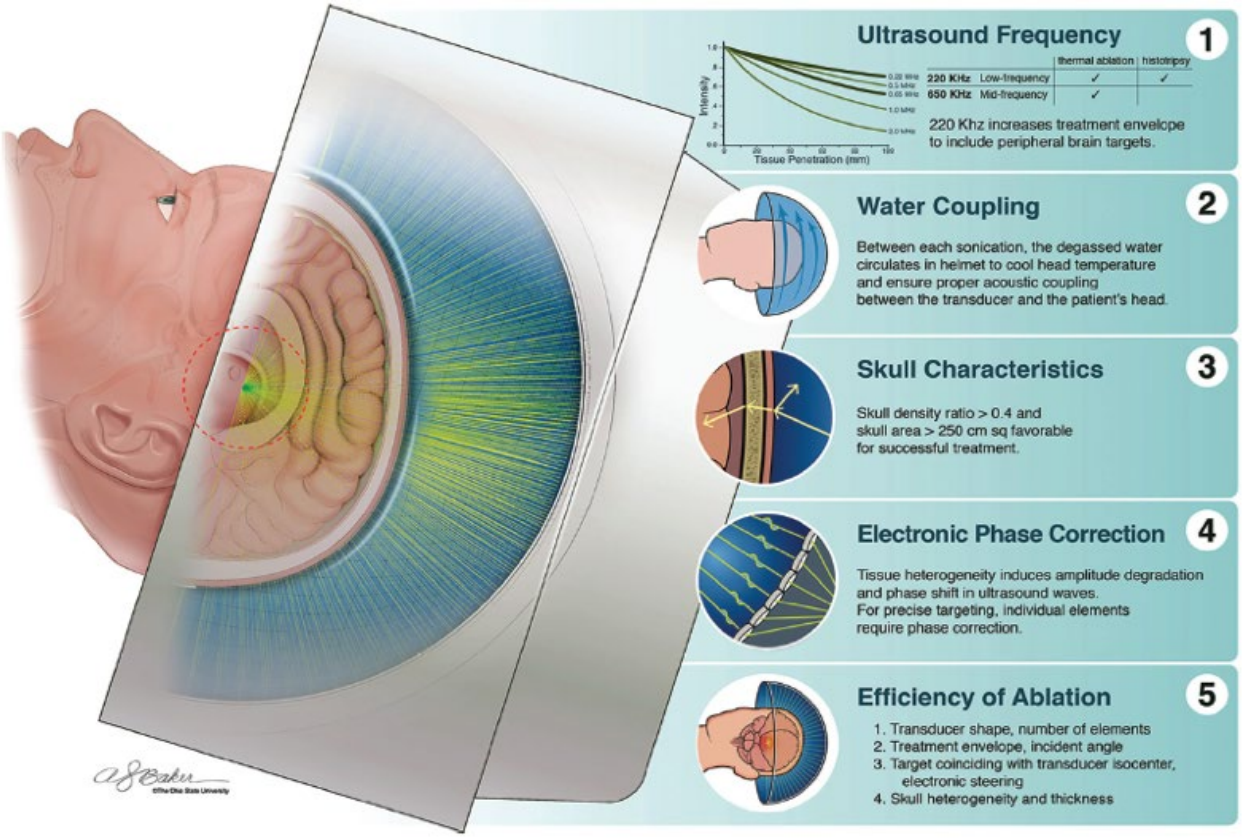

Figure 5. Shows how MRgFUS works by using ultrasound frequencies to burn the tremor out of the thalamus [20].

Vivo Gene Therapy

Gene therapy is transplanting normal genes in cells in place of missing or defective ones. Clinical trials showed that delivering glutamic acid decarboxylase into the subthalamic nucleus of patients with PD had therapeutic effects [21].

Gene therapy essentially is the use of viral vectors to remove harmful DNA. The viral vectors or viruses are carriers of the normal genes, these genes are used thereafter to make a protein of choice or eliminate a certain protein.

The Use of Viruses as a Vector Vehicle

Viruses work effectively in delivering nucleic acids to alter the genes of specific cell types. There are many types of viruses able to be used in the delivery of these nucleic acids including retrovirus, adenovirus, adeno-associated virus (AAV), and herpes simplex virus. Of these viruses, AAV has been the virus of choice in clinical trials regarding Parkinson's. The virus is in fact active when entering and delivering the nucleic acids.

Adeno-associated virus (AAV) is one of the most actively investigated gene therapy vehicles. AAV is a protein shell surrounding and protecting a small, single-stranded DNA genome of approximately 4.8 kilobases (kb) [22].

1. Cons of Gene Therapy[23].

a. The short-lived therapeutic effect, possibly requiring several rounds of therapy
b. Immune response, potentially reducing treatment effectiveness
c. Viral vector-associated toxicity, inflammatory responses, gene control (i.e., controlled turning on and off of gene expression), and off-target effects
d. Insertional mutagenesis, resulting from misplaced DNA integration, such as within a tumor suppressor gene.

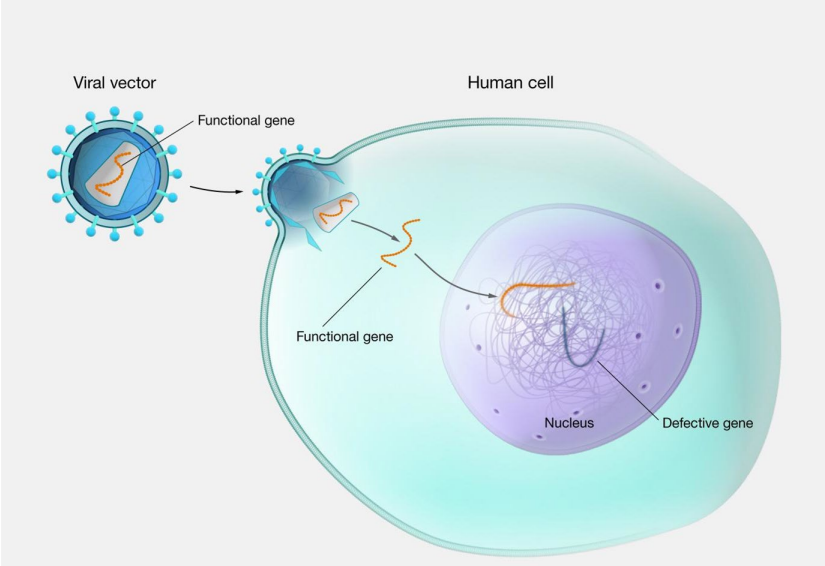

Figure 6. Gene therapy diagram depicting a viral vector being injected into a human cell [24].

Table 2. Efficacy of Certain Gene Therapy Trials [23]

Gene	Viral Vector	Study	Injection Site
Amino acid decarboxylase	rAAV	A Study of AAV-hAADC-2 In Subjects With Parkinson's Disease	Striatum
Amino acid decarboxylase; Tyrosine hydroxylase; GTP cyclohydrolase I	Lentivirus	Study of the Safety, Efficacy and Dose Evaluation of ProSavin for the Treatment of Bilateral Idiopathic Parkinson's Disease	Striatum
Glutamic Acid Decarboxylase (GAD 65/GAD 67)	rAAV	Safety Study of Subthalamic Nucleus Gene Therapy for Parkinson's Disease	Subthalamic nucleus
Glutamic Acid Decarboxylase (GAD 65/GAD 67)	rAAV	Study of AAV-GAD Gene Transfer into the Subthalamic Nucleus for Parkinson's Disease	Subthalamic nucleus
Neurturin	rAAV	Safety of CERE-120 (AAV2-NTN) in Subjects With Idiopathic Parkinson's Disease	Putamen

Neurturin	rAAV	Double-Blind, Multicenter, Sham Surgery Controlled Study of CERE-120 in Subjects With Idiopathic Parkinson's Disease	Putamen

Experimental Forms of Parkinson's Treatments

Park-in-Shape

Park-in-Shape a study and treatment used to determine the effectiveness of exercise as a therapeutic relief for PD[25]

Parkinson's Disease Vaccine

A vaccine for Parkinson's is in the process of being created. It works by targeting a protein in the brain called alpha-synuclein. Alpha-synuclein's true function remains unknown but in correlation with Parkinson's, it contributes to the death of neurons. The vaccine works as a guide for the body's defenses; it enables them to defend against molecules, like alpha-synuclein, that contribute to Parkinson's [26].

Repurposing Existing Drugs

Repurposing drugs is a process by which doctors prescribe already approved drugs by the Food and Drug Administration (FDA) for one reason, they are tested and shown to work for other purposes [27].

Table 3. Repurposing existing drugs

Drug Name:	Originally used for:
Amantadine	Prevention and treatment of influenza A
Ketamine	General anesthesia and depression
Nilotinib	Treats chronic myelogenous leukemia CML
Inosine	Multiple sclerosis, & stroke
Isradipine	To treat high blood pressure

Conclusion

The causes of PD and methods related to the prevention of PD are closely related to dietary regimes. The treatments discussed in this research are more advanced than current mainstream treatment methods; they specifically target the symptoms and areas of the brain stimulating the disease. Parkinson's is a neurodegenerative disorder that is a result of dying dopaminergic neurons that can be slowed by certain dietary regimes. The PD symptoms can be treated and symptoms can be resolved. New technologies like MRgFUS, Vivo Gene Therapy,

and a PD Vaccine are being developed to allow PD patients a better lifestyle and slow the progression of the disease and symptoms of the disease. There are genetic and environmental factors, mitochondrial dysfunctions, and drug use that result in PD.

Acknowledgments

I would like to express my very great appreciation to Dr. Rajagoppal Appavu and Jothsna Kethar for their valuable and constructive suggestions during the planning and development of the research work. Dr. Appavu's willingness to give his time so generously has been very appreciated.

References

Bethesda MD. National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 681, Dopamine. 2022 Aug. 1. pubchem.ncbi.nlm.nih.gov/compound/Dopamine. https://pubchem.ncbi.nlm.nih.gov/compound/Dopamine
Akanksha Mishra Sonu Singh and Shubha Shukla. Physiological and Functional Basis of Dopamine Receptors and Their Role in Neurogenesis: Possible Implication for Parkinson's disease. J Exp Neurosci. 2018 May 31. doi: 10.1177/1179069518779829. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5985548/

Garrett E. Alexander, MD; PhD. Biology of Parkinson's disease: pathogenesis and pathophysiology of a multisystem neurodegenerative disorder.Dialogues Clin Neurosci. 2004 Sep; 6(3): 259–280. doi: 10.31887/DCNS.2004.6.3/galexander. https://pubmed.ncbi.nlm.nih.gov/22033559/

Changliang Liu and Pascal S. Kaeser. Mechanisms and regulation of dopamine release. Curr Opin Neurobiol. 2019 Aug; 57: 46–53. Published online 2019 Feb 12. doi: 10.1016/j.conb.2019.01.001. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6629510/
Lauri Nummenmaa, Kerttu Seppälä, Putkinen Vesa. Molecular imaging of the human emotion circuit.March 2020. DOI:10.31234/osf.io/5w63q https://www.researchgate.net/publication/339755837_Molecular_imaging_of_the_human_emotion_circuit

Louise Morales-Brown, What is the connection between dopamine and Parkinson's disease?. Medical news today. 2021 June 1. https://www.medicalnewstoday.com/articles/dopamine-parkinsons#parkinsons-disease

Mark R Cookson.alpha-Synuclein and neuronal cell death.Mol Neurodegener..2009 Feb 4;4:9. doi: 10.1186/1750-1326-4-9. https://pubmed.ncbi.nlm.nih.gov/19193223/

Fabrizio Gasparini 1, Thérèse Di Paolo, Baltazar Gomez-Mancilla.Metabotropic glutamate receptors for Parkinson's disease therapy.Parkinsons Dis. 2013;2013:196028. doi: 10.1155/2013/196028. Epub 2013 Jun 19.
https://pubmed.ncbi.nlm.nih.gov/23853735/
Brian R Haas, Tessandra H Stewart, and Jing Zhang. Premotor biomarkers for Parkinson's disease - a promising direction of research.Transl Neurodegener. 2012; 1: 11. Published online 2012 May 31. doi: 10.1186/2047-9158-1-11
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3514104/

Mónica Gómez-Benito, Noelia Granado, Patricia García-Sanz, Anne Michel, Mireille Dumoulin, and Rosario Moratalla. Modeling Parkinson's Disease With the Alpha-Synuclein Protein.Front Pharmacol. 2020; 11: 356. Published online 2020 Apr 23. doi: 10.3389/fphar.2020.00356
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7191035/
Steeve H Thany, Pascal Reynier, Guy Lenaers. Neurotoxicity of pesticides: its relationship with neurodegenerative diseases.Med Sci. 2013 Mar;29(3):273-8. doi: 10.1051/medsci/2013293013. Epub 2013 Mar 27.
https://pubmed.ncbi.nlm.nih.gov/23544381/
Esther Gramage, Gonzalo Herradón. Connecting Parkinson's disease and drug addiction: common players reveal unexpected disease connections and novel therapeutic approaches.Curr Pharm Des. 2011;17(5):449-61. doi: 10.2174/138161211795164103.
https://pubmed.ncbi.nlm.nih.gov/21375485/
Haziq Kamal, Geok Chin Tan, Siti Fatimah Ibrahim,Mohd. Farooq Shaikh, Isa Naina Mohamed, Rashidi M. Pakri Mohamed, Adila A. Hamid, Azizah Ugusman and Jaya Kumar.Alcohol Use Disorder, Neurodegeneration, Alzheimer's and Parkinson's Disease: Interplay Between Oxidative Stress, Neuroimmune Response and Excitotoxicity.Front. Cell. Neurosci., 31 August 2020.Sec. Cellular Neuropathology. doi.org/10.3389/fncel.2020.00282
https://www.frontiersin.org/articles/10.3389/fncel.2020.00282/full
Klein C, Westenberger A. Genetics of Parkinson's disease. Cold Spring Harb Perspect Med. 2012 Jan 2.:a008888. doi: 10.1101/cshperspect.a008888.
https://pubi.nlm.med.ncbnih.gov/22315721/
Hyo Eun Moon and Sun Ha Paek. Mitochondrial Dysfunction in Parkinson's Disease.Exp Neurobiol. 2015 Jun; 24(2): 103–116. Published online 2015 Jun 8. doi: 10.5607/en.2015.24.2.103
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4479806/
Zahra Rabiei, Kamal Solati, and Hossein Amini-Khoei. Phytotherapy in treatment of Parkinson's disease: a review.Pharm Biol. 2019; 57(1): 355–362. Published online 2019 May 29. doi: 10.1080/13880209.2019.1618344
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6542178/

Weiyao Yin MD, PhD,Marie Löf MD, PhD,Nancy L. Pedersen PhD,Sven Sandin PhD,Fang Fang MD, PhD. Mediterranean Dietary Pattern at Middle Age and Risk of Parkinson's Disease: A Swedish Cohort Study. 20 October 2020.doi.org/10.1002/mds.28314
https://movementdisorders.onlinelibrary.wiley.com/doi/full/10.1002/mds.28314
Devin K.Binder, Binit B.Shah, W. JeffreyElias. Focused ultrasound and other lesioning in the treatment of tremor. 15 April 2022, 120193. doi.org/10.1016/j.jns.2022.120193
https://www.sciencedirect.com/science/article/pii/S0022510X22000557
Christian Pifl, Stephen J. Kish, and Oleh Hornykiewicz. Thalamic noradrenaline in Parkinson's disease: deficits suggest role in motor and non-motor symptoms.2012 Oct 4. doi: 10.1002/mds.25109

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4533102/
Agrawal M, Garg K, Samala R, Rajan R, Naik V, Singh M. Outcome and Complications of MR Guided Focused Ultrasound for Essential Tremor: A Systematic Review and Meta-Analysis. Front Neurol. 2021 May 7;12:654711. doi: 10.3389/fneur.2021.654711.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8137896/
Martin Niethammer. Chris C. Tang, An Vo, Nha, Nguyen, Phoebe Spetsieris, Vijay Dhawanz, Yilong Ma, Michael Small, Andrew Feigi, David Eidelberg. Gene therapy reduces Parkinson's disease symptoms by reorganizing functional brain connectivity.28 Nov 2018.Vol 10, Issue 469. DOI: 10.1126/scitranslmed.aau0713.
https://pubmed.ncbi.nlm.nih.gov/30487248/
Michael F. Naso, Brian Tomkowicz, William L. Perry, III, and William R. Strohl. Adeno-Associated Virus (AAV) as a Vector for Gene Therapy.BioDrugs. 2017; 31(4): 317–334. Published online 2017 Jul 1. doi: 10.1007/s40259-017-0234-5
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5548848/
Li Rebekah Feng and Kathleen A. Maguire-Zeiss. Gene Therapy in Parkinson's Disease: Rationale and Current Status.CNS Drugs. Author manuscript; available in PMC 2011 Mar 1.*Published in final edited form as:*CNS Drugs. 2010 Mar 1; 24(3): 177–192. doi: 10.2165/11533740-000000000-00000
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2886503/
Benjamin Solomon, M.D.Gene Therapy. National Human Genome Research Institute. 2022 July 29. genome.gov/genetics-glossary/Gene-Therapy
https://www.genome.gov/genetics-glossary/Gene-Therapy
Nicolien M van der Kolk, Sebastiaan Overeem,, Nienke M de Vries, Roy P C Kessels, Rogier Donders, Marc Brouwer, Daniela Berg, Bart Post, Bas R Bloem. Design of the Park-in-Shape study: a phase II double blind randomized controlled trial evaluating the effects of exercise on motor and non-motor symptoms in Parkinson's disease.BMC Neurol. 2015 Apr 16;15:56. doi: 10.1186/s12883-015-0312-6.
https://pubmed.ncbi.nlm.nih.gov/25880966/
Kiran Yanamandra,Marina A. Gruden, Vida Casaite,Rolandas Meskys,Lars Forsgren, Ludmilla A. Morozova-Roche.α-Synuclein Reactive Antibodies as Diagnostic Biomarkers in Blood Sera of Parkinson's Disease Patients. April 25, 2011. doi.org/10.1371/journal.pone.0018513.
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0018513

Sophie Holmes, PhD, Gerard Sanacora, MD, PhD. Using Ketamine to Treat Depression in Parkinson's Disease. The Michael J.Fox foundation for Parkinson's Research. 2021.
https://www.michaeljfox.org/grant/using-ketamine-treat-depression-parkinsons-disease