THE EVOLUTIONARY ANALYSIS OF PARKINSON'S DISEASE (PD) FROM SOURCES OLD AND NEW [NATURAL HISTORY OF PD REVISITED]

By

Kishore Athreya

A capstone project submitted for
Graduation with University Honors

March 17, 2018

University Honors
University of California, Riverside

APPROVED

_____
Dr. Richard Rodriguez
Department of English, Media and Cultural Studies

_____
Dr. David Song
Department of Health Sciences

_____
Dr. Richard Cardullo, Howard H Hays Jr. Chair and Faculty Director, University Honors
Interim Vice Provost, Undergraduate Education

Abstract

Ancient Indian scriptures are rooted in the sciences, philosophy, and religion. They often pre-date many of the contemporary sources of scientific and medical discoveries. The Ayurveda is a particular scripture and literary chronicle that covers numerous ailments of the human body and various types of neurological diseases (Vata Rogas in Sanskrit). Ayurveda, which is a subsection of the Vedas, is arguably one of the oldest forms of scriptures dating back 5000 to 3000 BC (the exact date is not known). This particular exploration will focus on the specific evolution of Parkinson's Disease (Kampavata in Sanskrit) through the lenses of the Hindu scriptures (homeopathic) and modern-day medicine/research (allopathic). Parkinson's Disease or PD is most common type of Parkinsonism, is an umbrella term for the many manifestations of the disease. The hallmark cardinal clinical features of PD are: 1) slowness of movement (bradykinesia); 2) stiffness or increased muscle tone (rigidity); 3) tremor that occurs at rest (resting tremors). The most common form is called idiopathic Parkinson's Disease or PD which is addressed in Vedic scriptures along with the various symptoms of this disease. To capture the pathogenesis of this disorder, it is vital to look at the imbalances that occur naturally at the time of Parkinsonism. The rapid degeneration of dopamine neurons (In Ayurveda; imbalance of the bio-entity/brain) and its treatment can clearly be seen in the homeopathic approach taken by Ayurveda. Unlike the homeopathic medicine, modern research is currently focusing on classifying the various stages of Parkinsonism and non-motor symptoms for early diagnostic and treatment plans. There is clear evidence to suggest that homeopathic medicine from ancient Hindu scriptures, studies by Galen and James Parkinson, plus modern research can provide a more holistic approach to the evolution of the neurological movement disorder of Parkinson's Disease.

Acknowledgments

Parkinson's Diseases, till this day remains an area shrouded by unanswered question of the pathogenesis of this neurological disease. Questions of what the earliest identifiable motor and non-motor symptoms are questions that are still being tackled today by clinicians and researchers till this day. The task of this critical analysis is shed more insight into this neurological complex disease. This stems from my passion for both ancient literature and modern-day research being made on this relatively unknown disease to many. Much of the inspiration for this criterial review comes from my research mentors; Dr. Michele Tagliati (Cedars Sinai Prof. of Neurology and Movement Disorders), UCR School of Medicine Faculty advisor Dr. David Song, and Prof. Richard Rodriquez from the English/Media and Cultural Studies Department. Furthermore, I would like to thank all the University Honor's Counselors and chair of this incredible program, Dr. Richard Cardullo. Their continued efforts in empowering students and learners from all walks of life continues to inspire me on my academic endeavors.

Table of Contents

List of Tables

List of Figures

Pathophysiology of the Parkinson's Disease

Pathophysiology of the Parkinson's Disease most obviously involves the degeneration of specific neurons in the substantia nigra called dopaminergic neurons[1]. The pathogenesis of this degeneration is unknown or also known as idiopathic[2] which is the most obvious and well known manifestation of this neurodegenerative disease. Dopamine[3] production and regulation is one of the most vital tasks carried out by the brain for normal behavior. It has a multifaceted function in the human brain such as movement, memory, cognition, sleep, mood and other physiology of the body. Movement is a critical area affected by the loss of dopamine production. The basal ganglia[4] which is linked to the Thalamus regulates coordinated movement and requires certain amount of dopamine to function efficiently. The action of dopamine occurs through the dopamine receptors[5] D1-5 (D1-5 are a family of receptors that control overall movement) and nigrostriatal pathway which creates a junction between substantia nigra and striatum. The nigrostriatal pathway[6] is the direct and indirect control factor of the thalamus. Dopamine reduces the influence of the indirect pathway and increases the functions of the direct pathway within the basal ganglia. The thalamus has an excitatory response signal for the motor cortex (allowing for movement) when unregulated results in the most common symptom; slowness of movement (bradykinesia). Motor symptoms occurs at approximately at the 80% loss of the dopamine neuron [See Figure 1]. Other common symptoms/issues associated with Parkinson's Disease such as sleepiness, fatigue, cognitive decline, impaired speech, anosmia, and altered mood levels.

[1] **Dopaminergic neurons**: releasing or involving dopamine as a neurotransmitter. Drugs with this effect are used in the treatment of Parkinson's disease and some psychiatric disorders; some are subject to abuse.
[2] **Idiopathic**: relating to or denoting any disease or condition that arises spontaneously or for which the cause is unknown.
[3] **Dopamine**: a compound present in the body as a neurotransmitter and a precursor of other substances including epinephrine.
[4] **Basal ganglia**: a group of structures linked to the thalamus in the base of the brain and involved in coordination of movement. [Figure 1]
[5] **D1-5**: are a family of receptors that control overall movement.
[6] **nigrostriatal pathway**: a biochemical and anatomy junction between substantia nigra and striatum. [Figure 1]

An Insight into Ayurvedic Medicine and Timeline

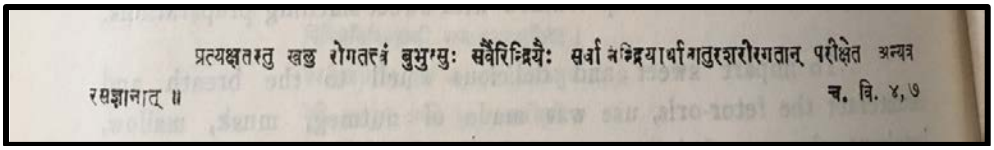
The earliest reference to "shaking palsy" in western medical literature comes from Galen[7] during 138-201 AD era and a complete picture was provided by James Parkinson[8] in 1817 regarding the symptoms to what became Parkinson's Disease (PD). These explorers of the human state definitely look to a more ancient form of medicine known as Ayurveda. Arguably one of the most comprehensive ancient literature, the Ayurveda sought to compile the knowledge of human imbalances and the counteractive treatment for it. This ancient system of health care is estimated to be originated and practiced in India between 5000 to 3000 BC. [Figure 2] The word *Ayurveda*[9] comes from the Sanskrit root of 'āyur' meaning 'life' and 'veda' meaning 'knowledge or science.' Quintessentially, Ayurveda stems from observations of systematic imbalances and seeks to counter act it with alternative and herbal-based treatment. Furthermore, it holds a historic precedence of being an alternative method to typical allopathic medicine in several countries such as Nepal, Tibet, Sri Lanka, Burma, Malaysia and Indonesia[iii]. These countries present a fertile ground for further research on the effective usage of non-allopathic medicine in parallel with allopathy practices. The Ayurvedic approach can be typically divided into three theoretical called Tridosha approach which are 'vata' (physical), 'pitta' (physiological), and 'kapha' (psychological)[iv]. This is treatment approach is similar to prevailing allopathic medicine as a way for patients to better manage their malfunctions or problem. But mostly allopathy focuses on mostly the 'vata,'which is considered the imbalance on the physical level[iv]. '*Shaky palsy*,' as a specific disorder[i], is described as '*kampavata'* which is derived from the sankrit root of '*kampa'* meaning *tremors* and '*vata'* being

[7] **Galen**: (129–199) Greek physician; full name Claudios Galenos; Latin name Claudius Galenus. While attempting to systematize medicine, he made important discoveries in anatomy and physiology.
[8] **Parkinson's Disease**: late 19th century: named after James Parkinson (1755–1824), English surgeon.
[9] **Ayurveda**: (medical literature/text) from the Sanskrit root of 'āyur' meaning 'life' and 'veda' meaning 'knowledge or science.' Ancient system of health care is estimated to be originated and practiced in India between 5000 to 3000 BC

a *physical* manifestation. Furthermore, the Ayurvedic literature uses various terminologies to tackle the diverse range of symptomatic severity such as 'kampana,' 'vepana,' 'vepathu,' and 'spandana'[iv]. The Ayurveda describes the typical motor and non-motor symptoms of PD as tremors (kampa), stiffness (stambha), and depression (vishada)[iii]. These predominant and identifiable symptoms are still used in modern-day prognosis made by medical doctors and specialists in the movement disorder field. This evidence suggests that the clinical symptoms of parkinsonism were identified much earlier than the time of Galen and James Parkinson[ii]. Furthermore, a precise therapy plan involved a combination of edible medications, enemas, massages, and nasal instillations of fixed solutions. The essential plant based drugs are derived from Aswagandha (*Withania somnifera*), Bala (*Sida cordifolia*) and Paraseekayavanee (*Hycocyamus reticulatus*) and the most critical plant being Atmagupta (*Mucuna prureins*)[ix].

Analysis of Ancient and Modern Literature

This primary section serves a purpose of comparing the diagnostic tools and identifying non-motor symptoms that were used by ancient physicians and modern-day clinicians. The physical examination according to contemporary medical sciences is consist of four methods – inspection, palpation, percussion, and auscultation. This same methodology is taught in Caraka which can be seen from the image below:


प्रत्यक्षतस्तु खलु रोगतत्त्वं बुभुत्सुः सर्वैरिन्द्रियैः सर्वा नेन्द्रियार्थानातुरशरीरगतान् परीक्षेत अन्यत्र
रसज्ञानात् ॥ च. वि. ४,७

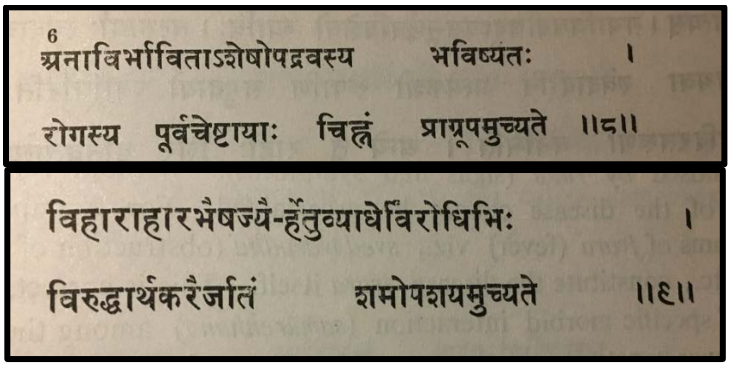
[Sample #1]

The rough translation of this is, "Seeking to know the nature of a disease by direct observation, the physician should explore by means of all his sense-organs except the tongue, the entire field of sensible data presented by the patient's body" (Caraka, Nidana Sthana). This methodology is

what is being used to the present day by the use of sensory inputs, within reasonable manner, as a prognostic tool. This is most pertinent to the Pitta's (physiology) of the Parkinsonism and Parkinson's Disease since it is almost inarguable that this neurological disorder is a systemic disorder of the body as well. This same aspect was discussed by Galen in *De tremore*[10], and Book II of *De Causis Morborum*[11], the deriving factors of a disease to a physician is through the four-fold system – vision, smell, taste, and to the touch. The similarities between both are clearly visible especially in the way diagnosis is made in the present day often involve these sensory systems. Furthermore, the specific diagnosis of Parkinson's disease and pre-motor symptoms are identified in the *Caraka* and *Sushruta* Samhita of the Ayurveda.

- [Sample #1] One particular part of Parkinson's Disease (PD) that needs to be focused on is pre-motor symptoms such as hyposmia. Modern science knows this as the potential dysregulation of the olfactory bulbs[12] situated below the frontal cortex of the brain results in the loss of smell. A popular hypothesis indicates that alpha-synuclein[13] begins to clump in these parts of the body before affecting the brain. This is a common pre-condition of PD is the pathological hallmark and Ayurvedic medicine addresses the potential causes of it along with many other non-motor symptoms.

[10] ***De Tremore, palpitatione, convulsion et. Rigore***: Περὶ τρόμου καὶ παλμοῦ καὶ ῥίγους καὶ σπασμοῦ by Galen
[11] ***De Causis Morborum****:* The cause of diseases by Galen
[12] **Olfactory bulb**: is a structure that is located beneath the forebrain is a sensory input receiver from the cells in the nasal cavity.
[13] **Alpha-synuclein** or ***α-synuclein****:* is a protein whose functionality in the brain is not fully known but is very important because it makes up the majority of Lewy bodies in the brain cells of PD patients.


6
अनाविर्भाविताऽशेषोपद्रवस्य भविष्यतः ।
रोगस्य पूर्वचेष्टायाः चिह्नं प्राग्रूपमुच्यते ॥८॥

विहाराहारभैषज्यै-र्हेतुव्याधेर्विरोधिभिः ।
विरुद्धार्थकरैर्जातं शमोपशयमुच्यते ॥९॥

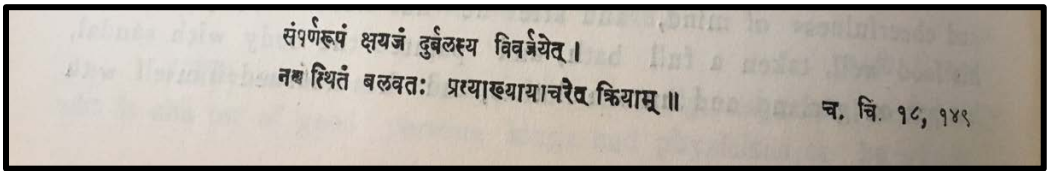
[Sample #2]

- [Sample #2] Building on the process of a diagnosis, the way diseases manifest themselves and their previous forms are also instilled in the Ayurvedic principles. These previous forms are called "pūrva rūpa" and play a significant role in building a comprehensive review of ailments and patient history (Caraka Samhita). Thus, a trained or even a trainee can follow a systematic approach to the treatment of a diagnosis especially major conditions such as PD. The prescribed tools in the treating physician's arsenal involve "vihara,[14]" "āhāra,[15]" and "bhesaja[16]." This systematic approach is driven three principles of treatment; "hetu" (causal agent), "vyādhi" (primary disease) and when combined become "hetu vyādhi" (cause and disease). Although many would argue that these methodologies are rooted in medieval notions of anatomy and physiology as seen with the middle English traditions of the humoral bodies[17]. In contrary, the resemblances of Ayurvedic is much more in line with contemporary parallels to Osteopathic/Medical philosophy and while supplementing it with a holistic medical approach. The shift towards holistic medicine begins with the fundamental change in the way modern-day physicians treat patients. This approach

[14] **Vihara:** regimens (modern translation of medical treatment plans)
[15] **Āhāra:** dietary treatment plan
[16] **Bhesaja: (Drugs)** Concocted combination of plants, minerals/vitamins, and other bioactive agents in forming drugs.
[17] **Humoral Bodies**: the medieval notion of anatomy and physiology being tied in with seasons and dispositions.

focuses not only on allopathic issues but also incorporating lifestyle factors and public health/policy.

- [Sample #3] This is developed further with the medical responsibilities, the nature of caregiving, and moral duties which have many similarities both in Ayurvedic times and the writing of even Hippocrates. Take for the line mentioned below from Caraka Samhita and a case study by the ancient physician Vaidya:


संपूर्णरूपं क्षयजं दुर्बलस्य विवर्जयेत् ।
नवं स्थितं बलवतः प्रत्याख्यायाचरेत् क्रियाम् ॥ च. चि. १८, १४९

[Sample #3]

Vaidya declares the patient incurable but adheres to regulations of society and medicine by saying, “The patient suffering from cough born of consumption with all the symptoms of consumption fully developed, who is debilitated should be considered incurable but if the cough is of recent origin and the patient is strong, the treatment should be undertaken despite declaring it to be of the incurable type” (Caraka Samhita).

- The Potential Early Diagnosis: Diabetes was treated by ancient Ayurvedic physicians through a series of medical drugs and lifestyle changes. This has great significance to PD due to the prevalence of Insulin resistance[vi] and Metabolic Syndrome playing a key factor in future dopamine receptors malfunction. This characteristic of PD plays a vital role in the cognitive and physiological deterioration of the day-to-day patient’s quality of life. It is a known fact in the contemporary clinical setting but in ancient time, it was a missed opportunity for an early diagnosis of PD. Although in ancient times there were up to 45 plants and their bioactive products which have shown to have a spectrum of hypoglycemic and anti-hyperglycemic properties[v]. These plants included widely accessible and

household essentials such as *allium cepa*[18], *allium sativum*[19], and *aloe vera* to more exotic plants such as *cajanus cajan,*[20] *capparis decidua,*[21] and several others. These plants were tested in a 2002 study by J.K Grover in rat models to see the direct potential antidiabetic properties, the results were truly astounding due to the active combating of IR through household ethnomedical approach[v].

Target Study: Mucuna Pruriens (Levodopa)

Isolation of levodopa from the seeds of Mucuna pruriens serves an important role in addressing the vital question on how the metabolic breaking down of levodopa in the human body. The earliest evidence of the isolated form of L-DOPA from M. pruriens in 1937. There is a clear line of symptomatic support and neuroprotective properties associated with L-DOPA content from M. pruriens. Artificial synthesis of L-DOPA in a laboratory setting have shown to be fantastic in the therapeutic usage because it is pure and relatively controllable in dosage regulation with patients. The important aspect that is often forgotten is that with M. pruriens has shown to have a significantly higher anti-Parkinson's capacity. There is an increased mitochondrial complex-I activity and the production of endogenous[22] amount of L-DOPA, dopamine, norepinephrine, and serotonin level associated with catecholamine pathway[23]. The two specific molecules that are

[18] **Allium cepa**: also known as onion
[19] **Allium sativum**: also known as garlic
[20] **Cajanus cajan**: also known as Pigeon pea
[21] **Capparis decidua**: also known as Caper plant
[22] **Endogenous:** having internal causes or origin which is typical within the organism.
[23] **Catecholamine pathway**: The process by which a series of precursors are broken down into their functional parts. (i.e. Levodopa » Dopamine)

formulated from the mitochondrial Complex-I[24] are NADH[25] and the Co-Enzyme Q10[26], which both have anti-oxidant properties[27] and thus decreasing the chances of free radicals[28] in the organic synthesis chains. Further evidence suggests that there are other bioactive properties such as n-propanol which has proven to be neuroprotective. Clinicians and medical researchers are aware of the complex nature of the delivery system of L-DOPA and the problems that arise from the intake of dopamine precursor. It is suggested by Hinz, M in a 2014 study that the natural inhibitor of dopa decarboxylase due to carbidopa is also a secondary cause of nausea and reversible dyskinesia. But subsequent usage of the lab synthesized version of carbidopa or benserazide has shown to have irreversible dyskinesia. The cause of this was the binding and deactivation of vitamin B_6 this resulting in a serious compromising of enzymatic action and protein synthesis. The method used by the ancient clinicians circumvented this but purely applying M. Prureins through enemas and oral intake which allowed for the previously discussed neuroprotective properties to be present along with targeted levodopa crossing into to the hematoencephalic barrier[29] (BBB). The pharmacological breakdown of M. prureins shows that there is a high content of the nicotinic acid which has counter effects to the laboratory synthesized L-DOPA. This will be further explored in the next passage which will focus on the mechanism by which Ayurvedic medicine addressed Parkinson's Disease.

[24] **Mitochondrial Complex-I**: is a primary mechanism for creating energy within an organism by producing several chemical compounds such as NADH and Co-Enzyme Q10.

[25] **NADH: (nicotinamide adenine dinucleotide) ($C_{21}H_{27}N_7O_{14}P_2$)** plays a vital role in energy production in the mitochondrial complex.

[26] **Co-Enzyme Q10:** ($C_{89}H_{90}O_4$) also known as ubiquinone and serves a role of being an antioxidant and free radical

[27] **Antioxidant**: serve a vital role of removing free radicals in the system which disrupt cell functions through degrading chain reaction.

[28] **Free radicals:** is a chemical structure that has an unpaired valence electron which makes it highly reactive in the cellular functions of organisms.

[29] **Blood Brain Barrier**: The semipermeable membrane barrier that separates the circulatory system and cerebral fluid which is tightly protected by endothelial cells which form tight junctions.

Allopathic Medicine and Ayurvedic Approach

To appreciative true ingenuity of both contemporary and homeopathic medicine, there need to be some understanding of pharmacology and physiology of the human body. The primary medication in Ayurveda for 'Kampavata' is *Mucuna prureins*[30] which contains 4%-6% of levodopa[31] which is a primary precursor[32] to neurotransmitters like dopamine, norepinephrine, and epinephrine which are all structural catecholamine[33] (one benzene ring and two hydroxyl tails). [See Figure 3] As previously noted, dopamine in the substantia nigra controls the thalamus and motor complex indirectly. Patients with PD have degenerative dopaminergic neurons which are unable to produce dopamine necessary to counteract many of the symptoms. Furthermore, treatment of PD would involve direct injection of dopamine into the brain since dopamine is a charged which is not permeable through the blood-brain barrier. So, the natural choice for physicians would be to work with the precursor levodopa or commonly known as L-Dopa which can pass through the BBB[34] and CNS[35]. Although in the peripheral blood system, levodopa, when administrated to the body, can be broken down in the blood before reaching the brain. The two specific enzymes that break down L-Dopa are dopamine decarboxylase (DDC[36]) and Catechol-O-methyl transferase (COMT[37]) which results in an ineffectiveness of the medication. Furthermore, the side of effects of consuming a large amount of L-dopa results in nausea and severe vomiting which can result in patient eventually developing anorexia. The two reducing agents for these

[30] **Mucuna prureins**: also known as 'kampavata' or velvet beans which are itchy to touch due to the serotonin in the surface but are good source of L-dopa.
[31] **L-dopa**: the levorotatory form of dopa, used to treat Parkinson's disease. Also, called levodopa.
[32] **Precursors**: a substance from which another is formed, especially by metabolic reaction.
[33] **Catecholamine**: any of a class of aromatic amines that includes a number of neurotransmitters such as epinephrine and dopamine.
[34] **Blood Brain Barrier**: The semipermeable membrane barrier that separates the circulatory system and cerebral fluid which is tightly protected by endothelial cells which form tight junctions.
[35] **CNS**: Central Nervous System
[36] **Dopamine decarboxylase (DDC):** catalyzes the conversion of amino acids into corresponding amines such the synthesis of dopamine and serotonin from L-DOPA and L-5-hydropxytrypotophan respectively.
[37] **Catechol-O-methyltransferase (COMT):** part of couple of enzymes that degrade catecholamines (dopamine, epinephrine, etc.)

enzymes are Carbidopa (Benserazide in Europe) and COMT-inhibitor which allow for more L-dopa to pass through the blood brain barrier. Usually, COMT inhibitors are not given due to carbidopa infused levodopa (Sinemat) taking care of dopamine decarboxylase. [Figure 4] This is not a flawless system since the operational time between each dosage slowly decreases as time progresses. This is called the wearing off phenomena, this usually common manifestation with most neurological related treatment since inhibitors become insufficient and dosage amounts have to be increased to compensate. [Figure 5] The Ayurvedic approach to the same diagnosis involves making a powdered Mucuna pruriens or atmagupta that contains a combination of natural seed extracts and the L-dopa. This naturally has same side effects as taking pure levodopa except with a muted side effects of nausea. Furthermore, atmagupta does not contain any traceable element of carbidopa which shows that small amount of L-dopa is handled well in patients in ancient practices. This has a domino effect on the wearing off symptoms being deterred for a longer stretch of time as compared to allopathic approach, which deals with 100-250 mg per capsule with a combination 10-25 mg of carbidopa. Wearing off from this allopathic approach results in motor fluctuations as the levodopa breaks down in the system. A typical medical diagnosis for wearing off would result in the medical professional to change dosage and schedule cycles of administration. This is further supplemented inhibitors like MAO-I[38] could prove quite effective when it comes dosage alteration between Carbidopa-Levodopa and Mucuna pruriens [Figure 6]. Although it is important to address that measurement of Mucuna pruriens is not easy unlike the exact quantity of Sinemet (Carbidopa and Levodopa) medication due to the content of levodopa varying from 4%-6%. But it would be a study of interest to pursue in the future to see the application of an Ayurvedic to an allopathic could lead to a new breakthrough for treating wearing off phenomena. A more palatable approach

[38] **Monoamine Oxidase B**: breaks down dopamine which inhibits the prolonged action of dopamine in the neuronal level.

is using Mucuna pruriens as an early treatment option when a patient is diagnosed with parkinsonism or PD. MAO-Inhibitors and COMT-Inhibitors can improve scores the Unified Parkinson Disease Rating Scale (UPDRS[39]) and in Motor Cognitive Assessment (MoCA[40]). These baseline scores improved with early therapeutic usage but as the 5-6 year range is met by longtime patients with Parkinson's Disease, there is a sharp drop in both scores of UPDRS III (Motor Examinations) and MoCA (cognitive and perception).

A Historical Review of Parkinson's Disease

The first identifiable version of Parkinsonism or PD emerges in 600 BC with the official written form of the Charaka Samhita. Although according to oral traditions, there is evidence of diagnosis and treatment as early as 5000-1000 BCE. [Figure 2] Much of the credit goes to the Rishi[41] known as Atreya Punarvasu who converted the oral tradition of medicine to a written and systematic form. This opened up access to the world in terms of medical practices where traces of it can be found in middle eastern and European philosophies of medicine. Although much of the hard copies of Atreya's medical literature is lost due to degradation of manuscripts, conquest, and translational efforts. Though the primary "Samhitā" remains understood due to the translational effort by the Indian government and private/public sponsorship. Rishi Atreya is credited also for establishing the original medical college in Indus Valley, about 1000 BCE, which rivals some of the medical schools and hospitals of modern day. This ancient medical institution is in many ways a body of work itself where the manuscripts, ancient physicians, and emerges of new diagnosis

[39] **UPDRS**: Specific rating system used to track the progression in longitudinal manner for both clinical and research settings.
[40] **MoCA**: A supplemental rating system used for variety of diagnosis including PD, relating to cognitive and mental capability of patients.
[41] **Rishi or Guru**: is a modern word which is synonymous teacher of a certain knowledge or academic level, in vedic terms, an inspired poet of hymns.

occurred. Inarguably, this institution would have been the birthplace of the first diagnosis of PD. This can be compared to the first Western identification of Parkinson's which began with Claudius Galen. Galen was able to isolate the primary symptoms of resting tremors, gait changes, which followed paralysis but was unsure as to the aetiology of this condition.

These observations on the emergence of PD were noted in the 2nd century CE. But the true lasting definition emerged on the "An Essay on Shaking Palsy" by Dr. James Parkinson in 1817. The essay and observation of Dr. Parkinson that took a structural natural history of the coined term "Shaking Palsy" which would eventually become known as Parkinson's Disease. Several other researchers gave a better spectrum of this debilitating condition with works by Charcot and Gower in terms of physiological issues as well as deformities. Building on Charcot and Gower, the official metrics of PD occurred with the famous study of *Hoehn and Yahr*[42] who gave the condition its various stages which appeared in 1967 publication. This scale is so universal and well adopted that it is used to this day by most physicians for quantifying the progression of PD.

The first synthesis of dopamine began by G. Barger and J. Holtz which occurred in 1910. While first administration of levodopa began in 1961, but the medicine for treating PD was only starting to be refined due to several issues. As previously mentioned, the effectiveness of lab synthesized or S-Levodopa and some acute side-effects made it difficult to adopt widely for patients. Furthermore, bioactive components could not effectively reach the targeted part of the brain which resulted in higher dosages being administered. This feasible option only became available after the early 1970s when inhibitors of DOPA decarboxylase allowed for the treatment of levodopa.

[42] **Hoehn and Yah Scale**: provided a universal metric for analyzing the stages of PD and its progress. (Stages 1-5)

The clinical availability occurred shortly after with the commercial production of carbidopa/levodopa combination. Neuronal agonists found a trademark location in modern-day physician practices due effectiveness, sustained usage, and the wearing off effect. [Figure 4] All of the scientific advances now focus on several frontiers; Deep Brain Stimulation[43] (DBS), Stem cells, and identifying earlier markers of this neurodegenerative condition. Current studies now focus on several early detection symptoms such anosmia, insulin resistance (IR), and cognitive decline. Several studies now focus on the Metabolic Syndrome[44] (M-Syn) and Insulin Resistance[45] (IR) in nondiabetic patients. The M-Syn plays a crucial role in the functionality of mitochondrial activity and the chronic inflammation response patients might feel. This coupled with a biochemical decrease in insulin functionality as shown to be significant in potentially diagnosing PD in advance.

The evolution of PD according to most allopathic medical literature originates with Galen and Parkinson's discoveries but the practices of Ayurvedic Medicine contradicts these notions. During the course of time, PD has been noted and treated with various manifesting forms in the Indus Valley civilization. Although the knowledge of these practices has been long since eroded by time, conquest, and lack of translational capabilities. The evidence of these works has been noted in European centric medical work due to the pass off the knowledge and craft during the establishment of the Asia-Euro trade systems. This can be seen by the Rishi Atreya who was able to establish a medical school in the early ages of civilization. The knowledge from this school

[43] **DBS**: Typically, a permanent implanting of electrodes into the brain, targeting the Substantia Nigra, to alleviate the hallmark movement related issues in PD.

[44] **Metabolic Syndrome**: grouped risk factors marked by high blood pressure, high blood glucose levels, high triglycerides, low HDL cholesterol, and high waist line. These factors play a role of many cardiovascular disease as well as neurological.

[45] **IR**: deals with a physiological or biochemical inability to process glucose due to denature or the loss of insulin functionality

encompassed a dynamic and systematic approach that rivals most contemporary hospital and teaching centers.

The history of PD is rich with not only the advances in medicine but has key figures who have shaped global and historical foundations of medical humanities. Several historical figures had or are diagnosed with PD including Mohammed Ali, Billy Graham, Janet Reno, Charles M. Schulz and many others. One key figure, Michael J. Fox (actor) established an entire foundation in 2000 for research and clinical initiatives to help speed along the cure for PD. These figures have used PD as a platform for global advocacy and scientific initiatives. Thus, the significance of PD has been established and its effect on modern day culture and history is firmly integrated.

Discussion

Ayurvedic medicine defined by principles from both allopathic and homeopathic medicine due to its approach in treating patients holistically. This form of medical practice is rooted deeply in a multidisciplinary and strategic approach to patient care and treatment. Key examples of this form of care are seen with the diverse arsenal by which ancient and modern-day physicians treat PD. The forefronts of PD research involve the address of three vital points; preventative care, early diagnosis/management, and potential solutions/cure. Ayurvedic Medicine address these points through the treatment of presymptomatic conditions and management of PD through the usage of herbology. This can be seen by which ancient physicians crafted a treatment plan that involved "vihāra,[46]" "āhāra,[47]" and "bhesaja.[48]" These plans involved the building of lifestyle plan, dietary support in order to maximize bioactive entities and the prescription of drugs by a practicing

[46] **Vihara:** regimens (modern translation of medical treatment plans)
[47] **Āhāra:** dietary treatment plan
[48] **Bhesaja: (Drugs)** Concocted combination of plants, minerals/vitamins, and other bioactive agents in forming drugs

physician. This is similar to contemporary physicians treating PD by address lifestyle struggles, implementation drugs, and dietary restrictions or supplements. Thus, the management and treatment of PD has been historically present for countless of years starting from 1000 BCE. This shifts the narratives by which philosophical the viewpoint of Hippocrates, Galen, and even Parkinson become less revolutionary but rather evolutionary. The description of the anosmia as a diagnostic tool and the previous treatment of patients with IR suggests that map of PD was being cleared up far before the modern era. These factors suggest that the road to an official diagnosis of PD begins with several influences deal with issues that deal with poor health outcomes and chronic ailments.

Focusing on the treatment plan involving levodopa (LD), the use of *mucuna prurines*[iii] was widely adopted as the baseline for treating kampavata or PD in ancient times[i]. Certain enzymatic factors such need to boost mitochondrial function such as NADH and Coenzyme Q10 have helped facilitate the uptake of LD across the BBB. Although the running hypothesis in this paper suggests certain other factors are co-promoting the natural uptake of LD. Especially in terms of effectivity Natural LD has better uptake and sustained release time as compared to a clinical synthesized version or S-LD. According to previous studies, the effectivity of N-LD lasts up to 30 mins longer at equivalent dosages[ix]. This is suggestive of potential bioactive and chemical properties that allow a greater receptivity in LAT receptors[49]. Furthermore, the lack of commonly used carbidopa, MAOB-I, and agonists suggests that ancient practitioners had figured out how to facilitate effective administering of dopamine into the brain.

This evident usage produces a questionable line of regarding what the potentiality of mucuna prurines and what biochemically rich properties it holds. Further studies definitely need

[49] **LAT Receptors**: (L-Amino Acid Transport) serves as the pathway for the administered levodopa to cross the BBB in order support neuronal functionality.

to be conducted to isolate organic compound or compounds that play a significant role in the treatment of Parkinson Disease. A potential line of inquiry must look at the retrospective usage of these mucuna legumes which were used with several ingredients for ancient clinical regiments. Potential factors include plants and legumes such as Aswagandha (*Withania somnifera*), Bala (*Sida cordifolia*) and Paraseekayavanee (*Hycocyamus reticulatus*). Furthermore, a comprehensive literature and translational efforts must be undertaken in order to restore much of the vernacular herbology and treatment plans to current clinical knowledge and research inquiries. From this analysis, the hallmark of medical knowledge and humanities can be updated to reflect the historical significance of Ayurvedic medicine and many other diverse forms of holistic sciences.

Conclusion

The use of ethnomedical approaches is a growing health trend in the modern era since holistic medicine address several areas with a combined effort in lifestyle management, treatment, and potential cure. Especially in terms of this paper, it is easy to see how PD has typically been marked with an arduous battle with a rapid on setting neurodegenerative condition. Thus, Ayurvedic medicine serves a role in not only retrospectively reviewing ancient practices but also potential areas of exploration and research. This paper expands the medical timeline or natural history of this condition in hopes of encouraging future research into the bioactive factors in levodopa treatment plan and potential cures for PD. This paper is a living testament to combining a scientific and humanities-based approach to medicine and clinical research. The significance of Ayurvedic medicine and other holistic forms serve in pushing the boundaries of an interdisciplinary field of medical humanities.

It serves a role of combining the fields of history, medicine, biochemistry, herbology, public health, and neuroscience in an effort of to show how Ayurvedic medicine can be much more than an ancient medical knowledge. The suggested approach of combining Ayurvedic medicine and contemporary allopathic approach would be to the combined effort. An early diagnosis of PD would follow an initial treatment with an Ayurvedic regiment, in order to explore more invasive options in the later stages of PD with allopathic treatment. This ideal scenario would lower the immune response due to more natural remedies as compared to initial high dosages of medication. I want to conclude by stating that the information present in this paper serves as a point of knowledge rather than a prescribed method since approached must be safely regulated by a specialist. The manifesting forms of PD are very much varied from patient to patient thus an approach must be tailored to each individual. Thus, this work is reflective of a scholarly review rather than a prescribed methodology for treatment of PD.

References

i. Dev, S. (1999). Ancient-Modern Concordance, *107*(10), 783–789. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1566595/pdf/envhper00515-0049.pdf

ii. Donaldson, I. M. L. (2015). James Parkinson's Essay on the Shaking Palsy. *Journal of the Royal College of Physicians of Edinburgh*. https://doi.org/10.4997/JRCPE.2015.118

iii. Dr. Marc Halpern. (2015). Parkinson' s Disease (Kampavata): Understanding the Ayurvedic Approach. Retrieved from http://www.ayurvedacollege.com/book/export/html/53

iv. Galib, Mashru, M., Patgiri, B., Barve, M., Jagtap, C., & Prajapati, P. (2011). Therapeutic potentials of metals in ancient India: A review through Charaka Samhita. *Journal of Ayurveda and Integrative Medicine*, *2*(2), 55. https://doi.org/10.4103/0975-9476.82523

v. Grover, J. K., Yadav, S., & Vats, V. (2002). Medicinal plants of India with anti-diabetic potential. *Journal of Ethnopharmacology*, *81*(1), 81–100. https://doi.org/10.1016/S0378-8741(02)00059-4

vi. Hogg, E., Athreya, K., Basile, C., Tan, E. E., Kaminski, J., & Tagliati, M. (2019). High Prevalence of Undiagnosed Insulin Resistance in Non-Diabetic Subjects with PArkinson's Disease. *Journal of Parkinson's Disease*, *Preprint*(Preprint), 1–7.

vii. Jansen, R. L. M., Brogan, B., Whitworth, A. J., & Okello, E. J. (2014). Effects of five ayurvedic herbs on locomotor behaviour in a Drosophila melanogaster Parkinson's disease model. *Phytotherapy Research*, *28*(12), 1789–1795. https://doi.org/10.1002/ptr.5199

viii. Jouanna, J. (2012). Greek Medicine from Hippocrates to Galen. *Studies in Ancient Medicine*, 403. https://doi.org/10.1017/CBO9781107415324.004

ix. Katzenschlager, R., Evans, A., Manson, A., Patsalos, P. N., Ratnaraj, N., Watt, H., … Lees, A. J. (2004). Mucuna pruriens in Parkinson's disease: a double blind clinical and pharmacological study, 1672–1678. https://doi.org/10.1136/jnnp.2003.028761

x. Katzenschlager, R., Evans, A., Manson, A., Patsalos, P. N., Ratnaraj, N., Watt, H., … Lees, A. J. (2004). Mucuna pruriens in Parkinson's disease: a double blind clinical and pharmacological study. *Journal of Neurology, Neurosurgery, and Psychiatry*, *75*(12), 1672–1677. https://doi.org/10.1136/jnnp.2003.028761

xi. Kühn, A. A., & Volkmann, J. (2017). Innovations in deep brain stimulation methodology. *Movement Disorders*. https://doi.org/10.1002/mds.26703

xii. Lanska, D. J. (2009). Chapter 33 The history of movement disorders. *Handbook of Clinical Neurology*. https://doi.org/10.1016/S0072-9752(08)02133-7

xiii. Leehey, M., Luo, S., Sharma, S., Wills, A.-M. A., Bainbridge, J. L., Wong, P. S., … Boyd, J. T. (2017). Association of metabolic syndrome and change in Unified Parkinson's Disease Rating Scale scores. *Neurology*, 10.1212/WNL.0000000000004572. https://doi.org/10.1212/WNL.0000000000004572

xiv. Manyam, B. V. (1990). Paralysis Agitans and Levodopa in "Ayurveda": Ancient Indian Medical Treatise, *5*(1), 47–48.

xv. Ovallath, S., & Deepa, P. (2013). The History of Parkinsonism: Descriptions in Ancient Indian Medical Literature Kampavata: The Vedic Analogue of Parkinsonism Etiopathogenesis of Kampavata Treatment of Kampavata in Ayurveda, *28*(5), 566–568. https://doi.org/10.1002/mds.25420

xvi. Pathak- Gandhi, N., & Vaidya, A. D. B. (2017). Management of Parkinson's disease in Ayurveda: Medicinal plants and adjuvant measures. *Journal of Ethnopharmacology*, *197*, 46–51. https://doi.org/10.1016/j.jep.2016.08.020

xvii. Patwardhan, B., Warude, D., Pushpangadan, P., & Bhatt, N. (2005). Ayurveda and traditional Chinese medicine: A comparative overview. *Evidence-Based Complementary and Alternative Medicine*. https://doi.org/10.1093/ecam/neh140

xviii. Poewe, W., Antonini, A., Zijlmans, J. C., Burkhard, P. R., & Vingerhoets, F. (2010). Levodopa in the treatment of Parkinson's disease: an old drug still going strong. *Clinical Interventions in Aging*. https://doi.org/10.2147/CIA.S6456

xix. Pole, S. (2006). *Ayurvedic Medicine*. *Ayurvedic Medicine*. https://doi.org/10.1016/B978-0-443-10090-1.X5001-4

xx. Singh, B. P., & Deepa. (2015). Critical analysis of kampavata (parkinsonism). *International Ayurvedic Journal*, *3*(6), 1767–1773.

xxi. Singh, R. H., Narsimhamurthy, K., & Singh, G. (2008). Neuronutrient impact of Ayurvedic Rasayana therapy in brain aging. In *Biogerontology* (Vol. 9, pp. 369–374). https://doi.org/10.1007/s10522-008-9185-z

xxii. Ven Murthy, M. R., Ranjekar, P. K., Ramassamy, C., & Deshpande, M. (2010). Scientific basis for the use of Indian ayurvedic medicinal plants in the treatment of neurodegenerative disorders: ashwagandha. *Central Nervous System Agents in Medicinal Chemistry*, *10*(3), 238–246. https://doi.org/ABSTRACT # 02 [pii]

xxiii. Weber, W., & Killen, J. (2015). Ayurvedic Medicine: In Depth | NCCIH. *National Center for Complementary and Integrative Health*. Retrieved from https://nccih.nih.gov/health/ayurveda/introduction.htm

xxiv. Zhang, P., & Tian, B. (2014). Metabolic syndrome: An important risk factor for Parkinson's disease. *Oxidative Medicine and Cellular Longevity*. https://doi.org/10.1155/2014/729194

Tables

Table 1

Class of Drug	*Generic Name*	*Brand Name*
Carbidopa/Levodopa		
	Carbidopa/levodopa	*Sinemet*
	Carbidopa/levodopa-controlled release	*Sinemet CR*
	Carbidopa/levodopa/entacapone	*Stalevo*
Rytary	Carbidopa/levodopa orally disintegrating tablet (ODT)	*Parcopa*
Dopamine Agonists (DA)		
	Pramipexole	*Mirapex*
	Ropinirole	*Requip*
	Rotigotine (transdermal system)	*Neupro*
COMT Inhibitors		
	Entacapone	*Comtan*
	Tolcapone (rarely used)	*Tasmar*
MAO-B Inhibitors		
	Selegiline	*Eldepryl*
	Selegiline ODT	*Zelapar*
	Rasagiline	*Azilect*
Others	*Amantadine*	*Symmetral*

Note: *Common Medication for Parkinson's with Brand and Generic Names*

Table 2

The Two Treatises of Ayurveda (Samhita):	Subcategories (Sthana):	General Focus:
Charak Samhita (kayachikitsa: Internal Medicine) ~ 12,000 verses	Sutra Sthana	Dietary regiment
	Sharira Sthana	Human anatomy/physiology/gynecology
	Nidana Sthana	Diagnostic approaches: signs/symptoms/pathogenesis
	Vimana Sthana	Medicinal Properties
	Chikitsa Sthana	Description of disease, cause, and treatment
	Kalpa Sthana	Formulations and treatment of disease. Panchakarma: a fivefold detoxification treatment involving massage, herbal therapy, and other procedures.
	Siddhi Sthana	
	Indriya Sthana	Ethnics of Medicine
Sushruta Samhita	Sutra Sthana	Dietary regiment (revisited)
	Nidana Sthana	Diagnostic approaches: signs/symptoms/pathogenesis (revisited)
	Sharira Sthana	
	Cikitsa sthana	
	Kalpa tantra	
	Uttara tantra*	
Ashtanga Samgraha & Ashtanga Hridaya	Samgraha (Compilation)	Information and DDX from Charak and Sushruta.

Note: Key medical literature dealing with various fields and pathology, these emerged from ayurvedic medicine in early days of the Indus-Valley Civilization.

Figures

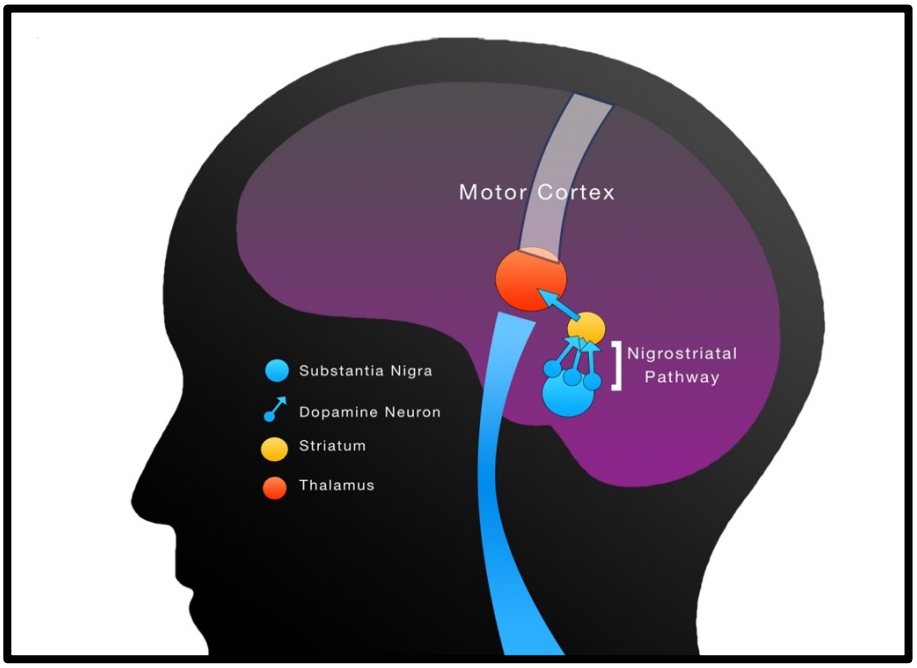


Figure 1: Abstract of the nigrostriatal pathway which a bridged direction of Substantia Nigra and Striatum via the dopaminergic neurons.

Figure 2: Established timeline of Ayurvedic Medicine according to the Department of Ayurveda. (edited for clarity)

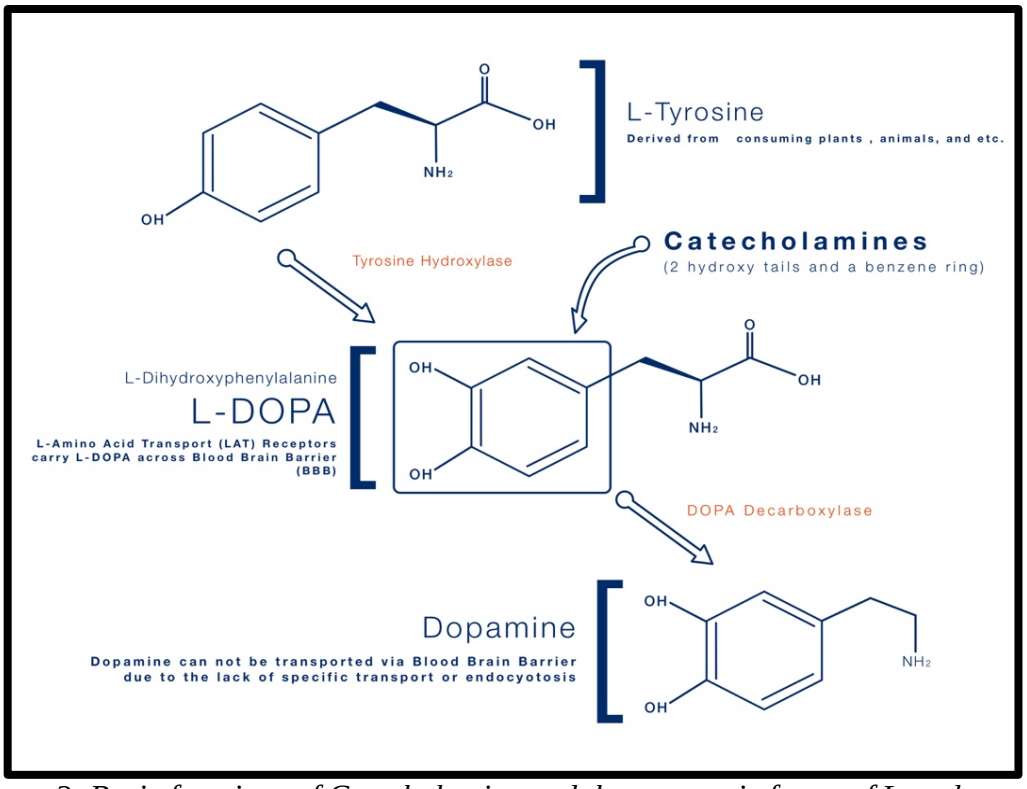


Figure 3: Basic functions of Catecholamine and the enzymatic forms of Levodopa and Dopamine.

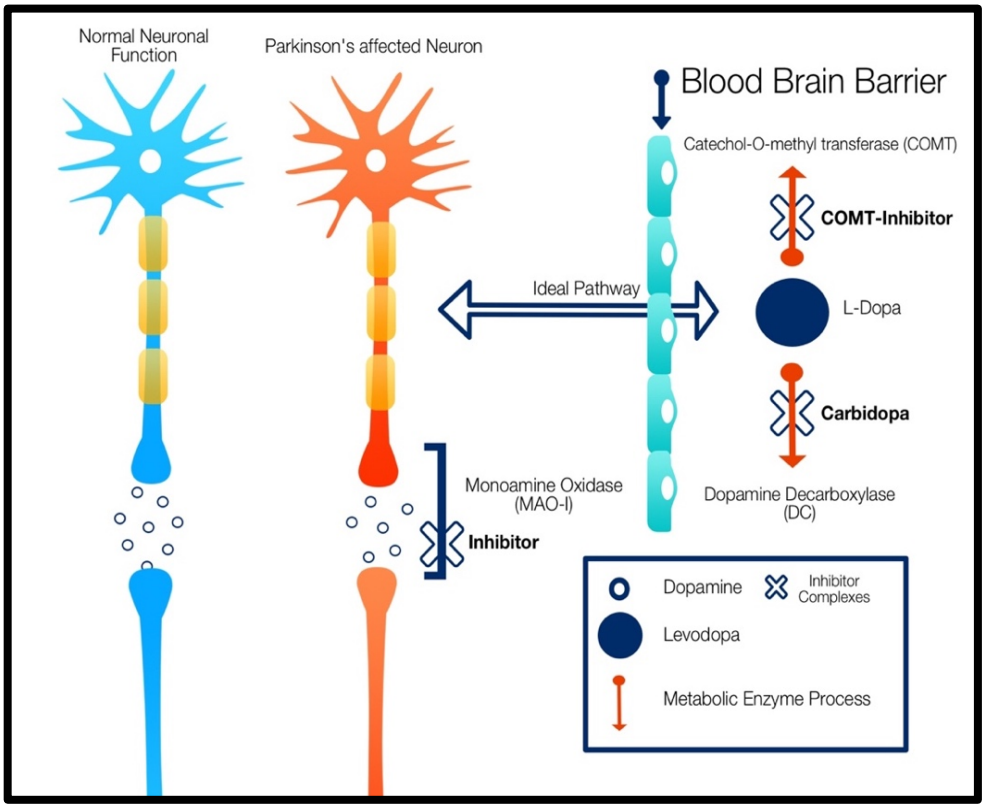


Figure 4: Biochemical pathway for levodopa and dopamine through BBB.

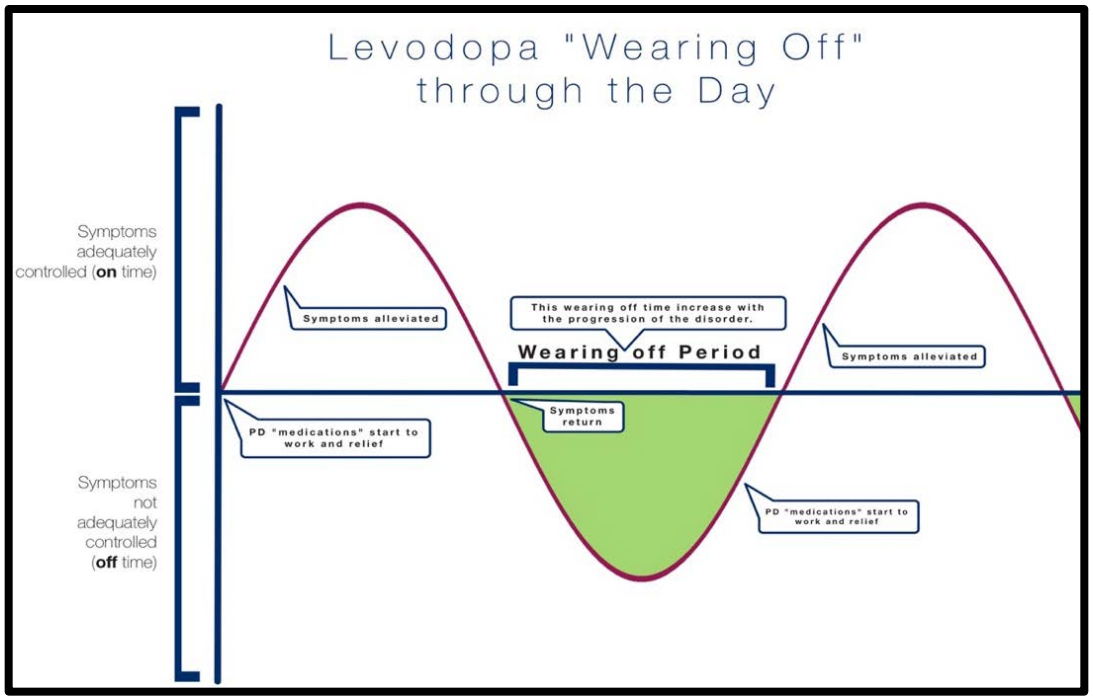


Figure 5: The general diagram of "Wearing Off" effect in PD cases related to levodopa treatment plan.

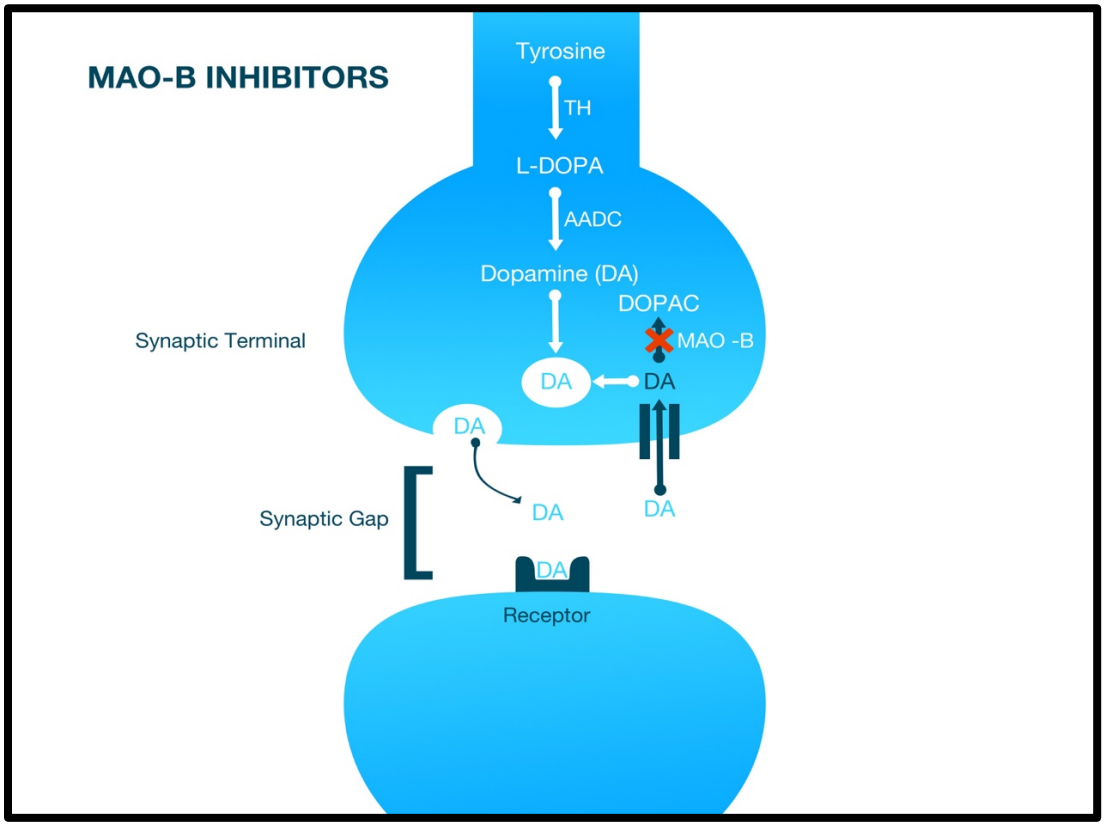


Figure 6: Biochemical pathway for MAO-B Inhibitors