Treatment options of Parkinson's disease: How far we are from the cure?

By

Nuraia Afreen
15146033

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Brac University
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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

Nuraia Afreen
15146033

Approval

The project titled "Treatment options of Parkinson's disease: How far we are from the cure?" submitted by Nuraia Afreen (15146033) of Spring, 2015 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on 7th January, 2021.

Examining Committee:

Supervisor:
(Member)

_____

Easin Uddin Syed
Lecturer, Department of Pharmacy
Brac University

Program Coordinator:
(Member)

_____

Dr. Hasina Yasmin
Professor, Department of Pharmacy
Brac University

Departmental Head:
(Chair)

_____

Professor Dr. Eva Rahman Kabir
Chairperson, Department of Pharmacy
Brac University

Ethics Statement

This study does not involve any human or animal trial.

Abstract

Parkinson's disease (PD) can be defined as a neurodegenerative disorder, which is associated with movement disorders and comprises of four prevalent cardinal indications, which are rigidity, bradykinesia, tremor and postural instability. During the progression of the disease, different movement and non-movement complications arise in patients. Different pharmacological and non-pharmacological treatment interventions are accessible for the control of Parkinson's disease. Levodopa, Dopamine receptor agonists, inhibitors of catechol-O-methyl transferase (COMT) and inhibitors of monoamine oxidase-b (MAO-B) are popular pharmacological treatment choices. The complications can be prevented through adjunctive therapy and recent discovered approaches has brought new dimension in the treatment process of this disorder. The aim of this review is to summarize and evaluate the existing literatures on treatment options of Parkinson's disease and also to focus on the recent advanced that is still in clinical trials and the possibilities of cure of this neurodegenerative disease.

Keywords: Parkinson's disease; Neurodegeneration; Treatment; Pharmacological; Non-pharmacological.

Dedication

Dedicated to My Parents.

Acknowledgement

With utmost respect, I would like to extend my heartfelt gratitude to all the people who have directly or indirectly helped me to accomplish the completion of this paper.

First and foremost, I am grateful to Almighty Allah for giving me the strength and ability that was required to understand, learn and complete my thesis.

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Table of Contents

List of Tables

List of Figures

List of Acronyms

Ach-I	Acetylcholinesterase Inhibitors
CT	Computed Tomography
CDNF	Cerebral dopamine neurotrophic factor
COMT	Catechol-O-Methyl Transferase
DBS	Deep Brain Stimulation
GDNF	Glial cell-line derived neurotrophic factors
GSH	Glutathione Peroxidase
LID	Levodopa Induced Dyskinesia
LRKK2	Leucine-rich kinase 2
MAO-I	Monoamine Oxidase Inhibitors
MRI	Magnetic Resonance Imaging
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahyropyridine
PD	Parkinson’s disease
PDGF-BB	Platelet derived growth factor
PINK1	PTEN-induced kinase 1
STN	Subthalmic Nucleus
TCA	Tricyclic Antidepressant
UPS	Ubiquitine Proteosome System
WHO	World Health Organization

Chapter 1

Introduction

The second most prevalent progressive neurodegenerative condition of the central nervous system is Parkinson's disease, (Alves et al., 2008) which creates problems with body movements. People with 60 years or above are usually affected by this disease (Olanow, 2004). Patients typically have four common characteristics such as resting tremor, bradykinesia, rigidity and postural instability (Lang, Anthony E., 1998). Neuropathologically, dopaminergic neurons are lost and there are intracytoplasmic eosinophilic inclusions called Lewy bodies, leading to a decline in dopaminergic nigrostriatal functions (Don, 1996).

As the disease worsens with time, different movement and non-movement problems are aroused, resulting in increased impairment and poor lifestyle of the patients (Alves et al., 2008). There are different treatment possibilities of this disorder. However, as there is still no cure, the main concern is minimizing the various complications through proper design of new treatment strategies and neuroprotective drugs, which will help the patients in maintaining the maximal quality of life.

The Figure 1 below shows a diagram which represents reduction of dopamine neurons in a patient's brain. So, to treat this condition exogenous levodopa is being administered, which transports to the brain and enhances striatal dopaminergic neurotransmission (View, 2012).

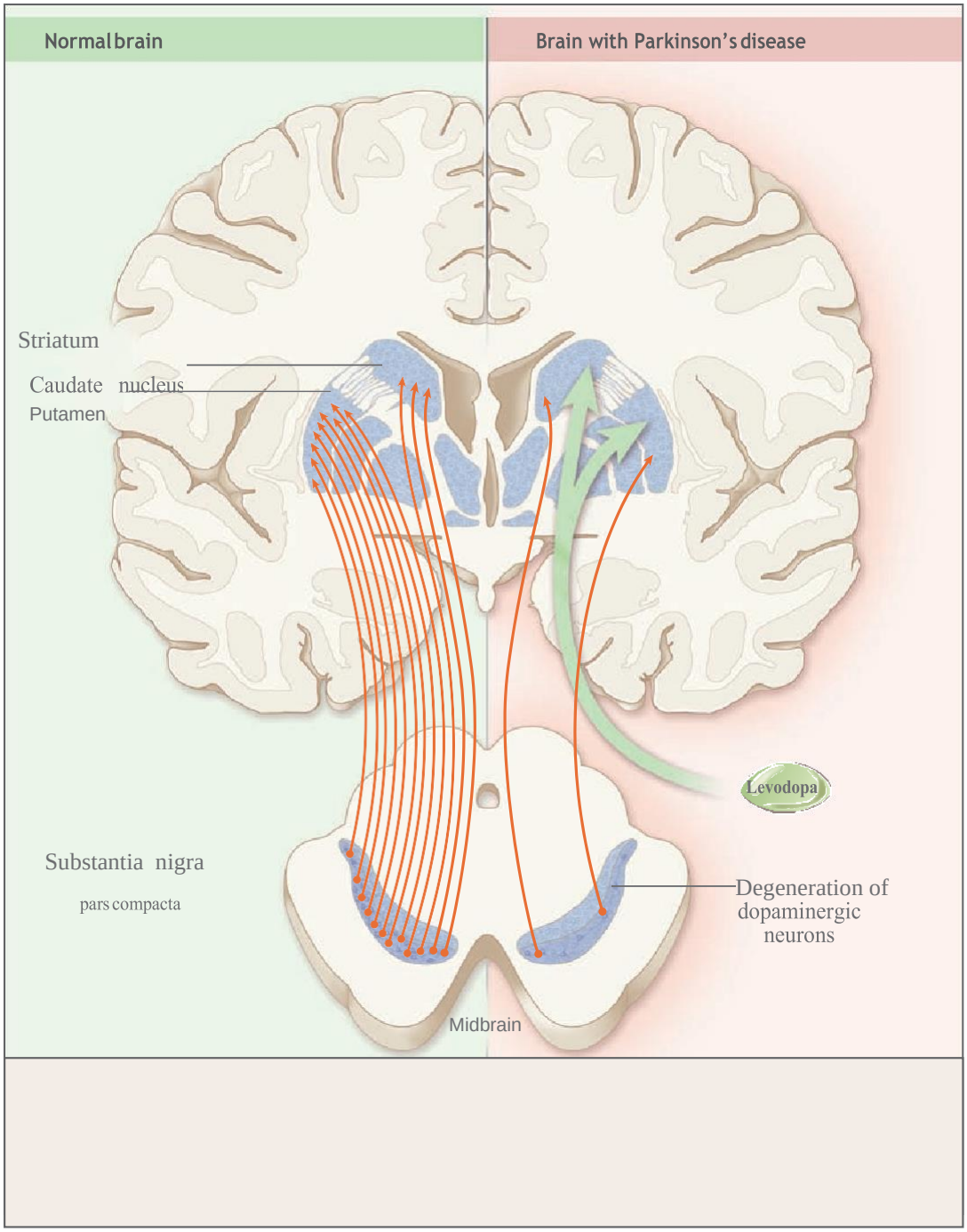

Figure1: Brain of a patient showing reduction of dopamine neurons due to PD (View, 2012)

1.1 Prevalence:

The prevalence of PD is expected to rise in the upcoming years globally, due to more aged-population, environmental factors and demographic factors. For this reason, it has been projected that the number of PD sufferers worldwide would double by 2030 (Tan, 2013).

In 2016 , it was estimated that about 6.1 million people worldwide were diagnosed with this disease, while in 1990, 2.5 million people were affected (Ray Dorsey et al., 2018). In the U.S. population, the approximate prevalence of this disease is 0.3 percent and the incidence grows from 4 to 5 percent in the aged people who are more than 85 years old (De Lau et al., 2004).

The prevalence of this neurodegenerative disorder is less in Asian countries compared to the non-Asian countries. To figure out the prevalence condition in Asia, 9 door to door studies were reviewed. From the door to door studies, it was found that the rates of affected people obtained were from 51.3 to 176.9 per 100,000 of population. Again, door to door studies in the non-Asian showed that the rates of affected people were higher than the rates of Asian countries. A report showed that the number of individuals affected by PD would grow from 4.1 million to 4.6 million in 2005 and from 8.7 million to 9.3 million people by 2030, respectively (Durães et al., 2018). It was predicted that individuals affected by PD would grow to 2.57 million in 2005 and 6.17 million by 2030 in the populous countries of Asia, which are China, India, Indonesia, Pakistan, India, Bangladesh and Japan (Durães et al., 2018) . PD is highly prevalent in China and the Parsi population of India (Muangpaisan et al., 2009). A study was also conducted to estimate the prevalence of this disorder in Korea based on age and gender. It was found that, in 2010, the number of cases was 115.9, which rose to 139.8 per 100,000 in 2015 (Park et al., 2019).

The number of this disease cases is increasing in the developing countries like Bangladesh. However, in Bangladesh, very few researches have been performed to observe the incidence and occurrence of this disease.

From 2009 to 2010, a study was conducted to observe the demographic and non-motor clinical profiles of 51 Parkinson's patients in Mymensingh, Bangladesh. It was found that, male patients were more susceptible to this disorder and showed non-motor symptoms more than female patients (Rahman et al., 2018).

A comparative cross-sectional study was conducted by BSMMU (Bangabandhu Sheikh Mujib Medical University), to determine the relevant aspects among 100 PD patients in the formation of depressive disorder through an interview session. However, only 80% patients participated where it was observed that 42% patients had depression (Sarkar et al., 2019).

Another hospital-based study was conducted in Dhaka from 2012 to 2013, to assess the incidence of depression in PD patients. Brain MRI was done among 137 Parkinson's patients. It was found that the prevalence of depression was 42% (Disorders & This, 2014).

Again, in 2018, a study was conducted in the district of Jashore, Bangladesh to evaluate the incidence of fall among the uncomplicated Parkinsonism patients. About 36.9% of fall events were analyzed among 111 idiopathic Parkinson's patients where no difference was found out between faller and non-faller patients (Kumar Acherjya, 2019).

According to the World Health Organization (WHO) data published in 2017, the total number of deaths due to Parkinson's disease reached 539, which is 0.07% of total deaths. In Bangladesh, the death rate according to age is 0.55 per 100,000 of the population. As a result, the WHO has ranked Bangladesh as a 152nd country globally. Therefore, Bangladesh also had deaths due to Parkinson's disease and various surveys had been conducted over the past

few years to assess the current condition of this disorder. Nevertheless, more studies and surveys need to be conducted to understand the scenario of this disease in Bangladesh.

1.2 Symptoms

Parkinson's disease is characterized by four cardinal symptoms, which are also termed as motor symptoms viz. bradykinesia, rest tremor, rigidity and postural instability (Lang, Anthony E., 1998). The slowness of movement is bradykinesia, which includes various problems such as planning, executing, performing multiple tasks etc. (J. Jankovic, 2008). Tremor at rest is one of the characteristic symptoms of this disorder, where rhythmic oscillary involuntary movement is involved (Massano & Bhatia, 2012). Rigidity is associated with resistance in the passive movement of the limbs. Postural instability is the most threatening signs of this disorder, because it can lead to falls and thus, results in fractures. Apart from that, people with this disease may also show symptoms like freezing which is known as motor blocks. Moreover, Parkinson's disease patients show non-movement signs as well. The usual indications of this disease are listed in Table 1.

Motor symptoms	Non-motor symptoms
Tremor, stiffness of posture, bradykinesia, rigidity	Cognitive deficits, bradyphrenia, tip-of-the-tongue
Hyposmia, difficulty in swallowing, hypersalivation, dysarthria,	Depression, apathy, fatigue, behavioural and psychiatric problems
Reduced arm swing, festination difficulty, gait disturbances,	Sensory symptoms: paresthesias, loss of sense of taste, shoulder or back pain, anosmia
Minute handwriting, slow activities of daily living	Autonomic dysfunction (constipation, urinary and sexual dysfunction orthostatic hypotension, sweating, seborrhoea, loss of weight)
Blepharospasm, dystonia, striatal deformity, scoliosis, Glabellar reflex,	Sleep disorders (REM behaviour disorder, vivid dreams, daytime drowsiness, restless legs syndrome)

Table1. Parkinson's disease Symptoms (J. Jankovic, 2008)

1.3 Etiology

Physicians generally address PD as idiopathic. Though, the actual cause of this disorder is usually unknown, there are indications that it is caused due to aging, genetic factors and non-genetic factors. The presence of these aspects typically triggers this disease.

Aging is considered to be the potential cause of this disease. This progressive disorder occurs during middle age or later ages. During this time, the brain cells of human body starts to damage. This creates an impact in the loss of striatal dopamine neurons, leading to show Parkinson's symptoms. However, aging is not the only reason for the progression of this disease.

The curiosity of the non-genetic causes of this disorder aroused, when Parkinsonism was developed by 1-methyl-4-phenyl-1,2,3,6-tetrahyropyridine (MPTP) (Science et al., 2010). Non-genetic variables have been expected to relate to the cause of the disease, such as susceptibility to pesticides, brain injury, excessive ingestion of milk, lipid, and calories (Chade et al., 2006).

Recent studies suggest that genetic mutations have also been alarming for the development of Parkinsonism. The main markers of this condition are alpha-synuclein gene and lewy bodies (Goedert, 2004). Alpha-synuclein is mainly responsible for inherited Parkinson's disease. These genes aggregate and then, deposits to form lewy bodies (Shafique et al., 2011). Due to these mutations, dopaminergic neuronal loss occurs and ultimately, leads to neurodegenaration. Due to the mutations of alpha-synuclein genes and LRRK2 (leucine rich repeat kinase 2) genes, the autosomal dominant PD is caused (Gasser, 2007). Again, autosomal recessive PD is mainly driven by the genes parkin, PINK1 and DJ-1 (Gupta et al., 2008). Therefore, Alpha-synuclein, Lewy bodies and LRRK2 are the major genetic factors that plays significant role throughout the neurodegenaration of this disease. Another cause of

this disorder is the unstable free radicals which are the by-product of oxidative stress. These free radicals results in neuronal cell deaths and leads to Parkinsonism (Shafique et al., 2011). So, more researches are necessary to discover the causes of this disorder, which will contribute to the prevention and treatment procedures.

1.4 Pathogenesis:

There is data that the first area to be impacted by neurodegeneration is substantia nigra pars compacta and the movement related complications in PD usually arises because of the depletion of neurons in this area. (Anthony H.V. Schapira, 2009). Various mechanisms were suggested to understand the growth of this disease, such as alpha-synuclein aggregation, mitochondrial dysfunction, proteosomal dysfunction, neuroinflammation. All these mechanisms play critical part in understanding the neurodegenaration and transformation of the disease. Usually, environmental and genetic factors are responsible for the alteration of alpha-synuclein protein which leads to lewy body formation in the nigral cells and thus, gives rise to neurodegeneration.. Figure 2 shows how the etiology of this disease is related to the pathogenesis.

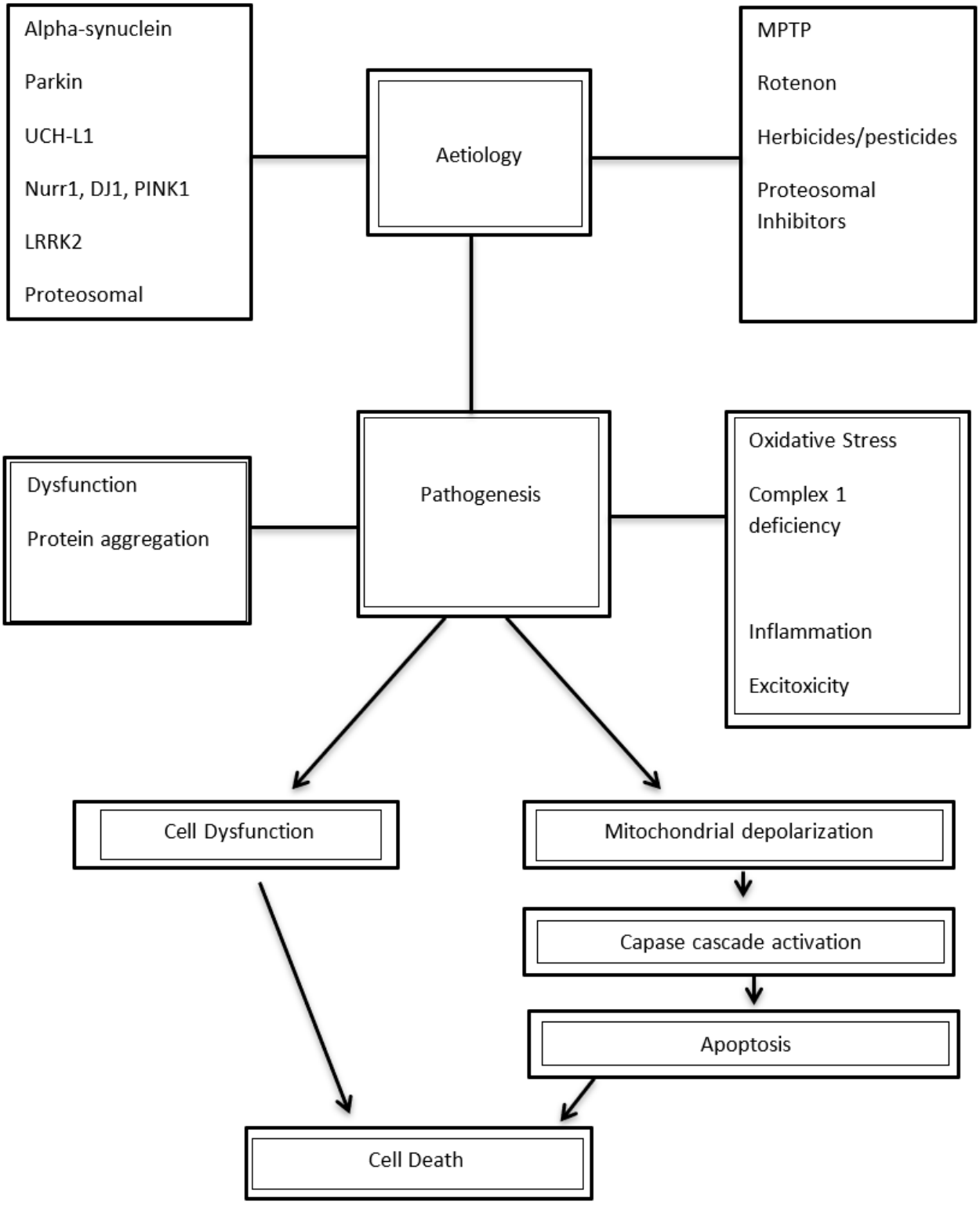

Figure 2: Factors associated with etiology and pathogenesis of PD (A. H.V. Schapira, 2005)

Alpha-synuclein proteins are normally unfolded inside the brain and usually resistant to aggregation. However, when they interact with negatively charged lipids they get folded into alpha-helical structures. Theses misfoldings of alpha-synuclein is found in the lewy bodies. Alpha-synuclein consists of various species which are thought to be responsible for the nerotoxicity. The oligomeric species mainly enhances protein aggregation in the brain (Zahoor et al., 2018).

Mitochondrion is vital for electron transport chain. A study in the SNpc of PD brains showed a deficiency in the mitochondrial complex-I in the PD patients. This data proved that the mitochondrial dysfunction is related to PD. Due to the defects in the mitochondrial complex I, dopaminergic neurons may be damaged. Mitochondrial dysfunction is associated with familial and idiopathic PD also. Alpha-synuclein also interacts with mitochondria and accumulates in the organelles, causing damage in the complex-I activity and resulting in mitochondrial dysfunction. Toxins and pesticides may also affect the activity of mitochondrial complex-I (Zahoor et al., 2018).

Inhibition of proteasome pathways can result in dopaminergic cell death. There are two protein-clearance pathways viz. ubiquitin proteasome system (UPS) and autophagy lysosome pathway (Pan et al., 2008). Abnormal proteins are usually broken down by UPS. However, compared to healthy brains, UPS activity is decreased in a patient's brain. Again, the reason of this disease can be because of malfunction in autophagy lysosome pathway. Alpha-synuclein is cleared by UPS and autophagy lysosome pathways. If damage occurs in any of the pathways, then it can result in aggregation of misfolded alpha-synuclein proteins (Zahoor et al., 2018).

In Parkinson’s disease, neuronal cell death occurs through apoptosis. Neuroinflammation is observed in Parkinson’s patients due to increased microglial activation. This can lead to

tumor necrosis and ultimately, can activate apoptosis (Sukendar et al., 2016). Alpha-synuclein can play role in activating microglial cells which can trigger the inflammatory process (Zahoor et al., 2018).

So, there are numerous pathological processes of PD. However, relationship among these mechanisms is still unclear and is not completely understood. Therefore, the proper understanding of these pathways can contribute to improved treatments procedures and may lead to the ultimate cure of this neurodegenerative disorder.

1.5 Diagnosis

Usually, in PD, the occurrence of neuronal degradation has not been properly understood. To treat this neurodegenerative disease, proper diagnosis is essential. The diagnostic process of this disease is usually clinical, as there is no accurate test to confirm the presence of this disease. However, it is difficult to diagnose the true idiopathic Parkinsonism as it coincides with other types of Parkinsonism disorders. The prevalent four forms of Parkinsonism disorders are “primary (idiopathic) parkinsonism, secondary parkinsonism which is acquired or symptomatic, heredodegenerative parkinsonism and the last one is multiple system degeneration” (J. Jankovic, 2008).

There are various characteristics that can be used to differentiate idiopathic Parkinsonism from other Parkinsonism disorders. Postural instability, tremors and response to levodopa are usually used. Improvement in treatment with levodopa is observed in idiopathic patients. Again, patients with multiple system atrophy when treated with levodopa, develop levodopa induced dyskinesia. So, response to levodopa cannot be the only diagnostic feature. Apomorphine which is injected subcutaneously has also been considered as diagnostic feature. However, it was observed that it was less reliable than levodopa.

In the recent days, special criteria are used for the accuracy of the diagnostic procedure (*Massano & Bhatia, 2012*) . The specificity of this method is about 98.6% and sensitivity is 91.1% approximately. Though this criterion is very useful, clinico-pathological studies showed that about 25% of patients were misdiagnosed through these criteria (Tolosa et al., 2006), which may lead to diagnosis of atypical parkinsonism disorders and create confusion with Alzheimer's disease. The Table 2 shows the criteria to diagnose this disorder.

Table 2. The UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria

Step 1: Diagnosis of parkinsonian syndrome
Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude or repetitive actions) **And at least one of the following:** **Muscular rigidity** **4 – 6 Hz rest tremor** **Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction**

Step 2: Exclusion criteria for Parkinson's disease
History of repeated strokes with stepwise progression of parkinsonian features **History of repeated head injury** **History of definite encephalitis** **Oculogyric crises** **Neuroleptic treatment at onset of symptoms More than one affected relative Sustained remission** **Strictly unilateral features after 3 years** **Supranuclear gaze palsy** **Cerebellar signs** **Early severe autonomic involvement** **Early severe dementia with disturbances of memory, language, and praxis** **Babinski sign** **Presence of a cerebral tumor or communicating hydrocephalus on CT scan** **Negative response to large doses of levodopa (if malabsorption excluded)** **MPTP exposure**

Table 2. A criteria representing the clinical diagnostic procedure of PD (Massano & Bhatia, 2012)

A single test cannot diagnose this disorder. As a result, for proper and accurate diagnostic procedure, various techniques and tests can be used to treat PD. For instance, various tests like MRI, olfactory testing, dopamine-transporter single-photon emission computed topography (SPECT) imaging and genetic testing can be done (Tolosa et al., 2006).

Step 3: Supportive positive criteria of Parkinson's disease
Three or more required for diagnosis of definite Parkinson's disease:
Unilateral onset
Rest tremor present
Progressive disorder
Persistent asymmetry affecting the side onset most
Excellent response (70% – 100%) to L-dopa
Severe levodopa-induced chorea Levodopa response for 5 years or more Clinical course of 10 years or more Hyposmia
Visual hallucinations

Table 2. A criteria representing the clinical diagnostic procedure of PD (Massano & Bhatia, 2012)

Brain imaging as an example, cranial computed tomography (CT) and magnetic resonance imaging (MRI) are performed in uncomplicated Parkinsonism (Tolosa et al., 2006). CT is used to determine lower body Parkinsonism and has less sensitivity towards other disorders. MRI is potentially sensitive than CT and provide better results. Fluorodopa Positron emission tomography (f-PET) and Dopamine transporter (SPECT) are one of the available imaging

techniques which are used to determine degeneration of dopamine functions in the striatum. Again, metaiodobenzylguanidine (MIBG) scintigraphy is used to examine the postganglionic impairment of the sympathetic nervous system (Reichmann, 2010). All these methods are highly sensitive and expensive. These techniques unveil the premotor impairment of the dopaminergic system and are highly used for distinguishing from atypical Parkinsonism.

Hyperchogenicity of the substantia nigra can be determined by the transcranial ultrasound midbrain imaging in PD patients. The method is applied to visualize and observe the brain parenchyma and is used as a differential diagnostic test (Tolosa et al., 2006).

Olfactory dysfunction is observed in most of the patients with Parkinsonism. It is identified in the initial movement phase of the disease. Olfactory tests are usually inexpensive and can add extra information regarding detection of idiopathic Parkinsonism. Motor tests are performed where the movement of the patient is being examined. The handwriting and speech of the patient are also observed. Moreover, patients with Parkinsonism suffer from visual disturbances viz. visual contrast sensitivity and color discrimination etc. By the use of Fransworth-Munsell 100 Hue test, the color discrimination can be examined (Przuntek, 1992). These tests are done in combinations of other tests, due to their less sensitivity and specificity.

Some laboratory tests viz. thyroid and liver function tests along with electrolyte measurement tests can be performed. The most common laboratory tests for diagnosing Parkinsonism are copper and coeruloplasmine tests (Reichmann, 2010). Genetic testing has created new innovation for diagnosing this disorder. The two most common mutations of PARK and LRRK2 genes can be used to determine Parkinsonism. However, this test has less clinical relevance and is still prohibited in research centers (Tolosa et al., 2006).

1.6 Drug history

The treatment of PD has brought variety of options since the disorder has been first discovered. More than 200 years have passed; James Parkinson discovered and wrote his 'Essay on the Shaking Palsy' in 1817 (Mcdonald et al., 2018). In his essay, he recognized about the cardinal symptoms and described about the degenerative nature of the disease that he observed in six individuals. From then, scientists have shown huge interest on the discovery of drugs for treating this neurodegenerative disorder by proper knowing of the disease condition. The scientists isolated levodopa from vicia faba and continued various trials to observe the effectives of various dosage forms of levodopa. Various trials were also run out to enhance the efficacy of the sustained releases Carbidopa- levodopa. Again, the use of different types of MAO-B inhibitors along with levodopa was observed to enhance the efficacy of levodopa. The COMT inhibitor, Entacapone, became active in treating this disorder through the adjunctive therapy procedure with Levodopa. Moreover, the dopamine agonist, Ropinirole, was proved effective through adjunctive therapy of levodopa. (Mcdonald et al., 2018)

The table 3 shows the history of development of these drugs starting from the year 1913 to 2017 (Mcdonald et al., 2018). This table explains about the process of approval of various classes of medications which are useful for the management of PD.

L-DOPA	Decarboxylase Inhibitor	MAO Inhibitor	COMT inhibitor	Dopamine Agonist
·1913 L DOPA isolated from vicia faba ·1957 Carlsson shows L-DOPA antagonises reserpine ·1959 Dopamine found to localise in caudate and putamen ·1960 Profound loss of dopamine found in brains of patients with PD ·1961 first reported trial of intravenous LDOPA in PD ·1967 effectiveness of oral L DOPA demonstrated ·1969 First RCT showing dopamine efficacy ·1986 continuous naso-duodenal levodopa improves on/off time	·1938 L-DOPA decarboxylase enzyme identified ·1967 DDC inhibition increases concentration of cerebral catecholamines ·1969 dopamine, in combination with a decarboxylase inhibitor (benserazide) found to be more effective than L-DOPA alone and reduce the gastrointestinal and cardiac adverse events ·1975 Madopar and Sinemet commercialized ·1989 sustained release carbidopa-levodopa shown to reduce "off" time	· 1957 DOPA more effective in reserpine treated animals when co-administered with MOA I iproniazid · 1961 Birkmayer and Hornykiwicz show that pre-treatment with MAO I iscocarboxazid prolongs efficacy of L DOPA · Use of MAO A+B inhibitors limited by adverse effects "cheese effect" · Selective MOA-B inhibitor developed · 1975 Birkmayer performs first clinical trial of selegiline in PD · 1978 Rasagiline identified · 1989 selegiline approved by FDA · 2005 Rasagiline approved in Europe, 2006 approved by FDA · 2015 safinamide approved by EMA, 2017 approved by FDA	· 1989 two orally active COMT inhibitors identified in animal models ·1997 Tolcapone becomes commercially available ·1998 Tolcapone associated hepatotoxicity reported. Regulatory agencies recommend LFT monitoring some subsequently suspend licence ·1999 Entacapone becomes commercially available ·2003 Stalevo (cabidopa-LDOPA-entacapone) becomes available ·2016 Opicapone commercially available	·1951 Apomorphine produced short-lived improvement in patients with PD ·1965 Apomorphine noted to be structurally similar to dopamine ·1965 Bromocriptine synthesised ·1970 Cotzais reintroduces Apomorphin e ·1974 Bromocriptine shown to be an effective adjunct to LDOPA in PD ·1982 first reports of fibrosis associated with ergot derived dopamine agonists ·1991 Ropinirole the first-non ergot derived dopamine agonist proves effective ·2003 initial reports of impulse control disorders associated with dopamine agonists

Table 3. The history of drug development (Mcdonald et al., 2018)

1.7 Methodology

All searches conducted for writing this review are based on articles and journals found in Google Scholars, Springer and Elsevier on the topic of the treatment of Parkinson's disease. All relevant papers have been obtained in full text and all associated relevant materials have been analyzed and reviewed.

Chapter 2

Treatment

Being the second common neurodegenerative disease, scientists and researchers have discovered different medications for the treatment approaches of PD. According to neuroscientists Arvid Carlsson and Oleh Hornykiewicz, the dopaminergic neurotranmission can be restored through pharmacological treatment (View, 2012). However, because of the dynamic nature of the disease, the treatment process is usually complex. As a result, the drugs used in the treatment process, need to be selected according to the symptoms and side-effects shown in the patient. The table below indicates the FDA approved drugs in USA, which is borrowed from the following website.

https://www.apdaparkinson.org/what-is-parkinsons/treatment-medication/medication/

Generic Name	Trade Name	Mode of Action
Carbidopa-levodopa	Sinemet	DOPA decarboxylase inhibitor/DA precursor
Carbidopa-levodopa (controlled release)	Sinemet CR	DOPA decarboxylase inhibitor/DA precursor
Carbidopa-levodopa (orally disintegrating tablet)	Parcopa	DOPA decarboxylase inhibitor/DA precursor
Carbidopa-levodopa (extended release capsultes	Rytary	DOPA decarboxylase inhibitor/DA precursor
Carbidopa-levodopa-entacopone (enteral suspension)	Duopa	DOPA decarboxylase inhibitor/DA precursor
Levodopa Inhalation powder	Inbrija	DA precursor
Entacopone	Comtan	COMT inhibitor, inhibits breakdown of Levodopa
Tolcapone	Tasmar	COMT inhibitor, inhibits breakdown of Levodopa
Opicapone	Ongentys	COMT inhibitor, inhibits breakdown of Levodopa
Carbidopa/Levodopa Entacopone	Stalevo	DOPA decarboxylase inhibitor/DA precursor/COMT inhibitor
Pramipexole	Mirapex	DA agonist

Table 4. List of FDA Approved drugs

Pramipexole (extended release)	Mirapex ER	DA agonist
Ropinirole	Requip	DA agonist
Ropinirole (extended release)	Requip XL	DA agonist
Apomorphine (injection)	Apokyn	DA agonist
Apomorphine sublingual film	Kynmobi	DA agonist
Rotigotine (transdermal patch)	Neupro	DA agonist
Selegiline	Eldepryl	MAO-B inhibitor; inhibits breakdown of dopamine
Selegiline (orally disintegrating tablet)	Zelapar	MAO-B inhibitor; inhibits breakdown of dopamine
Rasagiline	Azilect	MAO-B inhibitor; inhibits breakdown of dopamine
Safinamide	Xadago	MAO-B inhibitor; inhibits breakdown of dopamine
Amantadine	Symmetrel	Mixed mechanisms, including NMDA antagonism
Amantadine (extended release)	Gocovri	Mixed mechanisms, including NMDA antagonism
Amantadine (extended release)	Osmolex	Mixed mechanisms, including NMDA antagonism
Istradefylline	Nourianz	Adenosine 2A antagonist
Trihexyphenidyl	Artane	Anticholinergic
Benztropine	Cogentin	Anticholinergic

Table 4. List of FDA Approved drugs

2.1 Stage-based Symptomatic treatment

Usually, patients of PD show two types of indications, which is related to movement and non-movement complications. These indications are observed in different stages of this disease. During the onset and disease development period, the non-movement indications of this disease can usually be observed. For this reason, at the time of onset of functional impairment, the symptomatic treatment should be proceeded (Don, 1996). Different treatment approaches are necessary to treat these symptoms. So, based on the movement and non-movement indications, the treatment of this disease is divided into three stages:

- Early Stage
- Advanced Stage
- Complicated Stage

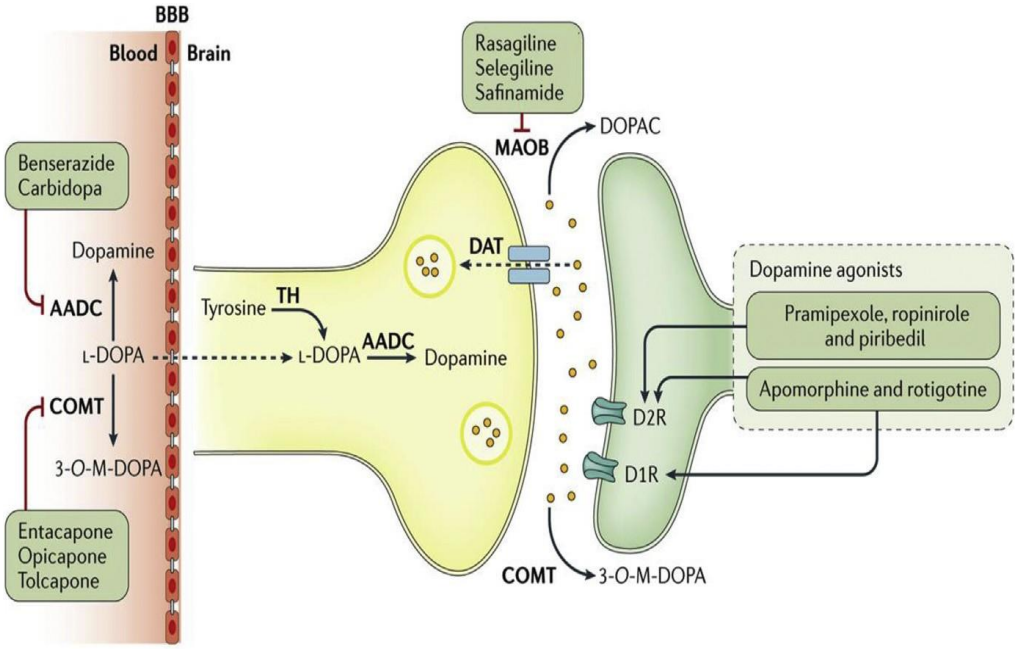

Figure 3: The diagram representing the location and mechanism of action of dopamine related drugs (Poewe & Mahlknecht, 2020)

2.1.1 Early stage treatment of Motor symptoms

Patients, who have been diagnosed with PD and have the disease with less than five years, are included in the initial phase of this disease (Clarke, 2004). They tend to grow very mild symptoms.

Levodopa is the most initial and effective treatment for this neurodegenerative disorder. It is used to treat the movement related indications of this disease. However, there is a concern on the correct administration time of levodopa. Because, it was observed that, patients may develop long term side effects of levodopa due to the preliminary introduction of this drug. As a result, scientists are recommending levodopa sparing strategy to younger patients as they are more susceptible to develop long-lasting effects of PD. Again, a research also found that even after stopping the drug for a few weeks, patients received positive feedback rather than delaying the medication (Fahn, 1999). It was also found that visual disturbances can be eradicated by levodopa therapy. Levodopa formulations are usually administered with carbidopa or with benserazide. However, levodopa-carbidopa combination shows more involuntary movements and gastrointestinal side-effects than levodopa-benserazide (Carrarini et al., 2019).

Dopamine agonists are also used during the initial phase of this disease. It usually has a role in mitigating motor complications of levodopa. When they are combined with levodopa, the motor complications of levodopa are usually reduced (Don, 1996). These drugs are avoided in patients over 70 years old as it may create toxicity.

The ergot derivatives are less used in the initial stage treatment, because of its tendency to have side-effects. Peritonial, pulmonary and cardiac fibrosis and also valvular heart are caused by pergolide and cabergoline due to their excessive use (Zanettini et al., 2007). As a

result, non-ergot derivatives are mostly used. However, bromocriptine, an ergot derivative, are used in combination of levodopa during early and later phases of this disease.

The non-ergot derivatives that are mostly used to treat initial phase of PD are Pramipexole, Ropinirole and transdermal Rotigotine. They are found to be more efficient in monotherapy of initial phase patients (Stowe et al., 2008). Pramipexole and Ropinirole are indicated as immediate and extended release tablets in treating early stage patients of this disorder. They need dose adjustments for renal insufficiency. Again, patients who cannot swallow the tablets or have renal problems are adviced to take transdermal Rotigotine (Carrarini et al., 2019). Some studies have been conducted and it was found that there is no difference in the efficacy among different dopamine agonists (Pezzoli et al., 1994).

Monoamine oxidase inhibitors (MAO-BI) have neuroprotective properties which help to prevent the disease progression. The forms of MAO-BIs used in the initial treatment of this disease are Selegiline and Rasagiline. Studies have proved that Selegiline has mild symptomatic benefit in early patients (Miyasaki et al., 2002). Again, it has also shown effective results in reducing the disease progression process in the DATATOP trial (Deprenyl and tocopherol Antioxidative Therapy of Parkinsonism) (Controlled et al., 2015). Rasagiline has also shown symptomatic positive effects in early patients, however, efficacy of MAO-BIs in initial phase prevention of this disease is still controversial (Carrarini et al., 2019).

Anticholinergic drugs have also demonstrated efficacy in the initial phase therapy of PD. They are usually advised to patients with problems like resting tremor and preserved cognitive functions. Anticholinergic are successful in treating patients having age of less than 70 years old. They are not used in older patients because they show gastrointestinal and antipsychotic adverse-effects (Don, 1996). Triphexyphenidil is the most used anticholinergic

drug for this disease. They are currently not regularly used in young and cognitive impaired patients because of showing neuropsychiatric side-effects (Carrarini et al., 2019).

Amantadine is usually antiviral agent and provides both anticholinergic and anti-glutamatergic properties. The N-D-methyl aspartate receptor inhibitor amantadine has evidence in treating akinesia, rigidity and tremor in Parkinson's disease (Don, 1996). Amantadine has been effective in initial phase management process of this disease, however, it is related with multiple health hazards for instance swelling of the foot, livedo reticularis and visual hallucinations (Carrarini et al., 2019).

2.1.2 Advanced stage treatment of Motor symptoms

Mostly, combination of drugs is used during the advanced phase management process of PD. Inhibitors of catechol-O-methyl transferase (COMT) are introduced and advised during this stage for managing the movement complications of this disease. Entacapone and Tolcapone are the COMT inhibitors that are combined with levodopa for ameliorating the motor complications and reducing Parkinsonian behavior (Davie, 2008). However, tolcapone needs to be used with proper care as it creates fatal hepatotoxicity (Don, 1996). For this reason, entacapone are mostly used. The triple indication of drugs of entacapone/levodopa/carbidopa is now available in single formulation (Stalevo). This combination drug is examined by undergoing some trials (Nissinen et al., 2009) and is found to provide better levodopa plasma levels and also decrease the rate of motor complications to a great extent. Again, newly discovered COMT inhibitor, opicapone, compared with entacapone and was found to be effective. It showed positive effects of reducing motor complications and did not raise the level of dyskinesia. This opicapone-levodopa combination was successful for 1 year without raising the dose of levodopa (Lees et al., 2017) (Carrarini et al., 2019).

Another combination, MAO-Is inhibitors with levodopa are also employed in the advanced management of PD. This combination reduces the development of levodopa complications because it inhibits the MAO-B and helps to enhance the dopamine release in the basal ganglia (O. Rascol et al., 2005). This combination was also efficient in reducing the disability progression in PD patients without causing any other effects (Shults, 1993).

Safinamide is a new MAO-B inhibitor which inhibits the breakdown of dopamine and production of toxic free radicals. The drug represents a dual mechanism that reversibly blocks MAO-B and releases glutamate through modulation processes (Carrarini et al., 2019). It was also found in a place-controlled study that when Safinamide is added to a single dopamine agonist, the dopaminergic activity is (F. et al., 2004).

Anticholnergic inhibitors are found to be effective in preventing falls and improving gait instability. A finding showed that when compared with placebo, Donepezil was successful in decreasing rate of fall (Chung et al., 2010) . Another research with Rivastigmine was also performed to investigate the effectiveness of improving gait instability. The placebo-controlled phase 2 trials has confirmed its efficacy, however, more trials are required to understand the efficacy of Rivastigmine (Henderson et al., 2016).

Dystonia is developed during the advanced stage of Parkinson's disease. Dopamine agonists give better response in treating dystonia. Dopamine replacement therapy can represent different sites as well. Moreover, combination drugs can also be used to treat dystonia such as beclofen, carbamazapine and benzodiazepines. Again, botulinum toxins are also used in the neurological treatments. The FDA approved BOTOX and botulinum toxin B has brought relief in cervical dystonia. In addition to that botulinum toxins are used in treating various other types of dystonia such as focal dystonia, oral mandibular dystonia (Geyer & Bressman, 2007).

2.1.3 Complicated stage treatment of Motor Symptoms:

The later or complicated stage of PD starts when the patients have taking treatments of combination of drugs for more than 5 years. During this stage, the patients usually develop motor complications due to long term use of levodopa. It was found that around 40 percent patients develop motor complications and dyskinesia (Ahlskog & Muenter, 2001). A list of motor complications that arise due to long-term levodopa is shown in the Table 5 below.

List of Motor Complications induced by Levodopa
Continuous dyskinesia
Peak-dose dyskinesia, diphasic dyskinesia, respiratory dyskinesia
Stereotypy, chorea, dystonia, multiple system atrophy
Limb, trunk, pharyngeal, oromandibular dystonia, off dystonia
On-effect, Off-effect, Wearing-off
Involuntary muscle jerk, Akathisia
Punding

Table 5. Levodopa induced motor complications (Joseph Jankovic, 2005)

Complications caused by motor indications such as dose failure, freezing of gait, levodopa induced dyskinesia, wearing off, on-off syndrome etc. are observed during complicated stage of PD. Motor complications induced by levodopa can be treated by increasing the dose of levodopa, using modified- release levodopa and by increasing the level of levodopa administration (Cabreira et al., 2019). In a plcebo-controlled study, medications such as pergolide, pramipexole, ropinirole, tolcapone and entacapone were found to be effective in reducing off time during day. One of the studies showed enhanced on-time without dykinesia

and reduced off-time (Guttman, 1997). Again, bromocriptine and cabergoline, orally active drugs, also showed efficacy in controlling motor complications. Despite of having fewer trials on surgical interventions, deep brain stimulation has shown effects on off periods and requires more examinations for gaining better efficacy (Olivier Rascol et al., 2002).

Opicapone, one of the new COMT inhibitor, is found to be more effective than other COMT inhibitor. Opicapone is used to reduce wearing-off effect and helped to improve motor symptoms. There is evidence that the effect of off-time has lowered and on-time effect has enhanced despite causing dyskinesia, by the use of this medication (Ferreira et al., 2019).

The response of apomorphine, a post synaptically acting dopamine agonist to the wearing-off and on-off phenomena is shortest and steepest and is capable of maintaining longer duration response (John G Nutt & Carter, 2000). Apomorphine, with a continuous subcutanous infusion doage form can improves sleep quality of patients, increases the on-time effect without causing dyskinesia. Subcutaneous apomorphine administration enhances the onset of action and bioavailability of drugs by eliminating gastrointestinal transit period (Papuć et al., 2019).

The continuous intake of levodopa for long-term purpose, results in motor complications. When there is a loss of levodopa in the striatal dopaminergic levels tends to fluctuate. For this reason, novel levodopa preparations with innovative routes of administration are currently prepared such as transcutaneous formulation of levodopa in a patch pump device, levodopa infusions and levodopa-carbidopca intestinal gels. Levodopa inhalation formulations have improved the early morning off effects to a great extent (Hauser et al., 2019). Again, a levodopa-carbidopa intestinal gel randomized controlled trial lowered off-time by 4 hours relative to baseline and 1.91 hours compared to regular oral formulations, and the on-time effect was also improved despite causing dykinesia problems (Timpka et al., 2016). However,

precautions need to be taken as levodopa intestinal gels may intervene with surgical procedures. These innovative formulations are mainly designed to increase the bioavailability of Levodopa.

2.1.4 Dyskinesia

Due to the long-term use of levodopa, after 5 years of treatment, the patients tend to develop dyskinesia. Based on onset timing of levodopa dosing, dyskinesia is divided into three types viz. peak-dose dyskinesia, off-dyskinesia and biphasic dyskinesia. Dyskinesia is low choreic movements and their phenomenon varies at a great extent.

Peak dose related dyskinesia is perhaps the most prevalent type of dyskinesia, which is observed during the highest levodopa plasma level concentration. Off-dyskinesia occurs at the time of off-state and usually causes painful foot and mostly observed during morning time. The less common is the biphasic dystonia which causes movements in legs. Biphasic dyskinesia usually affects male patients mostly. The management of levodopa induced dyskinesia is critical because it has a risk of increasing the off-time. The aim is to increase the dopaminergic stimulation by the use of non-dopaminergic drugs. Dyskinesia related to peak-dose can be treated through the reduction of single-doses of levodopa. However, the elevation of levodopa dose causes problems. As a result, dopamine agonists are taken as the first line of therapy. Again, another therapeutic approach can be applied through the reducing the levodopa dose and increasing the intervals of intake (Carrarini et al., 2019).

Moreover, non-dopaminergic therapy can also be essential in treating dyskinesia. Adjunctive therapy with amantadine and levodopa is useful in treating dyskinesia with few side-effects. Amantadine is a non-selective NMDA antagonist. Amantadine, combined with levodopa, can treat dyskinesia without causing other health hazards (Braak et al., 2003). It was found in a research that amantadine was efficient in preventing dyskinesia by nearly 45 percent (Thomas

et al., 2004). For this success, extended release amantadine preparations have been developed for better results.

2.2 Early stage Non-motor symptoms Treatment

PD is usually considered to be a movement disorder. However, there are some non-movement indications that can contribute to the cause of this neurodegenerative disease.

2.2.1 Olfactory dysfunction

Olfactory dysfunction is perhaps the most prevalent indication observed during initial phase of PD. Due to smell loss in the long run, patients may suffer from cognitive decline as well. It was found in a study that more than 40 percent patients have olfactory dysfunction followed by decreased dopamine receptor binding (Jennings et al., 2014). Hypsomia cannot usually be treated with any drugs.

2.2.2 REM sleep behavior disorder (RBD)

It is a sleeping disorder in which patient suffer from sleep atonia, motor jerks and vivid dreams. RBD is usually diagnosed by polysomnography to avoid the overlapping symptoms of other sleep disorder. The initial treatment of RBD is done with clonazepam and melatonin. Clonazepam, a benzodiazepine drug, usually prevents abnormal dream behaviors associated with RBD. Though clonazepam is almost 90 percent successful in treating RBD, it can create serious side-effects as well such as alopecia, depression, memory impairment etc. (Olson et al., 2000). The patients who have contraindications to clonazepam are treated with melatonin. As melatonin is a hormone which levels increase during night time, it can induce sleep in RBD patients. Some melatonergic drugs such as agomelatine, ralmeteon and tasimelton are used to treat sleep disturbances.

Disparities in efficacy parameters were observed in RBD while using dopamine related medications. A research revealed the existence of RBD after 1 year of levodopa therapy administration (Garcia-Borreguero et al., 2002). Again, it was found in a study that greater doses of levodopa was provided to Parkinsonism patients with RBD (Özekmekçi et al., 2005). Moreover, donepezil and rivastigmine which are acetylcholenesterase inhibitors, are found to be effective in treating RBD (Carrarini et al., 2019).

2.2.3 Constipation

It is among the usual indications of PD that patients suffer from many years back before the diagnosis of this disorder. The common treatment process for constipation is in taking mild laxatives, fluid intake, physical activity and avoid anticholinergics (Ellis & Fell, 2017). Moreover, recent studies found that prebiotic fibers and probiotics show satisfactory efficacy in treating constipation of Parkinsonism patients.

2.2.4 Depression and Anxiety

About 40 percent of Parkinsonism patients suffer from depression which results in hampering the patients quality of life (Olivier Rascol et al., 2002). Usually, antidepressants are advised for managing depression. However, recently various forms of drugs are used in treating depression. Tricyclic antidepressants (TCAs) can be used in initial stage. Moreover, patients may tend to observe side-effects while treatment with TCAs such as sedation, psychosis, daytime sleepiness and adverse effects such as cognitive dysfunction or delirium (Tom & Cummings, 1998). Another drug such as Venlafaxine is suggested to be mostly effective in depression. Again, SSRIs were observed to have more efficacies in managing depression than TCAs. Patients with anxiety suffer from more adverse effects, when it is associated with depression. Anxiety affects the motor functions, standard of life and causes cognitive

disturbances in PD patients. Anxiety in PD can be decreased with Benzodiazepines, SSRIs and Buspirone (Rana et al., 2015).

2.2.5 Impulse Control disorder

It is usually observed more in younger patients and they need to be carefully treated. The main treatment procedure is discontinuing the dopamine agonist therapy and levodopa dose should be properly adjusted. However, patients may suffer from dopamine agonist withdrawal and sleep disturbances, mood swings as well (Voon et al., 2011).

2.3 Advanced stage treatment for Non-motor symptoms

Advanced treatment is required after the early stage treatment of non-motor symptoms. The prevalent non-movement features observed in the advanced stage of Parkinson's disease are psychosis, apathy, cognitive deficits, dysphagia and dysautonomic symptoms.

2.3.1 Apathy

The patients with apathy suffer from loss of motivation and reduction in emotions. Rivastigmine is used to treat apathy in non-depressed patients of Parkinson's disease. Again, dopamine agonists such as Rotigotine, Ropinirole, Piribedil are found to be effective in treating apathy. It is necessary to take precautions while prescribing these drugs bceause, impulse control disorders can also occur by the administration of these drugs (Ravina et al., 2007).

2.3.2 Dysphagia

Dysphagia is swallowing difficulty which is observed during later phases of PD. Patients with dyphagia may further suffer from malnutrition, dehydration and ingestis pneumonia. This problem remains prevalent throughout the life-time of this disease as there is no pharmacological treatment for this condition. About 80 percent of patients suffer from dysphagia throughout their lifetime (Suttrup & Warnecke, 2016).

2.3.3 Cognitive deficits

The patients with cognitve impairment suffer from executive and attentional problems, language, memory problems. Mild cognitive impairment is observed in 26 percent of PD patients (Rolinski et al., 2012) Acetylcholenesterase inhibitors (ACh-Is) such as Donepezil and Rivastigmine are used in the treatment of mild cognitive impairment. However, tremor may occur while using ACh-Is. As a result, Donepezil is usually used in patients with tremor because; it has less side-effect than Rivastigmine (Pagano et al., 2015). Dementia is observed in older PD patients. A placebo-controlled study showed that, Rivastigmine showed positive results in managing dementia with Lewy bodies (Mckeith et al., 2000).

2.3.4 Psychotic disturbances

Drug induced psychotic disturbances are observed in advanced stage patients of PD. Patients with psychosis suffer from visual hallucinations, paranoid delusions, auditory and olfactive hallucinations (Ravina et al., 2007). The dose of the dopaminergic drugs cannot be reduced, as it will not be possible to maintain the motor control properly. As a result, antipsychotic drugs have been used. However, typical antipsychotic drugs may cause motor worsening. For this reason, atypical antipsychotic drug, Clozapine is usually used. Clozapine has shown efficacy in reducing the psychotic disturbances of Parkinson’s disease (Eng & Welty, 2010).

2.4 Non-Pharmacological treatment

With the discovery of PD, the scientists have established varied way of treating the disease. Though there are wide ranges of pharmacological treatment options of this disease to mitigate the movement and non-movement indications, it is necessary to focus on the non-pharmacological interventions for better management of this disease as well. The non-pharmacological treatments do not improve the usual indications of this disease. However, they can contribute in changing the standard of life of the patients.

It is necessary to educate the patients and the caregivers at the time of initiation of the disease for better understanding of different complications associated with the disease. During the later stage of the disease, patients are more dependent on the care givers. So, by educating the caregivers about PD, symptoms like mood and fatigue can be improved in the patients (Makoutonina et al., 2010).

Physiotherapy and exercise have significant effect in the later stage of this disease. Exercise has been shown to have beneficial effect on both movement and non-movement complications (Cusso et al., 2016). Different types of exercise such as aerobics, dancing, strength training be performed in the early stages of the disorder to gain better results in movement and disability. Aerobic exercise is used to improve cardiovascular fitness (Shulman et al., 2013).Again, physiotherapists can support the PD patients in maximizing moving quality and help in minimizing complications through self-management and participation programs (Van de Weijer et al., 2018). Physiotherapy can improve gait, balance and posture of PD patients (Carrarini et al., 2019).

Various complications arise during the later stages of PD like pressure ulcer, malnutrition, dehydration, aspiration pneumonia and fall. During this time, physiotherapist can advise exercises to improve and optimize the posture. Again, dietitian can advise food chart to keep

the body strong. Moreover, speech therapy and dietary treatment are essential in treating malnutrition, dehydration and aspiration pneumonia (Van de Weijer et al., 2018).

The cognitive impairments of the patients can be treated with proper speech and language therapy. Speech therapy helps in treating hypophonia and dysarthria in in PD patients (Carrarini et al., 2019). However, randomized controlled trials are necessary for better results and accuracy. Again, speech therapy is used to treat anxiety, depression and impulse control disorders in the PD patients. This therapy helps to eradicate emotional stress and improves patient's self-management skills (Dobkin et al., 2011).

Palliative care is important to create a holistic atmosphere throughout the life of a patient. It provides support to the patient and their families through proper counseling and minimizes the disease burden and the suffering. Thus, palliative care helps in changing the standard of life of the patients (Bouça-Machado et al., 2017).

Deep brain stimulation is a surgical treatment process that can be helpful after 10-13 years of the diagnosis of the disorder. Non-invasive methods are being currently researched for stronger evidences. It was found in a study that trans-cranial magnetic stimulation may be utilized to alleviate motor problems in patients with Parkinsonism (Gilat et al., 2018). It was found in another study that in a few Parkinsonism patients dopamine-resistant freezing of gait was decreased through trans-cranial direct current stimulation method (Valentino et al., 2014)

Chapter 3

New Approaches

Parkinsonism is related neurodegeneration and depletion of dopamine neurons. According to recent researches, it has been found out that this disease is not a single disorder. Rather, it is the complex form of different genetic and environmental factors (Olanow, 2004). Different abnormalities for instance, mitochondrial dysfunction, exitotoxicity, free radical mediated damage, inflammatory change and proteosomal dysfunction are responsible in the development of this disease (A. H.V. Schapira, 2005). There have been huge successful benefits due to the discovery of various disease-modifying therapies which may provide neuroprotection to prevent the neuronal loss and disease progression. Moreover, various neuroprotective agents also contribute in the management of PD.

3.1 Neuroprotective Agents

The dopamine related agonists and inhibitors of monoamine oxidase type B (MAO-BI) have drawn attention in neuroprotection and have diminished complications of this disease. Various researches had been conducted to evaluate the neuroprotection ability of dopamine related agonists. MPTP is one of the reasons for the destruction of dopaminergic neurons, which ultimately, leads to Parkinson's disease. Non-human primates were protected against MPTP toxicity during a clinical trial with dopamine agonists (Iravani et al., 2006).

Again, inhibitors MAO-B for instance, Selegiline and Rasagiline have also shown neuroprotective activity. DATATOP study was the first clinical trial in detecting neuroprotection in PD. In this study, it was found that in a study with Selegiline (deprenyl), the administration of levodopa was delayed by 9-12 months during the initial phase of this disease (*Effects-of-Tocopherol-and-Deprenyl-on-the-Progression-of-Disabil-1993*, 1993).

The delayed disease progression was due to symptomatic effect. So, it was not fully confirmed whether symptomatic effect of neuroprotective effect of Selegiline caused the disease progression (Olanow, 2004). In different in vitro and in vivo models of this disease, Rasagiline was found to have neuroprotective effects and had shown delayed disease progression (Am et al., 2004).

Co-enzyme Q10 factor has been analyzed as it plays role in mitochondrial oxidative phosphorylation. As mitochondrial dysfunction occurs in PD, it is thought to have neuroprotective effects also (Carrarini et al., 2019).

One of the usual mutations responsible for in familial PD is LRRK2. The alpha-synuclein can be blocked through the inhibition of LRRK2. A study was conducted with LRKK antisene oligonucleotides. It was found that, the decreased levels of LRRK2 reduces alpha-synuclein inclusions and provided positive effects in preventing PD (Zhao et al., 2017).

Moreover, nicotine, the main alkaloid in tobacco, is found to be useful in preventing age-related dementias. A study was conducted where a nicotinic agonist was co-administered with low dose of levodopa in non-human primates. The results were satisfactory which showed the same level of efficacy with high dose of levodopa (Schneider et al., 1998).

Selenium, which is a trace element, has found to be effective managing Parkinsonism. Glutathione peroxidase (GSH) is an antioxidant enzyme that has role in preventing the neurodgeneration. The GSH enzyme is been activated by Selenium and thus, it has shown positive effect in delaying the neurodegeneration of dopamine neurons (Chen & Berry, 2003).

Oxidative stress is also responsible for the neurodegeneration of this disease. A strong iron chelator, called Deferiprone, which has effective part in oxidative stress and can prevent neurodegeneration related to Parkinsonism (Mann et al., 1994).

3.2 Restorative Therapies

PD vaccine is recently been developed and various animal studies have demonstrated a positive effect of the vaccine (Mandler et al., 2015). The vaccine mainly targets the abnormal alpha-synuclein protein by the stimulation of immune system. Due to this, membrane and intra-cytoplasmic aggregates are generated, which ultimately leads to neuron regeneration. The vaccine is still in clinical trials (Singh et al., 2007).

Cell transplantation is another advanced approach that play role in treatment of PD. Most of the studies have been done by using allogenic ventral mesencephalic tissue derived from human foetuses. However, these tissues are rarely obtained and optimum amount of these tissues are required for efficacious results. For this reason, Stem cells have been used alternatively that can be present in numerous amount, which will help to generate mature dopaminergic cells. The cell transplantation preclinical trials have shown satisfactory results. Though the grafts have shown satisfactory results, the survival rate of graft cell is very poor. As a result, it has become very difficult to the furthermore trials (Singh et al., 2007).

Gene therapy has recently been used to supply the PD brain with tropic factors. GDNF called glial cell-line derived neurotropic factors are proven to be beneficial in enhancing the function of dopamine (Pahnke et al., 2004) . In a study was conducted with MPTP non-human primates. GDNF was intraventricularly administered to them. The results showed that the concentration of dopaminergic neurons was increased. The motor functions were also improved without causing dyskinesia (Grondin et al., 2002). Another, pilot study was conducted with 5 PD patients. They were given intraputaminal GDNF infusions. The results also showed positive effects in preventing motor complications and dykinesias of PD. Moreover, scans in PET showed increase in uptake of flurodopa improved without causing

dyskinesia (Gill et al., 2003). However, huge amount of blinded clinical trials of GDNF were terminated as it showed negative results and different side-effects (Lang et al., 2006).

3.3 Surgical Approaches

Surgical procedures have brought a new milestone in the management process of PD. Due to the excessive use of levodopa, motor fluctuations and dyskinesia occurs. When the motor symptoms and dyskinesia gets very hard to prevent, at that time, surgical interventions bring hope in the treatment process. After 10 to 13 years of diagnosis of PD, surgical options can be used to get better results (Carrarini et al., 2019). Though surgical procedures are very useful in treating motor indications of PD, it has minimal effect on treating motor symptoms of PD (Lee & Lozano, 2018). Surgical procedures show various types of adverse effects such as infarction, seizures, brain hemorrhage and can cause death as well (Beric et al., 2002). As surgery needs various kinds of equipment, malfunctions can also be observed in equipment, viz. lead breakage, hardware failure and pulse generator malfunction (Doshi, 2011).

Different types of surgical methods have been discovered for treating PD. Tremor can be treated by thalamotomy and thalamic stimulation. In thalamotomy, thalamus of the brain is removed as it is responsible for involuntary movements. This type of surgery is rarely used because of various complications. Again, in thalamic stimulation, an electrode is inserted into the thalamus. This process does not cause incision and is useful for treating tremors (Singh et al., 2007). Dyskinesia can be reduced by pallidotomy and pallidal stimulation. Pallidotomy is a surgical method in which a part of the brain responsible for producing motor complications is removed by an electric probe (Singh et al., 2007). Levodopa induced dyskinesia can be effectively prevented by Pallidotomy surgical procedure. However, complications can be

observed in bilateral pallidotomy (Calabresi et al., 2010). Hemorrhage, damage of internal capsule and optic radiation are side-effects of Pallidotomy (Olanow, 2004).

Among all the surgical procedures, deep brain stimulation (DBS) is considered to be the best because; it is safer than other options. DBS can stimulate a high frequency of 100-180 Hz. During the earlier years, the main location for conducting DBS was the ventral intermediate (VIM) thalamic nucleus, which offered long-lasting tremor prevention (Benabid et al., 1991). Through this stimulation, long-term relief of tremors within the PD patients can be prevented (Olanow, 2004).

The appropriate surgical targets for DBS are subthalmic nucleus (STN) and internal globus pallidum (GPi) (Olanow, 2004). Through the targets STN i.e. subthalmic nucleus and GPi i.e. internal globus pallidum, DBS can ameliorate the motor complications of PD with reduced dyskinesia. A randomized, blinded pilot study was conducted with advanced stage Parkinsonism patients to compare the effectiveness and safety of STN and GPi. It was found that through both the stimulation of STN and GPi, dyskinesia was reduced to a great extent (Follett et al., 2010). The side-effects caused by DBS are paraesthesias, worsening dyskinesia, speech and gait disturbances (Larson, 2014). Moreover, new developed nano-technological devices, carbon nanochips and nanotubes can increase the safety and reduce side-effects of DBS. Recently, non-invasive procedures DBS have been making remarkable progress in PD management. Essential tremors have been treated by using lesion procedures with ultrasound. In a study it was found that motor complications of PD can be treated by another non-invasive DBS method, called transcranial magnetic stimulation (TMS) (Carrarini et al., 2019).

Chapter 4

4.1 Importance of Cure

It has been over 200 years since Parkinson's disease has been discovered (Mcdonald et al., 2018). After Alzheimer's disease, this condition is considered to be the second most prevalent neurodegenerative disease (Maetzler et al., 2009). To date Parkinson’s disease remains an incurable disorder.

Parkinson's disease is a condition of the progressive nervous system. It primarily influence motion and typically has indications such as tremor, rigidity, unstable posture (Singh et al., 2007). For the treatment of this disease, many pharmacological and non-pharmacological ways have been discovered. However, it was found that the present therapies only focus on improving the functional aspects of the patients and provides symptomatic relief. These existing therapies are very less effective in changing the neurodegenerative behavior of the disorder. With the advancement of science, scientists and researchers have discovered various drugs and methods to reduce the symptomatic aspects of this disorder. Levodopa, dopamine receptor agonists, inhibitors of Catechol-O-methyltransferase (COMT), inhibitors of monoaminoxidase-b (MAO-B) are the medicines often used to treat Parkinson's disease. To treat this condition, neurosurgical techniques such as deep brain stimulation are already being used. As there is no cure for this disease, patients have to go through these medical treatment processes in which they have to suffer from some complications and side-effects as well (Singh et al., 2007).

Although, levodopa is viewed as the most strong medication for controlling Parkinson's motor symptoms, dyskinesias, wearing-off illness and other movement inconveniences are reported by nearly 80 percent patients (Joseph Jankovic & Stacy, 2007). Moreover, it doesn't influence non-motor manifestations nor stops dopaminergic nigral neurons (Singh et al.,

2007). Again, monoaminoxidase-b (MAO-B) inhibitor and dopamine agonists are used as an alternative medication for this disease. Nevertheless, MAO-B inhibitors give a mild effect on managing this disorder (Don, 1996). Besides, dopamine receptor agonists show psychiatric disturbances and cardiovascular problems. A high-grade precision technique is deep brain stimulation (Chan et al., 2009). It might give continued advantage to Parkinson's traits; it does not stop this disease from advancing. Though many treatment options have been developed, it is not enough to cure this disorder looking at the complications above. That is why, better treatment options are important.

The patients of Parkinson’s disease are usually old. They need a caregiver to take care of them. Patients suffer from various other complications during the treatment process such as anxiety disorder, rapid eye movement sleep disorders, constipation (Savica et al., 2010). These complications are treatable; however, it is a burden for the patients.

Due to increasing use of levodopa, dyskinesia is produced in the patients. Usually, changes in the dose of levodopa cause dyskinesias. Increased doses of levodopa are associated with prolonged dyskinesia (B. Thanvi et al., 2007). Levodopa induced dykinesias (LID) produces fatigue, exhaustion, weight loss, discomfort. LID usually occurs when the disease is progressing and needs an increase in the dose of levodopa. However, dyskinesias get worsen by increasing the dose of levodopa. Again, a decreased dosage of levodopa is associated with impaired regulation of Parkinson's disease. Some methods for the prevention of LID have been recommended. However, the management process is less than satisfactory (B. R. Thanvi & Lo, 2004). As a result, better therapeutic targets and strategies need to be developed to mitigate this complication.

As an early indicative treatment of Parkinson's disease, dopamine receptor agonists are included (Thobois et al., 2005). They are mainly divided into two classes viz, a) ergolines and

b) non-ergolines. Derivatives of ergoline include bromocriptine, cabergoline, pergolide, lisuride, and non-ergoline derivatives include apomorphine, pramipexole, rotigotine (Bonuccelli et al., 2009). Both these derivatives are used to give symptomatic relief and act as an adjunctive therapy with levodopa to improve motor complications. However, dopaminergic agonists can also cause adverse effects such as hallucinations, confusions, orthostatic hypotension, found out during pre-marketing clinical trials. Again, other adverse effects such as impulse control disorder, somnolence and heart valve fibrosis were found out during post-marketed clinical trial (Perez-Lloret & Rascol, 2010). Since ergoline derivatives cause pleuropulmonary fibrosis and fibrotic heart valvular disease, they are considered as second-choice drugs in the prevention of this disease.

In addition to levodopa, COMT inhibitors are used to minimize its degradation and to improve the half-life of levodopa (Don, 1996). It is also used to reduce motor complications. The common COMT inhibitors are talcapone and entacapone which are associated with side-effects for instance, sleep disorders, dyskinesias, insomnia (Singh et al., 2007). Tolcapone is associated with fatal hepatotoxicity. As a result, entacapone is usually used to treat motor complications.

Anticholinergics for instance trihexyphenidyl or benzotropine are used to control tremor and has little influence on bradykinesia. Dry mouth, constipation, urine retention and an increase in intraocular pressure are side effects of these agents (Olivier Rascol et al., 2002). Therefore, the development of more newer and effective agents need a lot of focus (Singh et al., 2007).

Although it is not a deadly disorder, patients can die because of its complications such as traumatic falls, various types of sepsis, and aspiration of food. The most familiar cause of death with Parkinson’s is aspiration pneumonia. Advanced treatment options have been proposed, but, yet, this is not the ultimate remedy. As there are many complications of the

existing treatment process, we need advancement treatment options to mitigate the existing complications and thus, a cure is a must to give patients an improved way of life.

4.2 Cure Possibilities

Many potential pharmacological and disease-modifying therapies have been approved for the management of PD. However, as the disease progresses, the available treatments fails to put an impact in the prevention of the disease progression. Since there is no management for this disease, current drugs continue to be tested using various alternatives in clinical trials. Through the successful outcomes of the clinical trials, prevention of the disease progression or a possibility of cure can be found out. Moreover, the rapid advancement of researches in this field has made the researchers hopeful to have a potential cure in the upcoming years.

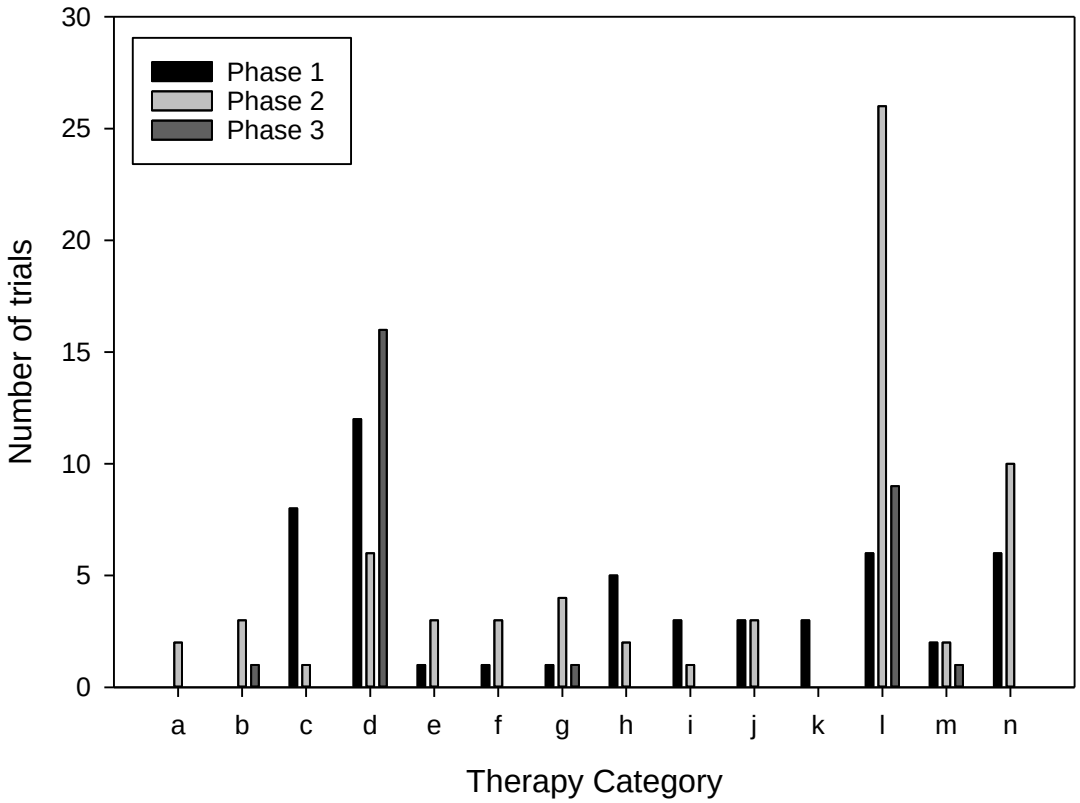

Figure 3. A graph representing vital drug trials of PD (McFarthing et al., 2020)

A study was conducted to bring all the clinical phase trials of PD in one platform. The clinical trials regarding different therapies were classified into symptomatic treatment and disease-modifying therapies. A total of 145 trials were conducted so far based on the different therapy categories (McFarthing et al., 2020). The graph above shows the functioning PD trials. Here, on the x-axis, 'a' indicates antioxidants, 'b' indicates botanicals, 'c' indicates cell therapy, 'd' indicates dopaminergic symptom relief, 'e' indicates energy and mitochondrion, 'f' indicates GBA, 'g' indicates GLP-1, 'h' indicates immunotherapy, 'i' indicates kinase inhibitor, 'j' indicates microbiome, 'k' indicates neurotropic factors, 'l' indicates non-dopaminergic symptom relief, 'm' indicates targeting alpha-synuclein and 'n' indicates other existing categories and the y-axis represents the number of different phase trials (McFarthing et al., 2020).

Different types of symptomatic treatment approaches have been discovered in these intervening years. However, none of the approaches has targeted the pathological biology of PD. At this time, novel disease-modifying therapies are necessary to bring a new change in the treatment of PD which will ultimately, help to prevent or cure the neurodegeneration of the disease (McFarthing et al., 2020).

Disease-modify therapies have brought new dimension in the treatment of PD, which can further implicate potential cure of Parkinson's disease. Neurotropic factors such as GDNF, Neurturin, PDGF-BB (Platelet derived growth factor) and CDNF(Cerebral dopamine neurotropic factor) can bring possible outcomes in reducing the disease progression of PD (Huttunen & Saarma, 2019).

Initially, GDNF was injected intra-cerebrally into monkeys which have the symptoms and pathological features of PD. The receipts showed improvements in the cardinal symptoms of PD. After that time, several clinical trials have been performed to assess the effectiveness of GDNF for enhancing the condition of this disease. In a study, GDNF injection was administered intraputamenally to 5 patients. The findings indicated promising results on the reduction of motor complications and dyskinesias of PD (Gill et al., 2003). The UPDRS motor score was improved after 1 year by 39 percent and an increase in the uptake of Flurodopa was observed in the PET. Another place-controlled phase and phase 2 studies was conducted with 50 patients. The GDNF was administered lateral ventricularly to the patients with monthly bolus for 8 months. The results were not satisfactory as no improvements were observed in UPDRS score and patients also suffered from various adverse effects (J.G. Nutt et al., 2003). Another placebo-controlled phase 2 trial was conducted with 34 patients who were in advanced stage of PD. They were intraputamenally injected with GDNF. The results show improvement in Flurodopa update but there were no significant changes in UPDRS scores (Lang et al., 2006). Another open label study is on-going right now evaluate the efficacy of GDNF in PD (Huttunen & Saarma, 2019).

NRTN which is a member of GDNF family was chosen for alternative clinical trials. A phase 1 open-labeled study was conducted with 12 patients, by injecting them with adeno-associated virus 2-neurturin. The drug was well-tolerated and the results showed improvements in motor symptoms (Marks et al., 2008). Another phase 2 sham-surgery controlled study was conducted with AAV2-neurturin. However, the results were not satisfactory (Marks et al., 2010).

Active PDGF-BB dimer is formed by growth factor PDGF. Restorative effects have been shown by PDGF-BB through both in vitro and in vivo tests in the dopamine system. PDGF-BB infusions were administered in 12 patients in a randomized phase 1 and 2 clinical trial.

The results were satisfactory as PDGF-BB was safe and well-tolerated. After 3 months follow-up, improvement in UPDRS mother scores was established (Paul et al., 2015).

CDNF(Cerebral dopamine neurotropic factor) is another newly discovered growth factor that is currently on clinical trials (Huttunen & Saarma, 2019). Most of the growth factors have shown positive impacts in ameliorating the motor complications of PD in their clinical trials of phases 1 and 2. So, it is necessary to perform more clinical trials for more accurate results.

There are other disease-modifying therapies which are capable of slowing down the continuation of the disease. In the above mentioned graph, 4 kinase inhibitors have been shown. One of the studies was with LRRK2 kinase inhibitor. Studies show that LRRK2 inhibitors are capable of bringing neuroprotection (West, 2017). Again, the other 3 clinical trials were with c-Abl which is protein kinase inhibitors. The c-Abl protein kinase inhibitor also showed satisfactory results in regulating neuroprotection in PD (Lindholm et al., 2016). GLP-1 agonists have also shown promising results in enhancing neuroprotection in PD models. The phase 2 clinical trial of Exenatide have provided satisfactory results in neuroprotection (Athauda et al., 2017). Studies of immunotherapy drugs against alpha-synuclein have shown positive outcomes. Immunotherapy has potential in modifying the disease progression through the interpretation of alpha-synuclein (George & Brundin, 2015).

The overview of all the clinical trials gives an overall understanding of different therapies, encourages and inspires the scientists to implicate more clinical trials and researches in the upcoming years. Most of the completed Phase 1 and Phase 2 trials have provided more encouraging results. Moreover, the completed clinical trials of phases 1 and 2 need to go for more clinical trials to give a more profound knowledge on the new discovered therapies which can help preventing the disease progression and will give a clear idea to find a cure.

Chapter 5

Conclusion

This review gives an outlook on the pharmacological and non-pharmacological treatment approaches of PD. In this review, the pharmacological treatment approaches are explained on the basis of early, advanced and complicated stages for improving the motor and non-motor symptoms of this disease. This will give a clear knowledge of the drugs, to use them effectively in different stages of the treatment process. A better presentation of the non-pharmacological treatment approaches based on the symptoms of PD is also explained in this review. The conventional treatment with levodopa therapy only focuses on improving the motor complications and its excessive use causes motor fluctuations. The management of motor fluctuations caused by levodopa is being explained in the complicated stage treatment part of the review. This review also reflects on the recent advanced treatment approaches, for instance, surgical procedures, neuroprotective agents and restorative therapies, which are used for preventing continuation of the disease and regeneration of dopaminergic neurons. Moreover, new discovered drugs and disease-modifying therapies are being analyzed through the concept of clinical trial to address a possibility of cure in future. Scientists and researchers should concentrate on the new advancements to bring a potential cure of Parkinson’s disease.

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