“A Review on Parkinson’s Disease”

[In the partial fulfilment of the requirements for the degree of Bachelor of Pharmacy]

Submitted To

The Department of Pharmacy,

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Approval

This project paper, "**A Review on Parkinson's Disease**" is submitted to the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, has been accepted as satisfactory for the partial fulfilment of the requirements for the degree of Bachelor of Pharmacy and approved as to its style and contents.

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Abstract

The neurodegenerative condition Parkinson's disease (PD) is rather prevalent. It is progressive and neurodegenerative, with symptoms including impaired balance, walking, and falls even at the time of diagnosis. Variables such as age, family history, pesticide exposure, and environmental factors are linked to the development of idiopathic Parkinson's Disease, which is caused by the pathophysiological loss or degeneration of dopaminergic neurons in the substantia nigra of the midbrain. Improvements in the knowledge of the disease's pathophysiology have been made in recent years. In addition to the more well-known motor problems, it has been more clear that the condition may also be linked to major non-motor abnormalities. There is mounting circumstantial evidence that certain existing therapies for PD may have a neuroprotective impact, although this has yet to be definitively shown. Even though PD has no known cure, it may be managed in a number of ways if caught early. Additional therapeutic options become available as the illness advances; nevertheless, late-stage motor problems and non-motor symptoms remain very tough to manage, and future discoveries in PD are anticipated to center on the notion of disease-modifying medications that provide neuroprotection.

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List of Abbreviation

Sr. no.	Abbreviation	Stands For
1	PD	Parkinson's Disease
2	UPS	Ubiquitin Proteasome System
3	PSP	Progressive Supranuclear Palsy
4	DLB	Dementia with Lewy Bodies
5	MRI	Magnetic Resonance Imaging
6	CT	Computed Tomography
7	EMG	Electromyography
8	EEG	Electroencephalography
9	SPECT	Single Photon Emission Computerized Tomography
10	DAT	Dopamine Transporter
11	PET	Positron Emission Tomography
12	MAO-B	Monoamine Oxidase-B
13	COMT	Catechol O-Methyltransferase
14	AADC	Amino Acid De-Carboxylase
15	DBS	Deep Brain Stimulation

Chapter One
Introduction

1. Introduction

1.1 Parkinson’s disease

Those parts of the brain responsible for movement, posture, and equilibrium are particularly vulnerable to the debilitating effects of Parkinson's disease. Due to the wide variety of symptoms, not everyone who has the ailment has the same difficulties. Even while PD develops with time and affects everyone differently, it is still a very individual illness. Symptoms of Parkinson's disease may vary in intensity from patient to patient, and not everyone who has the disease will experience all of them. In addition, everyone develops at their own pace. However, doctors have identified distinct phases that characterize the development of the illness. Medical professionals all around the globe utilize the Hoehn and Yahr Scale, which consists of five phases, to categorize patients for scientific investigations. [1]

1.2 History of Parkinson’s disease

Parkinson's disease is named for the British physician who published the first book on the subject in 1817. Parkinson termed this condition "paralysis agitans" (or "the shaking palsy"). Earthquakes were called "agitans" in his day. It was formerly thought to be a disease of weakness and tremors since the word "palsy" meant "weak" and the word "paralysis" meant "paralyzed," but as we will see, this is not quite accurate. In addition to his scholarly works on geology and his development of the truss, which helped people with hernias before surgery was accessible, Parkinson was well-known in his day for his political actions as an advocate for the underprivileged.

It took a another 50 years for most doctors to concur that the main brain alterations seen in persons with Parkinson's disease were in fact the illness process itself. The discovery of dopamine's (di-ortho-phenylalanine) central role in the brain in the early 1960s led to the development of L-Dopa, the first effective therapy for Parkinson's disease. Prior to this, there was a severe lack of effective therapy options for Parkinson's disease. It was Parkinson who suggested inserting cork into a vertical incision at the back of the neck to prevent the wound from healing. He reasoned that the infection's pus was a representation of the infected fluids themselves, and that draining it would help the patient. Predictably, this was never a huge hit with the public. L-Dopa, while having a far

superior scientific explanation, was first unpopular because it produced so much nausea and vomiting. Sinemet (sine=without, emesis=vomiting) is a combination drug consisting of carbidopa and levodopa. It was created shortly after carbidopa to counteract the side effect of vomiting. In the fight against Parkinson's disease, this medication is still the gold standard.

Presence of PD is widespread. Between half a million and one million Americans are afflicted by this condition, or around 1 percent of the population over 60. As a degenerative neurological ailment, it is second only to Alzheimer's in prevalence in the United States. Only one million individuals call Rhode Island home, yet among them are an estimated 2,000 people living with PD. Despite a great deal of study, the causes of PD remain unknown. And there are instances when we have problems identifying it.

As research into Parkinson's disease progresses, we learn more and more about the complexity of the illness. Most people consider of it as a problem with physical coordination and balance, but it may also have an impact on how a person acts. It's only been in the last 15 years or so that medical professionals have begun to look into this crucial topic. Up until recently, treatments for PD have only focused on the movements, but we now have a more realistic, holistic view of the disorder. As we cope with a disease for which there is currently no cure, improving patients' quality of life has taken on increased importance. [1]

1.3 Types of Parkinson’s disease

The two main subtypes of Parkinson's disease are those characterized by tremor predominance and by postural instability or gait disorder, respectively. Below, I'll compare and contrast two distinct Parkinson's disease presentations.

1.3.1 Tremor predominant Parkinson's

The whole body trembles or shakes. Although this kind of Parkinson's disease often manifests in older individuals, it sometimes manifests in younger individuals and advances more slowly. The likelihood of cognitive (brain function) deterioration is smaller, but the tremors may be more humiliating and harder to cure than other symptoms.

1.3.2 People with postural instability

Walking and balancing difficulties are exacerbated in those with this disease. Although it strikes at a later age, this form of Parkinson's disease often advances rapidly. There is an increased risk of cognitive impairment, even if persons have fewer or no tremors at all. [2]

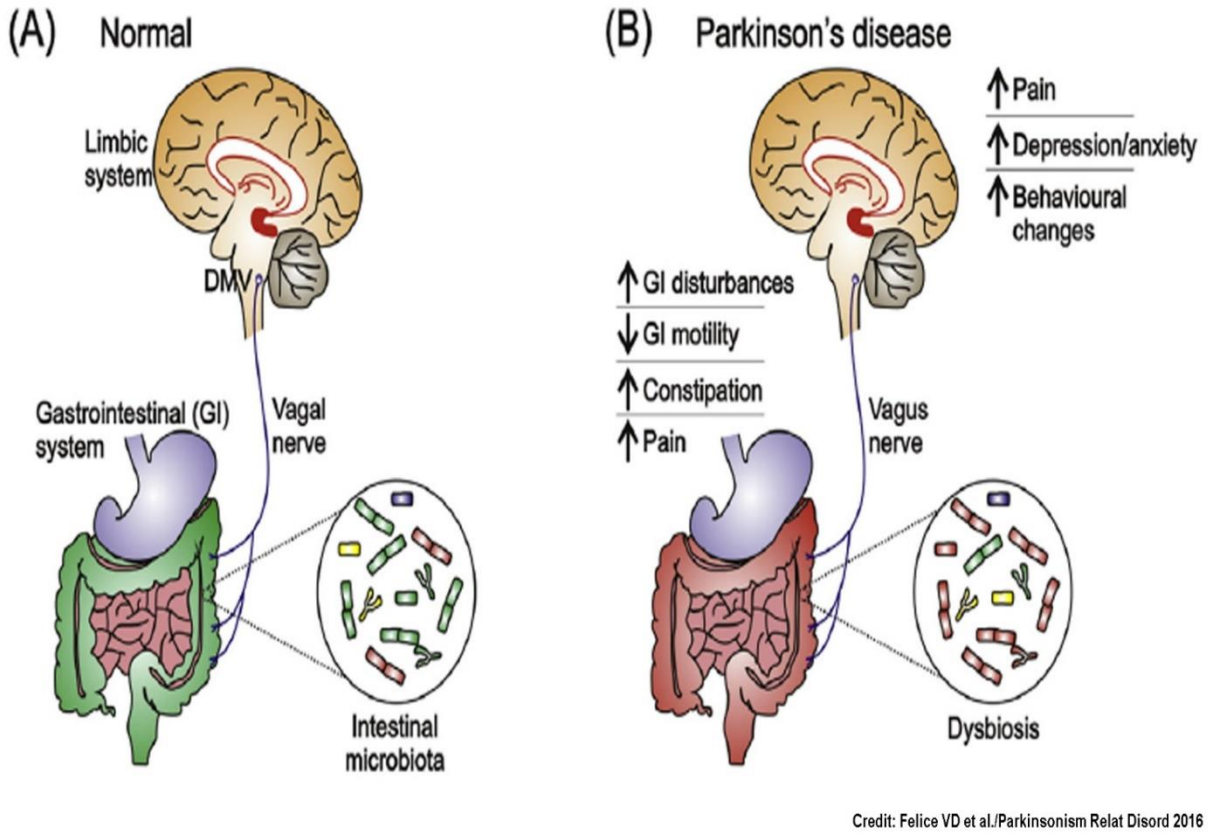

Figure 1.1 Significant difference between normal and PD patients (A) Normal and (B) Parkinson's disease

1.4 stages of Parkinson’s disease

1.4.1 Stage one of Parkinson’s disease

In the first, earliest stage of PD, symptoms are mild, affecting only one side of the body (unilateral involvement), and typically cause little to no functional impairment. Parkinson's disease (PD) often goes undiagnosed in its early stages because the symptoms are so subtle. Tremor, especially intermittent tremor of one hand, rigidity, or one hand or leg feeling more clumsy than the other are all possible symptoms in stage one. It is very challenging for a doctor to make a diagnosis at this stage, so he or she may wait to see if the symptoms worsen.

1.4.2 Stage two of Parkinson’s disease

Stage 2 PD is still considered early illness and is characterized by symptoms on both sides of the body (bilateral involvement) or in the midline without affecting balance. As much as a year or more may pass between stages one and two. Stage two PD symptoms include a loss of facial expression on both sides of the face, decreased blinking, speech abnormalities (such as a soft voice, monotone voice, fading volume after starting to speak loudly, slurring speech), stiffness or rigidity of the trunk muscles (which can cause pain in the neck or back), a stooped posture, and a general slowness in all activities of daily living. At this point, however, the person is still capable of carrying out basic activities of daily life. If the patient has a tremor at this point, the diagnosis may be straightforward; however, if the tremor was missed in stage one and the only symptoms in stage two are slowness or a lack of spontaneous movement, PD may be misunderstood as just increasing age.

1.4.3 Stage three of Parkinson’s disease

The third stage, which occurs halfway through the disease's progression, is marked by a decrease in mobility and an inability to maintain balance. Falls are prevalent at this age because of impaired balance caused by a lack of the fast, reflexive, and involuntary modifications essential to avoid them. Stage three PD is characterized by the presence of all other PD symptoms and is usually diagnostically conclusive. To evaluate whether a patient has difficulty keeping balance and falls backward at this point, a doctor would often stand behind them and gently tug on their shoulders

(the physician of course will not let the patient fall). During this third stage, the patient still does all of their own personal care, including dressing, bathing, and eating.

1.4.4 Stage four of Parkinson's disease

At this late stage, PD may significantly limit a person's daily activities. Patients in the fourth stage of PD may be able to walk and stand alone, but they are severely impaired. For mobility, many people rely on walkers. The patient is now reliant on others for help with basic daily tasks and can no longer live independently. In this phase, the individual need assistance with activities of daily life. It is still considered stage three if the patient can continue to live independently.

1.4.5 Stage five of Parkinson's disease

The fifth stage is the most severe and is characterized by the inability to stand or turn without assistance, a propensity to fall, and a tendency to freeze or stumble when walking. At this point, the patient needs round-the-clock care to lower the danger of falling and aid with all everyday tasks. The patient may also have delusions or hallucinations in stage five. Even while the symptoms become worse with time, it's important to remember that some PD patients never make it to stage five. Additionally, each person takes a varied amount of time to get through the various levels. Not every symptom will manifest in every person. For instance, a person's equilibrium could be unaffected by a tremor. Additionally, there are medications that are effective at every stage of the illness. The effectiveness of the medication, however, in reducing symptoms increases with earlier diagnosis and earlier stage of the illness. [4]

1.5 Prognosis

Currently, we solely refer to treating the symptoms of Parkinson's disease when we speak about treatment. The illness itself affects the brain's nerve cells, as well as certain nerve cells outside the brain to a lesser degree. Our present treatments have been found to reduce symptoms, i.e., the tremor, stiffness, slowness, movement, etc. by aiding in the restoration of a more normal chemical balance in the brain. However, we haven't truly changed the mechanism that is producing the harm. Treating a cold is pretty comparable to it. We take drugs to lessen the discomfort of the sore throat, the cough, and the hurting, but nothing has been done to stop the infection that is causing the issue.

Over the following days, our body fights it off as we take comforting drugs. Naturally, it is unfortunate that PD is a chronic condition.

Many people think that five years after starting Parkinson's disease drugs, they cease functioning. I've met physicians who said they learned this in medical school, and this is really something that is written in numerous places. That is FALSE. Parkinson's disease treatments may not be able to keep up with the illness's development. They can begin to have negative consequences. However, they always continue to be useful. It is true that sometimes, and this is very seldom, when the sickness has become quite bad, the meds cease working. [5]

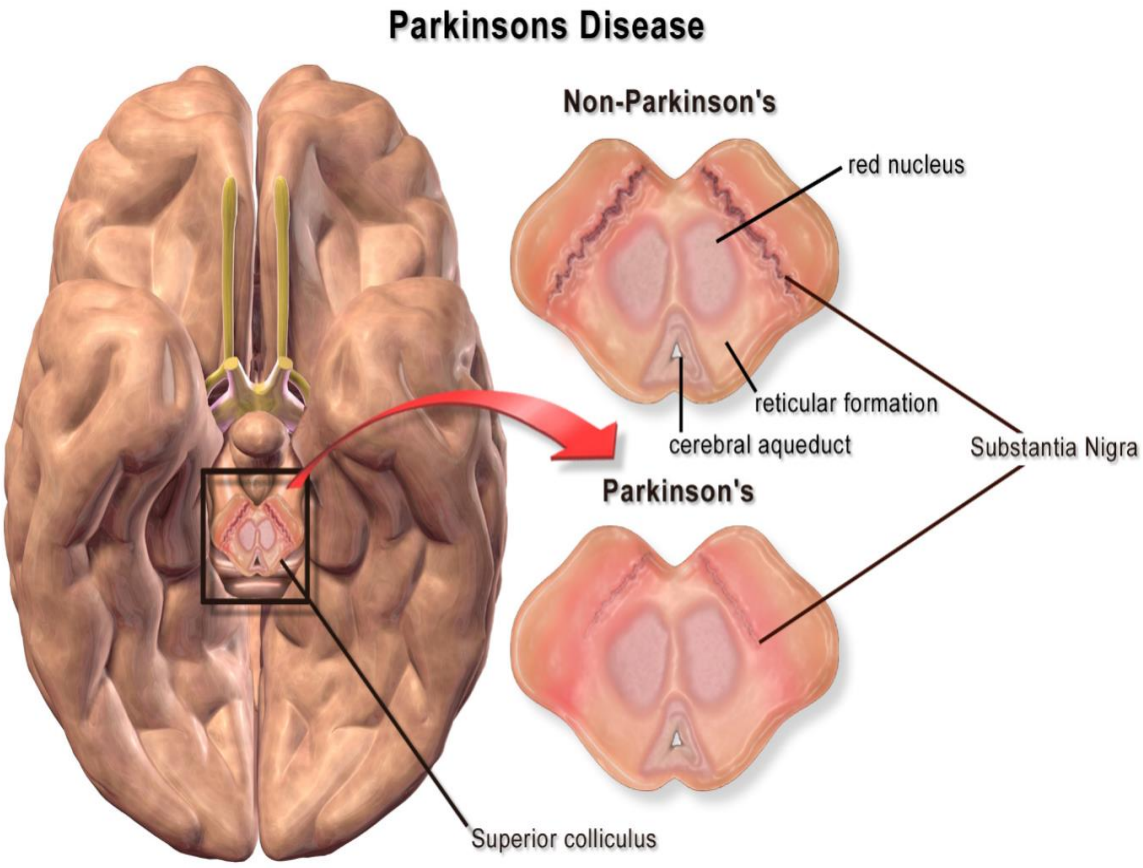

Figure 1.2 Parkinson Disease

1.6 Epidemiology of Parkinson's disease

1.6.1 Prevalence

Prevalence is the percentage of all current PD patients in a population at any particular period. According to door-to-door studies, the crude prevalence of PD ranges from 100 to 250 in North America and Europe and from 15 to 657 per 100,000 people in China. For similar populations, the prevalence estimates obtained using this approach are higher than those obtained using other methods. Socioeconomic variables and those that influence survival rate might easily have an impact on prevalence.

1.6.2 Incidence

The number of new cases of PD in a population during a certain time period is known as its incidence, which is a more precise measure of frequency than simple prevalence. When compared to other variables that impact the likelihood of surviving a sickness, this one is very resilient. However, it is challenging to get reliable estimates of the prevalence of PD since the disease often has a protracted latent phase before revealing itself clinically and has a very sluggish clinical course. Rates of PD have fluctuated widely over the last four decades, from 1.5% per 100,000 in China in 1986 to 14.8% per 100,000 in Finland in 1968-1970. Variation may be attributable to factors unique to each research, such as diagnostic criteria and case ascertainment procedures.

1.6.3 Age distribution

The rates of occurrence and prevalence of PD are highly age-dependent. The incidence of PD decreases before age 50 and then rises consistently into the eighties and nineties. Some studies have shown a reduction among the extremely old, which may represent diagnostic and ascertainment challenges, but is more likely due to the small size of this population.

A recent research conducted in Yonago City, Japan, found that the prevalence rose from 80.6 (per 100,000 population) in 1980 to 117.9 (per 100,000 population) in 1992, but that the prevalence after adjusting for age and sex reduced from 103.9 (per 100,000) to 99.5 (per 100,000). After comparing the years 1980 and 1992, there was no statistically significant variation in the overall

incidence rate; however, when adjusting for age, the incidence rate was lower in 1992 among individuals under the age of 55 than it had been in 1980. According to the results of this research, the aging of the population may be a major contributor to the rise in incidence.

1.6.4 Gender differences

Although there is more variation due to differences between the sexes than there is due to the correlation between age and PD, most studies show that men have a 1.2:1 to 1.5:1 prevalence of the disease compared to women.

1.6.5 Ethnic distribution

The racial makeup of the surveying population may have an effect on the reported prevalence and incidence of PD from country to country. The frequency is highest among whites in Europe and North America, where there are between 100 and 350 cases per 100,000 persons. Rates are around one-fifth to one-tenth of those in whites among Asians in Japan and China and black Africans. A door-to-door screening in Mississippi, USA, found no statistically significant difference in PD frequency between whites and blacks after adjusting for age.

Meanwhile, two studies found that the rates of PD in people of Asian descent in the United States and African descent in the United States were comparable to those in people of European descent in the United States. The prevalence of PD was found to be 119 per 100,000 in a door-to-door survey conducted on the island of Kinmen, Taiwan, which is comparable to a white community but much higher than that found in earlier studies of Asian populations. It's possible that these findings are due to environmental influences rather than racial ones. Prevalence estimates for Parkinson's disease in people of African descent should take into account the potential biases introduced by inadequate case ascertainment and high selective mortality..

1.6.6 Time trends

An annual incidence of PD increased from 9.2 per 100,000 for the interval between 1935 and 1944 to 16.3 per 100,000 for the interval between 1975 and 1984, according to a population-based study

evaluating the incidence of PD in Olmsted County, Minnesota from 1935 through 1988. However, Zhang and Roman performed a meta-analysis by adjusting reported data with a single standard population and found no change in the prevalence or incidence of PD over a 40-year time period. For now, it is challenging to reliably evaluate shifts in PD time trends because there are so few longitudinal data for PD incidence and the data may lack consistency for diagnostic criteria and study methods over time.

1.6. 7 Geographic distribution

It has been noted that the incidence of PD varies among regions. In China, the crude prevalence is 15 per 100,000, in India it is 328 per 100,000, in Mississippi, USA, it is 131 per 100,000, and in Argentina it is 657 per 100,000, according to door-to-door surveys. A recent research in the United States looked at where PD deaths were being reported and found that there were significant decreasing gradients for white mortality rates from north to south, regardless of gender, but no such gradient from west to east. According to data on prevalence, the pattern Zhang and Roman observed in the regional distribution of incidence seems to be consistent with. It's possible that this indicates the role of the environment in However, reports have surfaced of notable geographical variances, namely northwest to southeast gradients in both Canada and the United States, which may play a role in producing PD.

1.6.8 Mortality

Although the life expectancy of PD patients has been prolonged, the life span of PD patients is still somewhat less than that of the general population. Improved survival as the result of introducing effective symptomatic therapy and decreased or delayed mortality from other disorders may partly account for the decreased mortality in younger people.

Tanner and colleagues reported that relative survival for people with PD diagnosed before age 60 is similar to that for the general population, but relative survival is less than expected for those who are older at diagnosis. A study examining prognosis of PD patients in Japan showed that the most common cause of death for all patients, regardless of age, was pneumonia. This suggests that

in addition to providing improved antiparkinsonian therapy to patients, PD-related conditions such as pneumonia should also be treated more aggressively. [6]

1.6.9 Survival

Life expectancy for people with PD has increased, although it remains shorter than the average lifespan. The drop in death rates among the young may be attributable, in part, to the introduction of effective symptomatic treatment and the reduction or postponement of mortality due to other conditions.

Patients with PD who are diagnosed before the age of 60 have a survival rate that is comparable to the general population, whereas patients who are diagnosed later in life have a survival rate that is lower than predicted, as documented by Tanner and colleagues. According to a Japanese research on the long-term outcomes of PD patients, pneumonia is the leading cause of mortality across all age groups. As a result, it's clear that people with Parkinson's disease need more than just better antiparkinsonian medicine; they also need their PD-related diseases, such pneumonia, treated more aggressively. [6]

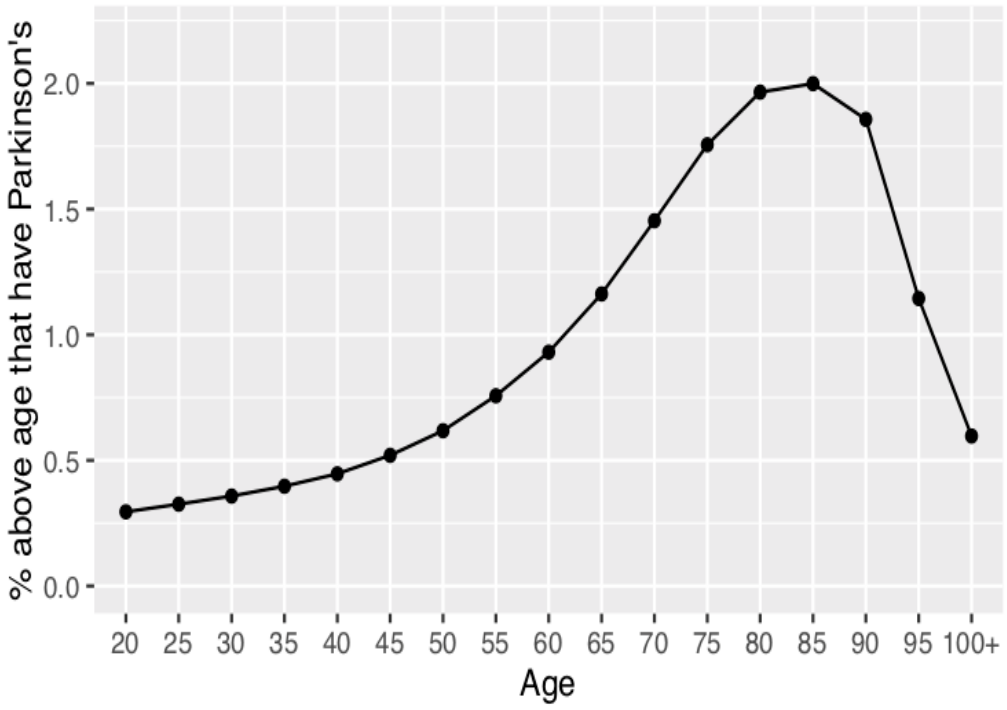

Figure 1.3 Percentage of population above each age that has Parkinson's

Chapter Two

Etiology and Pathophysiology

2.Etiology and pathophysiology of Parkinson’s disease

2.1 Early signs

Among the first Parkinson's symptoms are:

One may experience a trembling in the hands as a result of movement.

People with poor coordination and balance are more likely to drop whatever they are carrying. This might make them more prone to falling.

- ✓ Gait: The individual's posture shifts, giving the impression that they are rushing. Another possible side effect is a shuffling walk.
  Changes to the nerves that regulate face muscles may cause expressions to become permanent.
- ✓ Voice: The individual may be experiencing a tremble in their voice or speaking more quietly than usual.
  It's possible that handwriting may become more condensed and smaller.
  One such indicator is a diminished capacity to smell.
- ✓ Sleep disturbances: These occur often in people with Parkinson's and may be an early indicator of the disease. This might be exacerbated by restless legs.
- ✓ Mood swings, especially sadness, are also prevalent, as are difficulties with eating and swallowing, passing urine, constipation, skin issues, and falling asleep.

2.2 The importance of recognizing early symptoms

The first symptoms of Parkinson's disease are often dismissed as inevitable consequences of getting older. Because of this, they might not go for assistance.

A person with Parkinson's disease has a better chance of benefiting from treatment if they start taking it before the disease has progressed too far. Because of this, it's crucial to catch any problems early on.

The effectiveness of treatment decreases if it is delayed until after the patient has developed noticeable symptoms. [7]

Moreover, a number of other conditions can have similar symptoms.

These include:

- drug-induced Parkinsonism
- head trauma
- encephalitis
- stroke
- Lewy body dementia
- corticobasal degeneration
- multiple system atrophy

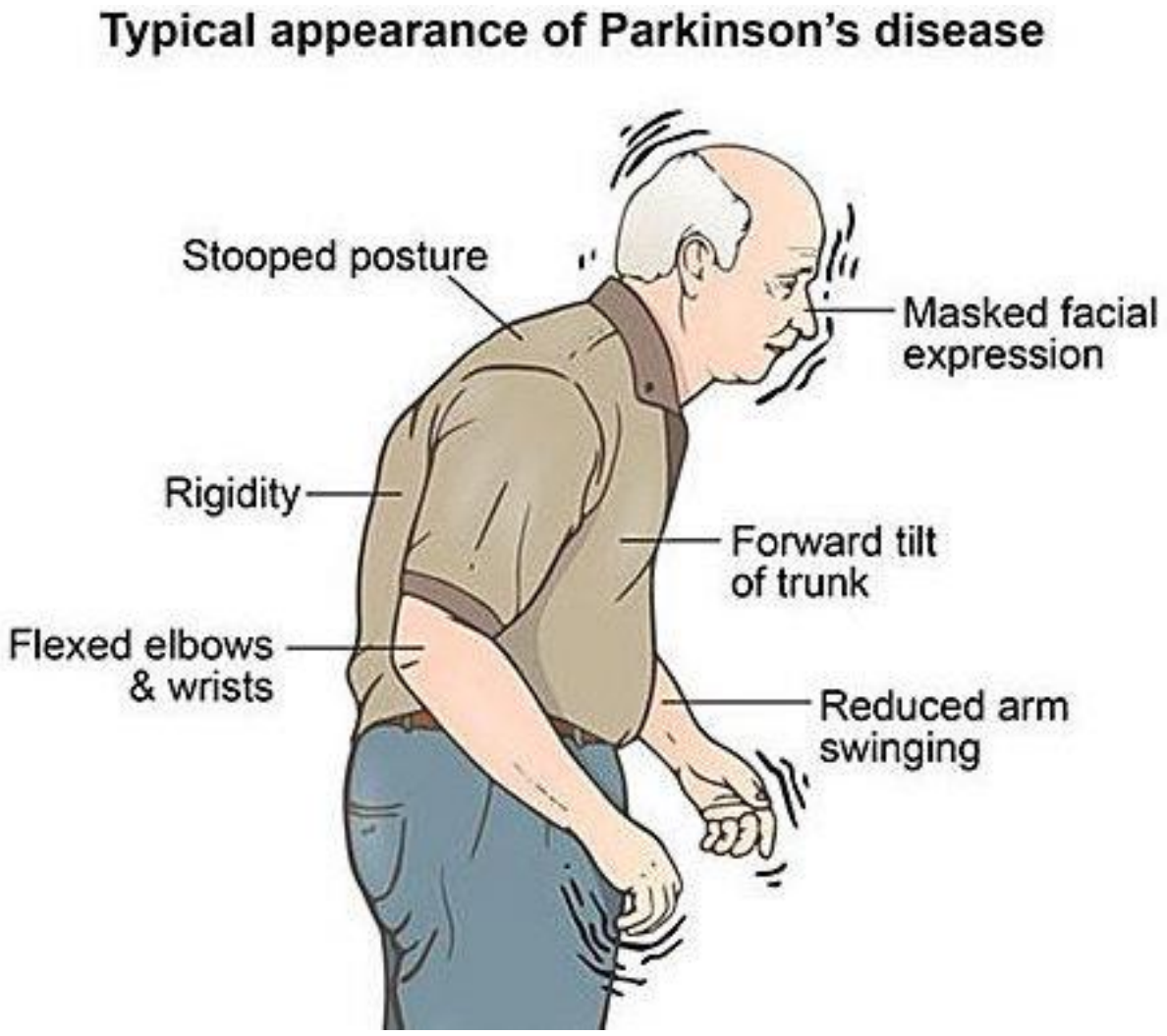

Figure 2.1 Typical appearance of Parkinson's disease

2.3 Pathophysiology

Cell death in the ventral par's compacta region of the substantia nigra is a characteristic of the pathology of Parkinson's disease. At death, this area of the brain has lost between 50 and 70 percent of its neurons, compared to the same area in healthy people. Pathological alterations in PD3 have first been described in the olfactory bulb and medulla oblongata/pontine tegmentum. Patients in Braak stage 1 and 2 have no noticeable symptoms at this point. The substantia nigra, as well as other regions of the midbrain and basal forebrain, get affected in Braak stages 3 and 4. The neocortex is the last region to show signs of pathology.

The presence and location of lewy bodies provides the basis for this disease classification. The pathological characteristic of PD is the presence of Lewy bodies. Neurofilament proteins and proteolytic enzymes are found inside these -synuclein-immunoreactive inclusions. Ubiquitin, a heat shock protein, is one of those proteins that helps direct the breakdown of other proteins. Some familial types of PD characterized by the presence of lewy bodies are caused by mutations in the -synuclein gene. When the parkin protein is mutated in children, they acquire parkinsonism without the presence of lewy bodies, which suggests that parkin has a significant function in the maturation of the lewy body. Parkin has been found to have a role in the development of lewy bodies by promoting ubiquitin binding (ubiquination) to other proteins, including the -synuclein interacting protein synphilin-1. Lewy bodies are a pathological feature of Parkinson's disease (PD) and Dementia with lewy bodies (DLB), however they are not present in any other neurodegenerative disorder.

As single gene abnormalities in PD have been discovered, researchers have begun to investigate the ubiquitin-proteasome system (UPS) as a possible contributor to cell death.

5 Intracellular proteolysis, along with many other vital cellular processes, rely on the UPS to function properly. How? By getting rid of proteins that are no longer needed by the cell. Abnormal aggregation of proteins, such as -synuclein, a key component of lewy bodies, is caused by UPS failure. The olfactory bulb is one of the earliest brain regions to show LB deposition in early PD. In this light, it is intriguing to consider the possibility that LB formation is integral for the activation of pathways leading to neuronal dysfunction and death, as alterations in smell and taste are often among the earliest clinical features in PD.

Several mutations in genes encoding proteins involved in the ubiquitin-proteasome system have been found in Parkinson's disease, adding weight to the theory that UPS plays a role in this neurodegenerative disease.[8]

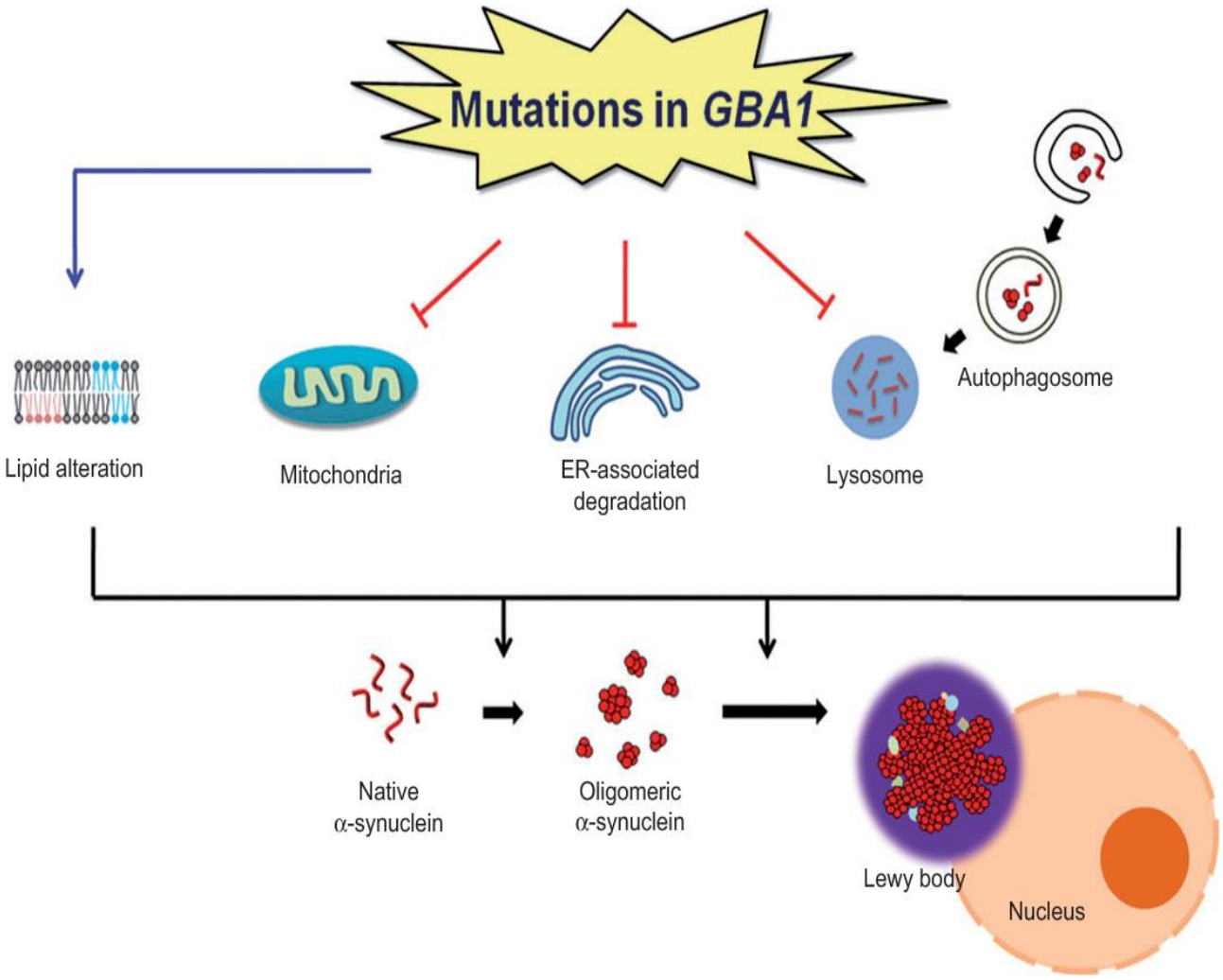

Figure 2.2 Mutations in GBA1

2.4 Environmental factors

It has been difficult to pin down specific environmental risk factors for Parkinson's disease (PD). Some epidemiological research have indicated an association between exposure to pesticide usage and wood preservatives, which might explain why people in rural areas have a higher chance of developing PD. Cigarette smoking is the only constant environmental component, and there is a substantial negative link between the two. Additionally, environmental pollutants may play a role in triggering PD-related mitochondrial dysfunction.

2.5 Clinical diagnosis of PD

bradykinesia, stiffness, and rest tremor are the hallmark symptoms of PD. All of these may not be there. One possible symptom is postural instability, however regressive postural instability at a young age, especially in conjunction with a history of falls, is more indicative of progressive supranuclear palsy (PSP). In PD, the symptoms tend to manifest in an asymmetrical fashion. The clinical diagnosis may look clear cut; nevertheless, postmortem investigations have showed a different diagnosis in as many as 25% of people with PD who were first diagnosed by general neurologists. Importantly, patients identified in specialized movement disorder clinics had a far lower rate of misdiagnosis, adding weight to the need for prompt referral to these clinics.

However, it is important to inquire about a diminished sense of smell since it may be one of the first indications of early PD. Later stages of the illness may include hypophonia, salivary drooling (due to decreased swallowing), and postural reflex dysfunction. In many cases, the non-motor symptoms of the condition grow more challenging as the disease worsens. Inquiring about depressive symptoms is beneficial since they affect roughly 40% of PD patients. Examples of more prevalent causes of alcohol-related parkinsonism symptoms. It's also possible that you're experiencing trembling in your head or voice. There should be no indication of stiffness or bradykinesia on examination, and the tremor may be inherited in an autosomal dominant pattern. Some individuals formerly labeled as "benign tremulous PD" may really have adult onset dystonia, which may present with asymmetrical rest tremor despite the absence of little signs of dopaminergic defecit. [8,9]

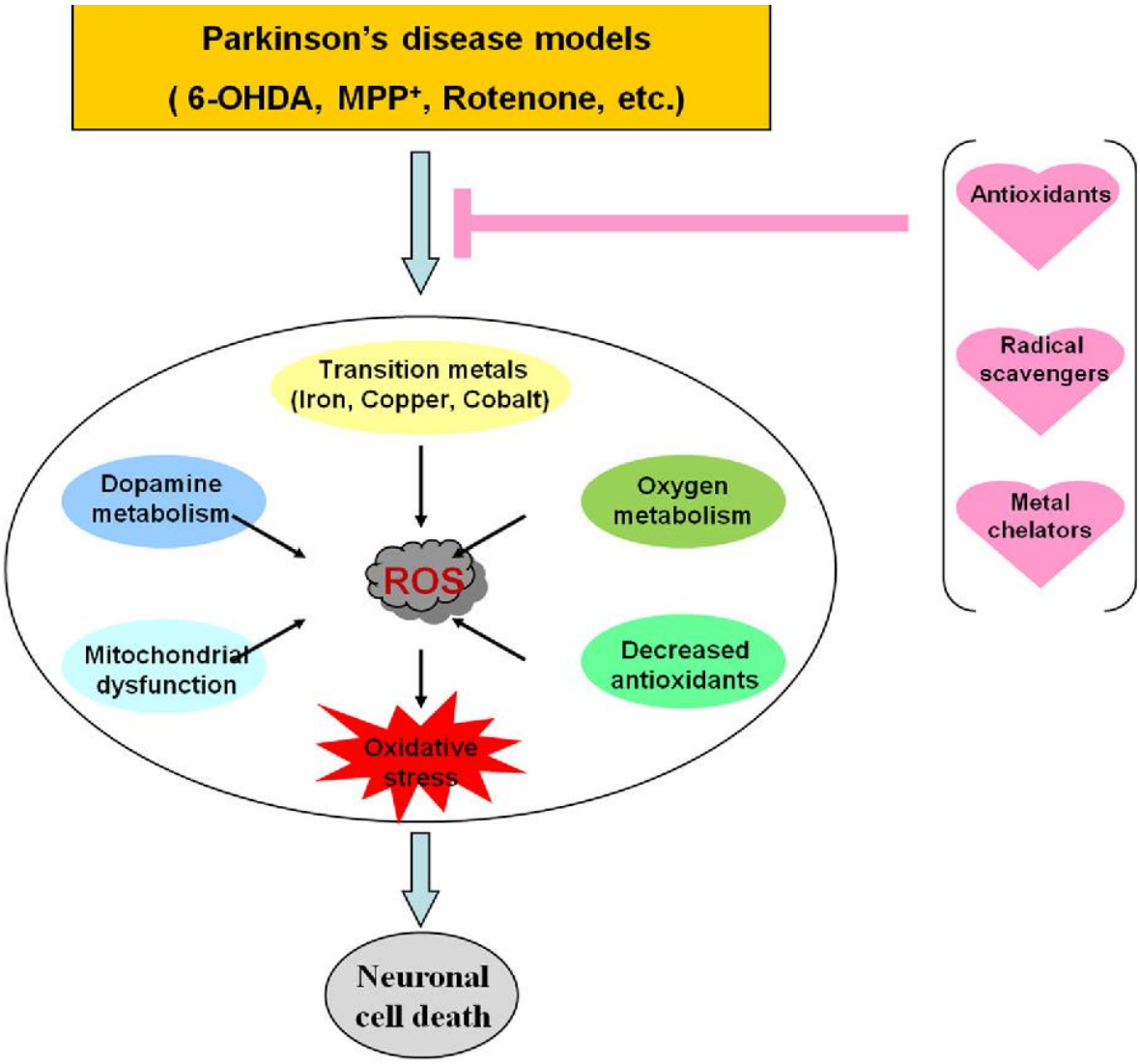

Figure 2.3 Parkinson's disease model

2.5.1 Diagnosis of a parkinsonian syndrome

One or more of the following, in addition to bradykinesia (slowness of beginning of voluntary movement with increasing decrease in speed and amplitude of repeating actions): I muscle stiffness; (ii) rest tremor at 4–6 hertz; and (iii) postural instability not due to main problems with vision, balance, cerebellum, or proprioception.

2.5.2 Exclusion criteria for PD

Table 1.1 Exclusion criteria for PD

History of repeated strokes with stepwise progression of parkinsonian features
History of repeated head injury
History of definite encephalitis
Oculogyric crises
Neuroleptic treatment at the 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's sign
Presence of cerebral tumour or communicating hydrocephalus on CT scan

2.5.3 Supportive criteria for PD (three or more required for diagnosis of definite PD)

Table 2.2 Supportive criteria for PD

Unilateral onset
Rest tremor present
Progressive disorder
Persistent asymmetry affecting side of onset most natures
Excellent response (70–100%) to levodopa
Severe levodopa-induced chorea
Levodopa response for 5 years or more
Clinical course of 10 years or more

Several additional clinical symptoms should be included as well. Micrographia, a shift in handwriting that typically occurs early on, is characterized by a lack of facial expression and a decrease in the speed of penning. One such early and helpful diagnostic sign is a lack of arm swing on one side. There is no indication that a glabellar tap is especially sensitive or specific.

Table 2.3 Differentiating commoner causes of Parkinsonism.

Condition	History	Clinical features	Investigations	Management
Drug-induced parkinsonism	Previous exposure to drugs mainly neuroleptic treatment and anti-emetics	May be associated with akathisia and oro-mandibular dystonia	Based on history	Discontinue offending drug. Anticholinergic drugs may be helpful for tremor
Multisystem atrophy	Parkinsonism and or gait unsteadiness with or without autonomic dysfunction	Orthostatic hypotension, absence of tremor, symmetrical signs, cerebellar features, erectile dysfunction, poor response to levodopa	MRI brain, sphincter EMG	Levodopa trial, amantidine measures to control postural hypotension, e.g., fludrocortisone
Progressive supranuclear palsy	Early falls backwards, cognitive or behavioural changes	Gaze palsy (down more than up), axial rigidity, frontal and pyramidal signs, poor response to levodopa	MRI brain	Levodopa trial
Normal-pressure hydrocephalus	Urinary incontinence, ataxia, cognitive impairment	Dementia festinating gait	CT or MRI brain, therapeutic lumbar puncture	Evaluate for ventriculoperitoneal shunt

Condition	History	Clinical features	Investigations	Management
Multiple lacunar strokes	Stepwise neurologicl impairment	Focal findings, sensory or motor loss	CT or MRI brain	Antiplatelet treatment, control of risk factors (e.g., diabetes, hypertension, increased cholesterol)
Cortico basal degeneratin	Associated cognitive impairment	Marked asymmetry of clinical findings, dyspraxia, cortical sensory loss, myoclonus, dystonia, alien limb phenomenon, absence of response to levodopa	EEG, psychometry	
Dementia with lewy bodies	Dementia occurring before or concurrently with parkinsonism	Visual hallucinations	MRI brain, psychometry	Consider cholinesterasae inhibitor

Although the diagnosis of PD is a clinical one, there are certain situations where investigations can prove useful. Conventional brain imaging with MRI or CT is usually not required unless an alternative diagnosis is suspected such as normal pressure hydrocephalus or vascular parkinsonism.

Differentiating PD from other conditions with normal DAT scans, such as essential tremor, dystonic tremor, neuroleptic-induced Parkinsonism, and psychogenic parkinsonism, is facilitated by single photon emission computerized tomography (SPECT) imaging using a dopamine transporter (DAT). In PD, parkinsonian syndromes, and DLB, uptake within the basal ganglia is diminished. [10,11]

Chapter Three
Diagnosis and treatment

3. Diagnosis and treatment of Parkinson’s disease

3.1 Diagnosis

Unfortunately, the diagnosis of Parkinson's disease is now impossible. Parkinson's disease may be diagnosed after a thorough neurological and physical examination as well as analysis of the patient's medical history by a specialist in disorders of the nervous system (neurologist). To diagnose your condition, your doctor may order a dopamine transporter (DAT) SPECT scan. This is helpful in confirming a diagnosis of Parkinson's disease, but the final diagnosis will be based on your symptoms and a neurologic exam. As a general rule, a DAT scan is unnecessary for the average person.

To rule out other possible causes of your symptoms, your doctor may prescribe lab testing such blood tests.

Imaging studies, such as magnetic resonance imaging (MRI), computed tomography (CT), brain ultrasonography, and positron emission tomography (PET), may be performed to rule out other diseases. Diagnosing Parkinson's disease using imaging studies is difficult.

Carbidopa-levodopa (Rytary, Sinemet, etc.) is a drug for Parkinson's disease that may be prescribed in addition to an evaluation. As taking a little quantity for only a day or two won't reliably demonstrate any improvement, you'll need to be given a much larger dose to prove its effectiveness. The diagnosis of Parkinson's disease may frequently be confirmed by the patient's response favorably to this medicine.

Parkinson's disease is a condition that might be difficult to identify. In order to monitor your progress and get an accurate diagnosis of Parkinson's disease, your doctor may advise you to see a neurologist who specializes in movement disorders for frequent checkups. [12,13]

3.2 Management of early PD

After a clinical diagnosis has been made, it is critical to talk to the patient and their loved ones about what that means. Some individuals may need more time to process and accept the news of their diagnosis. It might be quite beneficial to connect patients with local PD nurse experts and PD charity groups.

When to begin pharmacological therapy for PD may be challenging, especially in the early stages of the disease when there may be no functional loss. The severity of the physical impairment in comparison to the risks associated with drug therapy will influence the choice that should be taken with the patient's full participation. The question of whether earlier therapy increases the chance of neuroprotection is become more important. Despite many in vitro, in vivo, and human investigations, many of which used PET or SPECT imaging as surrogate measures of nigrostriatal dopaminergic activity, this issue is still unclear.

Since a result, only symptomatic treatments exist at this time, as there are no proven neuroprotective medicines.

When both the doctor and patient agree that treatment is necessary, what kind of treatment should be initiated? The patient's age, the severity of any cognitive impairment, the existence of any other medical issues, and the patient's own preferences will all factor into this choice. In the first phase of treatment, the goal is to reduce symptoms so that the patient may function normally and live independently. Maintaining good tolerance for therapy is crucial. This is why it's common sense to choose monotherapy. There is little doubt that the introduction of medication has been successful if patients are able to continue on it with tolerable side effects, experiencing a significant decrease in symptoms and a sense of well-being that enables them to live freely and productively.

Patients with mild to moderate impairments may still benefit from starting therapy early. Even though the validity of the rating scale has been called into doubt in this patient population, one research found that untreated PD patients reported a worsening of their health using the Parkinson's Disease Questionnaire (PDQ)-39 at first consultation and for up to 18 months. [14,15]

3.3 Treatment of Parkinson’s disease

Although there is currently no cure for Parkinson's disease, drugs may significantly improve symptom management. Surgery may be recommended in certain later situations.

Changes to your lifestyle, such as regular aerobic activity, may also be suggested by your doctor. Balance and stretching exercises are crucial components of physical therapy for several conditions. If you're having trouble communicating, a speech therapist may be able to assist. [16,17]

3.4 Medications

Tremor, difficulty walking, and other movement issues may all be treatable with medication. These drugs either boost dopamine levels or act as a replacement for it. When it comes to dopamine in the brain, those who suffer from Parkinson's disease are severely lacking. However, dopamine cannot be administered directly since it is brain-accessible. After commencing therapy for Parkinson's disease, you may see a significant improvement in your symptoms. However, many medications lose their effectiveness or consistency as time goes on. In most cases, you will have a reasonable amount of symptom management. [18]

Medications your doctor may prescribe include:

3.4.1 Carbidopa-levodopa: The most effective treatment for Parkinson's disease is levodopa, a substance found in nature that is absorbed by the body and transformed into dopamine in the brain. Lodosyn is a combination drug that contains both levodopa and carbidopa, which prevents levodopa from being converted to dopamine too soon outside the brain. This helps keep nausea and similar symptoms at bay. Nausea and dizziness are possible side effects (orthostatic hypotension).

It's possible that the positive effects of levodopa may fluctuate over time as your illness worsens ("wearing off"). Also, greater dosages of levodopa might cause uncontrollable movements (dyskinesia). To mitigate these side effects, your physician may reduce your dosage or shift your dosing schedule..

3.4.2 Carbidopa-levodopa infusion: The combination of carbidopa and levodopa forms the brand-name drug Duopa. On the other hand, the gel-like drug is delivered to the intestines through feeding tube. Individuals with advanced Parkinson's disease who show some response to carbidopa-levodopa but who have significant swings in responsiveness may benefit from duopa. The regular infusion of Duopa ensures that the two medications are always at the same concentration in the circulation.

A little operation is needed to place the tube. Tube-related hazards include tube loss and infusion site infections.

3.4.3 Dopamine agonists: Dopamine agonists are not converted into dopamine, unlike levodopa. Alternately, they are designed to make you feel "high" by acting like dopamine. They won't alleviate your condition as much as levodopa would. In contrast, their effects are more consistent over time, and they may be used with levodopa to lessen the drug's sporadic on/off behavior. Pramipexole (Mirapex), ropinirole (Requip), and rotigotine are all examples of dopamine agonists (Neupro, given as a patch). As an injectable dopamine agonist, apomorphine (Apokyn) provides rapid relief but wears off quickly. Dopamine agonists have several adverse reactions with carbidopa-levodopa. However, hallucinations, fatigue, and compulsive behaviors like hypersexuality, gambling, and overeating are all possible. Talk to your doctor if you take these drugs and notice any changes in your behavior.

3.4.4 MAO B inhibitors: Selegiline (Eldepryl, Zelapar), rasagiline (Azilect), and safinamide are examples of such drugs (Xadago). By blocking the activity of monoamine oxidase B in the brain, they assist preserve dopamine levels (MAO B). There is an enzyme in the brain that breaks down dopamine. Nausea and sleeplessness are examples of possible negative effects. Taking these drugs in conjunction with carbidopa-levodopa raises the risk of experiencing hallucinations. Because of the small but real risk of adverse responses, these drugs are seldom used along with other classes of drugs like antidepressants or opiates. Before adding another drug that contains an MAO B inhibitor, talk to your doctor.

3.4.5 Catechol O-methyltransferase (COMT) inhibitors: The most well-known drug in this category is entacapone (brand name: Comptan). By inhibiting an enzyme responsible for degrading dopamine, this medicine somewhat increases the duration of the effects of levodopa treatment.

An increased levodopa impact is the primary cause of unwanted side effects, such as dyskinesia. Diarrhea and other amplified levodopa side effects are two more possible adverse reactions.

Another COMT inhibitor that is infrequently recommended because of the risk of severe liver damage and liver failure is tolcapone (Tasmar).

3.4.6 Anticholinergics: The tremor associated with Parkinson's disease was previously treated with these drugs for a considerable amount of time. Some examples of anticholinergic drugs are benztropine (Cogentin) and trihexyphenidyl.

Constipation, dry mouth, and difficulty urinating are just some of the common negative reactions to these drugs that might outweigh their little advantages.

3.4.7 Amantadine: For mild, early-stage Parkinson's disease, doctors may give amantadine alone to offer short-term alleviation of symptoms. Later in the course of Parkinson's disease, it may be used with carbidopa-levodopa treatment to mitigate the drug combination's side effect of causing uncontrollable movements (dyskinesia).

Purple mottling on the skin, swollen ankles, and hallucinations are all possible adverse reactions.

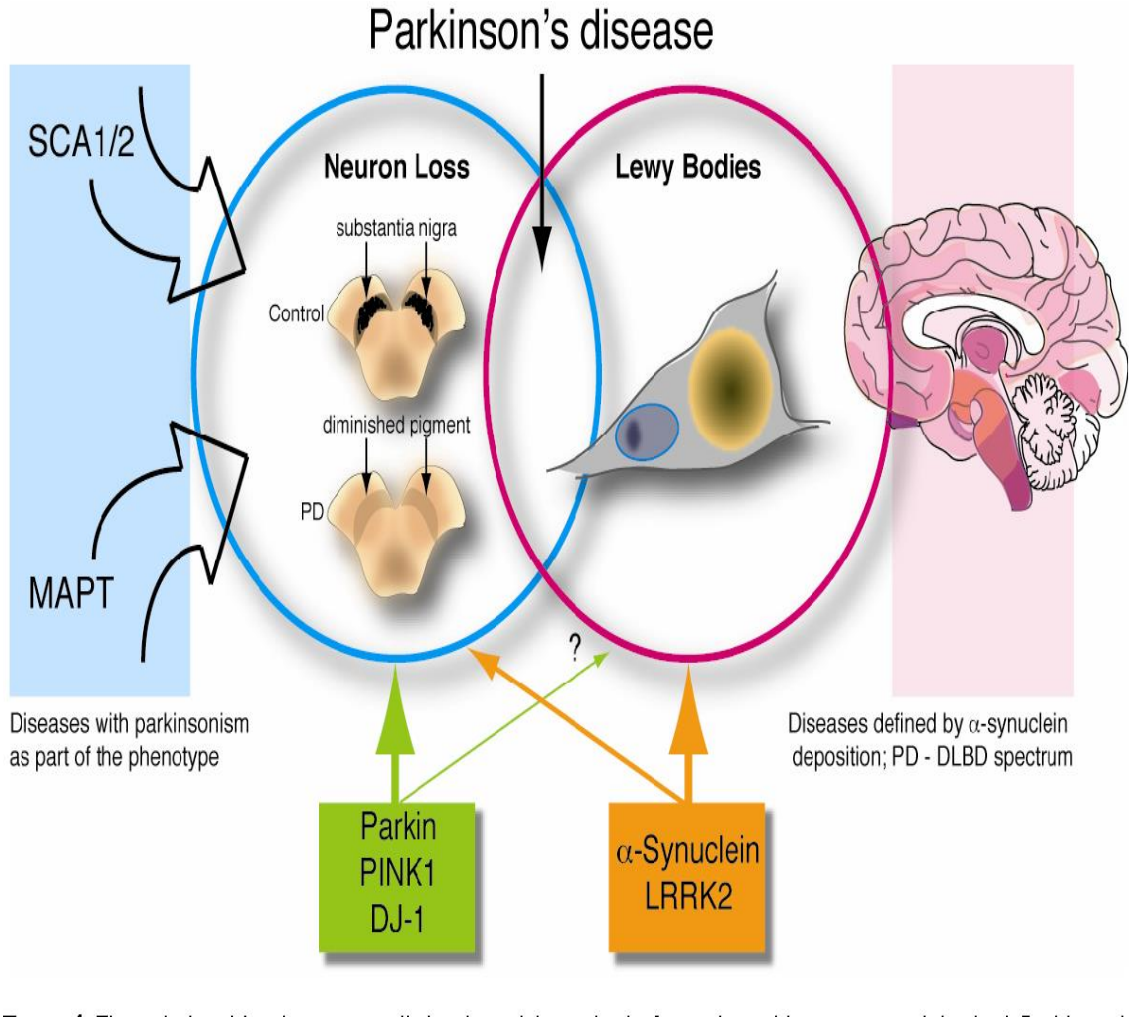

Figure 3.1 Genetic neuropathology of Parkinson's disease

3.5 Treatment begin with levodopa, a dopa agonist or MAO-B inhibitor

3.5.1 First line levodopa treatment

For the last four decades, the therapy of choice for PD has been levodopa in conjunction with a peripheral decarboxylase inhibitor. In many ways, it is still the most effective medication available. On the other hand, the rewards earned don't usually come free. Adverse effects from levodopa treatment, especially when given for an extended period of time, may be quite debilitating. The incidence of levodopa-induced dyskinesias is around 10% per year after starting levodopa, but it is greater in individuals with earlier onset. Dyskinesias are mostly caused by how long you've been

taking levodopa, whereas motor fluctuations are most closely associated with how long you've had the condition. Intermittent activation of dopamine receptors seems to be linked to the development of drug-induced dyskinesias in PD. Considering that the half-life of levodopa is just 60 to 90 minutes, it is plausible that the pulsatile delivery of levodopa to a denervated striatum plays a significant role in the etiology of PD. The severity of nigral neuronal loss at the time of levodopa initiation is also correlated with the onset of unfavorable characteristics. The potential neurotoxicity of levodopa has sparked debate. The ELLDOPA research was an attempt to address this via a large, randomized, placebo-controlled clinical investigation of people with early PD who had not previously received symptomatic therapy. The study's primary objective was to determine whether or not levodopa therapy slowed the pace of illness development. After a 2-week washout period, the UPDRS scores of patients treated with all three doses of levodopa were better than those of the placebo group in a dose-responsive pattern. Though this might be suggestive of a neuroprotective impact, it is likely that the 2-week washout time was inadequate. However, there was a dose-dependent increase in the prevalence of motor problems such as dyskinesias in the treated groups. A subset of patients received ß-CIT SPECT imaging to serve as a marker for intact nigrostriatal dopaminergic neurones in addition to clinical results. As the dosage was increased, the inhibition of DAT binding in the striatum became more pronounced. However, it is also possible that the uptake variations represented a pharmacological influence of levodopa on DAT activity, rather than a causal relationship between the two. The question of whether or not levodopa causes neurotoxicity or neuroprotection has yet to be resolved. Smaller, patient-specific dosages of levodopa are desirable due to the potential for dose-dependent motor problems over time.

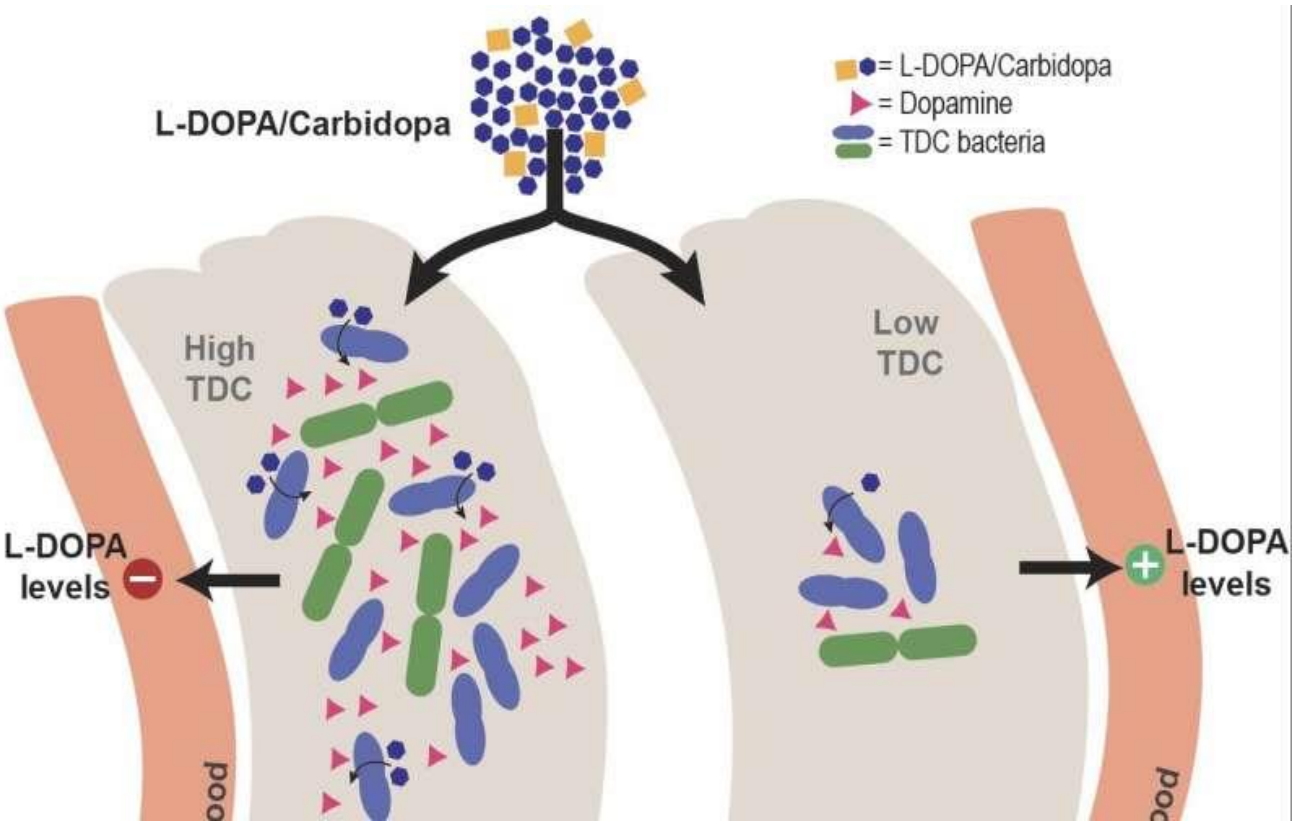

Figure 3.2 Treatment begin with levodopa

3.5.2 First line dopamine agonist treatment

There are now six dopamine agonists on the market that can be used orally. Bromocriptine, pergolide, cabergoline, and lisuride are the four ergot derivatives; ropinirole and pramipexole are the two non-ergot medicines. Transdermal rotigotine is a non-ergot agonist that may be applied to the skin. These medications function by increasing activity at post-synaptic dopamine receptors. Initially, dopamine agonists were approved to be used in combination with levodopa for those with advanced PD. The ability to postpone the introduction of levodopa and the subsequent development of levodopa problems led to their adoption as first-line treatments, which in turn led to their effectiveness in relieving motor symptoms. Dopamine agonists and levodopa have both been tested as monotherapy. There was no impact on the commencement of motor fluctuations, although the onset of dyskinesias was delayed in the first bromocriptine experiment, which took place in the 1980s. Compared to levodopa, patients who started treatment with a newer dopamine agonist saw a substantial decrease in the development of motor problems during trials of agonist

monotherapy. Although patient and physician ratings for the two groups were identical throughout the trials, individuals treated with levodopa demonstrated better UPDRS scores (parts II and III) compared with those on dopamine agonists. Over the course of the study's four years, both the levodopa and pramipexole groups had similar QoL (quality of life) outcomes on assessments. Dopamine agonists have a similar side effect profile as levodopa, except they are more likely to cause mental fuzziness and hallucinations.

Therefore, the conundrum of first-line therapy in PD is that dopamine agonists result in fewer motor problems and the same QoL ratings, but at the cost of a greater frequency of side effects and poorer effectiveness as measured by the UPDRS. Patients above the age of 75 may take dopa agonist monotherapy without serious adverse effects, contrary to popular opinion and evidence from recent trials with more strong agonists. However, more care must be used while utilizing agonists in the elderly, as was mentioned above.

Choosing a dopamine agonist to start is generally a guessing game. Few direct comparisons have been made between the antagonists and agonists. A powerful D2 and D3 receptor agonist, cabergoline is derived from ergot. Ergot agonists, especially cabergoline and pergolide, used to be advised as first-line therapy, but this advice has now changed due to rising reports of non-inflammatory fibrotic deterioration of heart valves. If you are still taking an agonist derived from ergot, you should have regular monitoring exams such an erythrocyte sedimentation rate (ESR), chest X-ray, and echocardiogram every six months.

Ropinirole, pramipexole, and rotigotine are examples of popular non-ergot-derived dopamine agonists. Increased risk of compulsive gambling is the pramipexole adverse effect that has been documented most often to far; this is a rare but significant finding. [20]

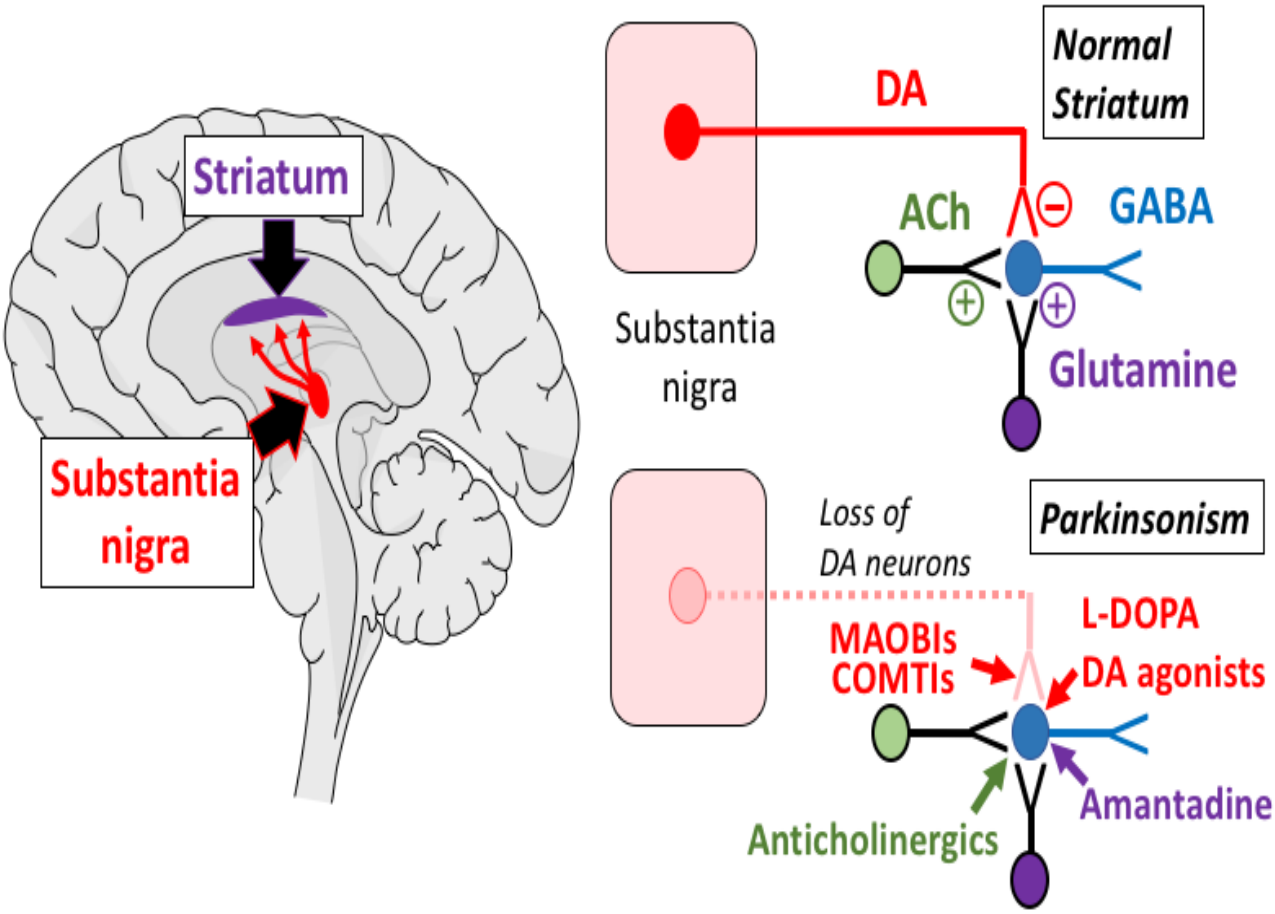

Figure 3.3 Treatment for Parkinson's

3.6 The treatment of late motor complications of PD

Most people with PD suffer changes in motor function, the impact of a single levodopa dosage becoming increasingly shorter, after a period of years of consistent, continuous response to levodopa medication (wearing-off phenomenon). In addition, most advanced patients have periods of immobility that are not correlated with levodopa administration (on–off phenomenon). More than half of patients will have motor fluctuations and dyskinesias between 5 and 10 years after initiating levodopa, and 20-30% will develop dyskinesias after 2 years. The situation is much more dire among individuals under the age of 40, with almost all of them experiencing motor problems within 6 years after levodopa's initiation. Levodopa-induced dyskinesias continue to be

inadequately treated. Often, patients become stiff and inflexible with only a daily dosage reduction. [21,22]

Additionally, involuntary choreic-dystonic movements exist with motor response to levodopa in most individuals with motor fluctuations. Dyskinesias often occur at the peak of motor response (peak-dose dyskinesias) or during the whole ON phase (square wave dyskinesia), but they may also occur in a diphasic pattern, where they occur at the onset and offset of motor response. High plasma concentrations of levodopa are linked to peak-dose dyskinesias, which may be mitigated by administering levodopa in divided doses. Peak-dose dyskinesias may also be mitigated by amantidine. The constant dopaminergic stimulation provided by long-acting dopamine agonists like rotigotine may also be useful. When plasma levodopa levels are fluctuating, this might cause biphasic dyskinesias. [23,24] Most of the time, the lower limbs are hit the worst. Higher dosages of levodopa or a fast-acting agonist such subcutaneous apomprphine injection may help manage their symptoms. Lower limbs are also more often affected by off-period dystonia, which is likewise linked to mobility impairment. A subcutaneous injection of apomorphine or a dispersible levodopa formulation could help. We still know just a fraction of what we need to know about the pathogenesis of motor problems after chronic levodopa medication (levodopa long-term syndrome). Presently, it is thought that they are a reflection of both the development of the underlying illness and the results of a pulsatile, intermittent supply of levodopa to a striatum that has lost its nerve endings. [25]

Multiple therapies have been used to lessen the incidence and severity of motor problems. Dopamine agonists have been demonstrated to be effective in reducing 'off' time and, therefore, levodopa dosage in the latter stages of the illness. However, the risk of developing dyskinesias must be considered. Sleepiness and hallucinations are two more prevalent negative effects. Pramipexole and ropinirole, two relatively new agonists, seem to be superior than bromocriptine in terms of cutting down on "off" time.

The NMDA receptor antagonist amantadine was first created as a drug to combat viruses. Its usefulness in treating PD was found out of the blue, along with its other qualities. Although the evidence for amantadine's effectiveness was deemed weak in a Cochrane review, there is evidence that it may lessen the incidence of motor problems such freezing, "off" spells, and dyskinesias.

Confusion, hallucinations, ankle edema, and livedo reticularis are some of the most common adverse reactions, especially among the elderly.

Dopamine agonists, such as subcutaneous apomorphine, may be effective as an adjuvant to therapy since they shorten "off" time without increasing the propensity for dyskinesias or disorientation. Duodenal levodopa infusion treatment has also been found to enhance motor function and quality of life in individuals with advanced PD without increasing dyskinesias. [26,27]

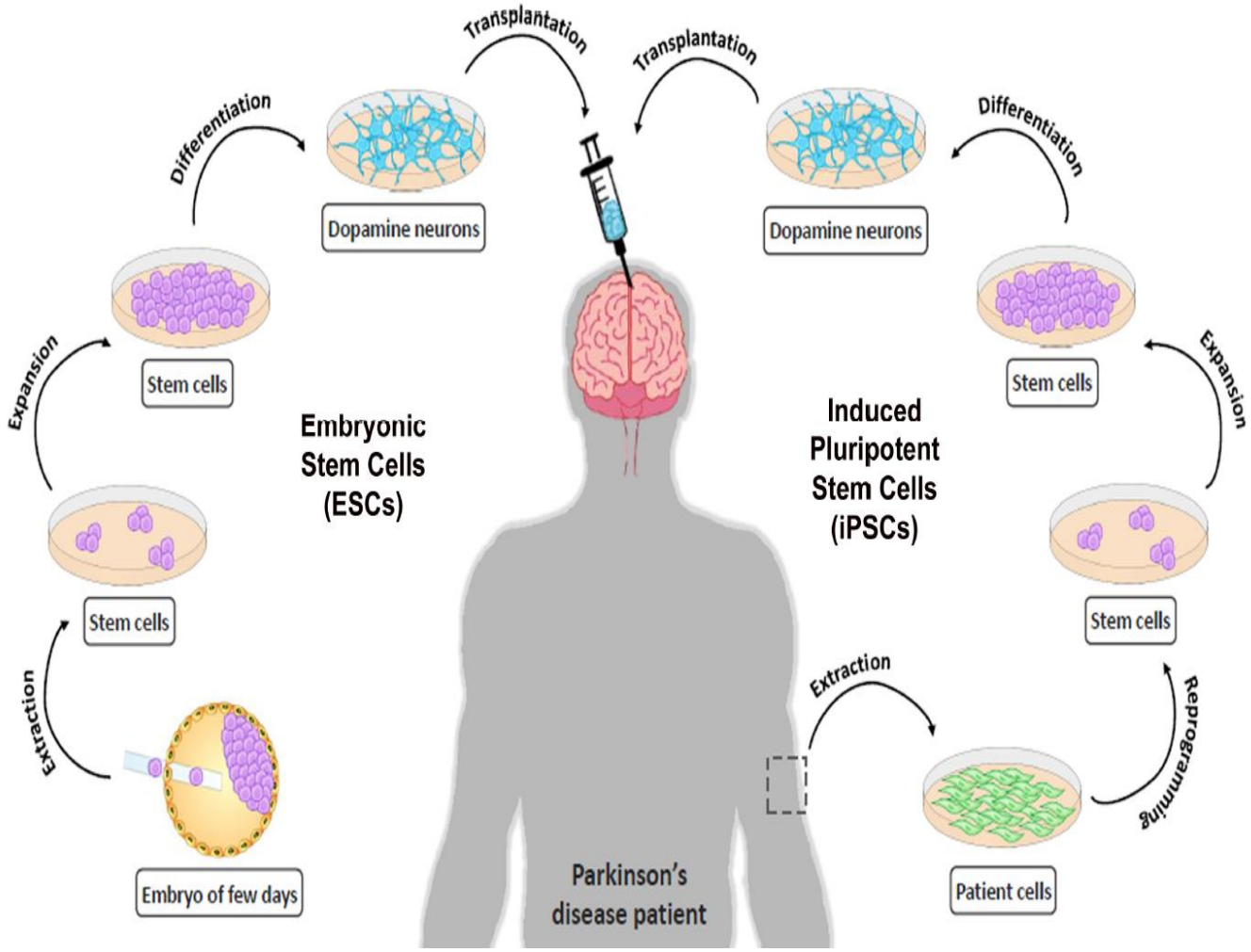

Figure 3.4 Embryonic stem cells therapy

3.7 COMT inhibitors

Entacapone, an inhibitor of peripheral catechol-O-methyltransferase COMT, enhances the effectiveness of drugs that block the enzyme alanine aminotransferase (AAAT). To put it another way, entacapone adds around 45 minutes to the plasma half-life of levodopa after each dosage, assuming the volume of distribution stays the same. Similarly, tolcapone, which is administered separately from the levodopa dosing schedule, increases the half-life of levodopa in a dose-dependent fashion. With the addition of entacapone or tolcapone to levodopa/AADC-inhibitor therapy, plasma and CNS dopamine levels are increased and maintained for a longer period of time than with levodopa/carbidopa alone, resulting in a longer duration of antiparkinsonian action and subsequent improvements in motor function. As a result, the plasma concentrations of levodopa are more stable and the effects of each dosage of levodopa last for a longer period of time when COMT is inhibited. Reintroduced for limited usage with close supervision, tolcapone was first pulled from the market due to complaints of hepato-toxicity. Entacapone, on the other hand, may be used alone or as part of a triple treatment (including levodopa and an AADC inhibitor) designed to boost compliance. [28]

To reduce motor response variations, it may be possible to use a COMT inhibitor in a safe and effective manner. Inhibitors of cyclooxygenase (COMT) lengthen 'on' time while decreasing levodopa dosage by extending 'off' time. To the contrary, they do not reduce the need for levodopa.

Potent, selective, and reversible COMT inhibitors like entacapone and tolcapone provide substantial advantages, especially for the management of motor fluctuations in individuals with advanced Parkinson's disease. They are also expected to play an increasingly important role in the onset of disease. To see whether the combination of levodopa and entacapone may slow the progression of dyskinesias more than levodopa alone, researchers are conducting a study. [29,30]

3.8 The role of surgery in PD

There has been a history of more than 50 years of surgical intervention for PD. Patients with severe tremor were sometimes sent for ablative surgery in the early 1950s, and this was often performed on the contralateral thalamus. Thanks to the development of levodopa, surgical procedures are no longer often used to treat Parkinson's disease. It's ironic that surgeons and doctors have had to

reexamine the field of surgical intervention because of the broad knowledge of levodopa-induced problems. This at first zeroed on on pallidotomy and other forms of lesion surgery that have shown effective, especially for levodopa-induced dyskinesias. [31]

The use of stimulators is a further advancement. High-frequency deep brain stimulation (DBS) of localized brain regions achieved this by inducing transient but lasting inhibition of the intended brain circuitry. Several subregions of the basal ganglia are potential targets. Bilateral subthalamic stimulation is the most frequent operation used to alleviate bradykinesia, tremor, and stiffness, and it also minimizes drug-related motor problems. The results may surprise you with their magnitude. The procedure is technically challenging, but the risk of complications is minimal in expert hands. However, the availability of such therapy is limited by the infrastructure and support team necessary for assessing, carrying out, and monitoring patients. Concerns have also been raised concerning a possible rise in mental adverse effects, notably depression, in patients who have had DBS. Therefore, this kind of therapy is not appropriate for patients with cognitive impairment or severe depression. Patients under the age of 75 without significant systemic co-morbidity and in the absence of obvious structural abnormality on MR imaging are typically the best candidates for STN DBS. These individuals should also be levodopa-responsive, meaning they are dependent when not taking medication but are fully functional when taking it. It is expected that most patients will have had their condition for at least 5 years, allowing time for alternative causes of atypical parkinsonism to become apparent. [7,32]

In Vim DBS, which is done to disable tremor, age does not seem to be as important. DBS of the pedunculopontine nucleus has shown promise in recent studies for enhancing axial stability. An experienced multi-disciplinary team is needed to evaluate a patient for DBS. [32]

3.9 Surgical procedures

3.9.1 Deep brain stimulation: Surgeons implant electrodes into a targeted area of the brain to perform deep brain stimulation (DBS). The generator, which is placed in the chest below the collarbone, transmits electrical pulses to the brain via the electrodes, which may help alleviate the symptoms of Parkinson's disease. [33]

Your doctor may find it essential to make certain changes in order to best treat your condition. Infection, stroke, and brain hemorrhage are just a few of the dangers associated with surgery. In the event that you or a loved one develop issues related to DBS stimulation, your doctor may need to make adjustments or replace certain components of the system.

People with severe Parkinson's disease whose medication (levodopa) responses have become unstable are often candidates for deep brain stimulation. Involuntary movements (dyskinesia) may be mitigated or stopped entirely with DBS, along with tremor, stiffness, and slowness.

DBS is useful for managing dyskinesia that does not improve with medication changes and for stabilizing unpredictable reactions to levodopa.

Aside from tremor, DBS is not beneficial for issues that do not respond to levodopa medication. In certain cases, DBS may be used to manage tremors that don't respond well to levodopa.

DBS may give long-term relief from certain Parkinson's symptoms, but it does not halt the progression of the illness itself.

[34,35]

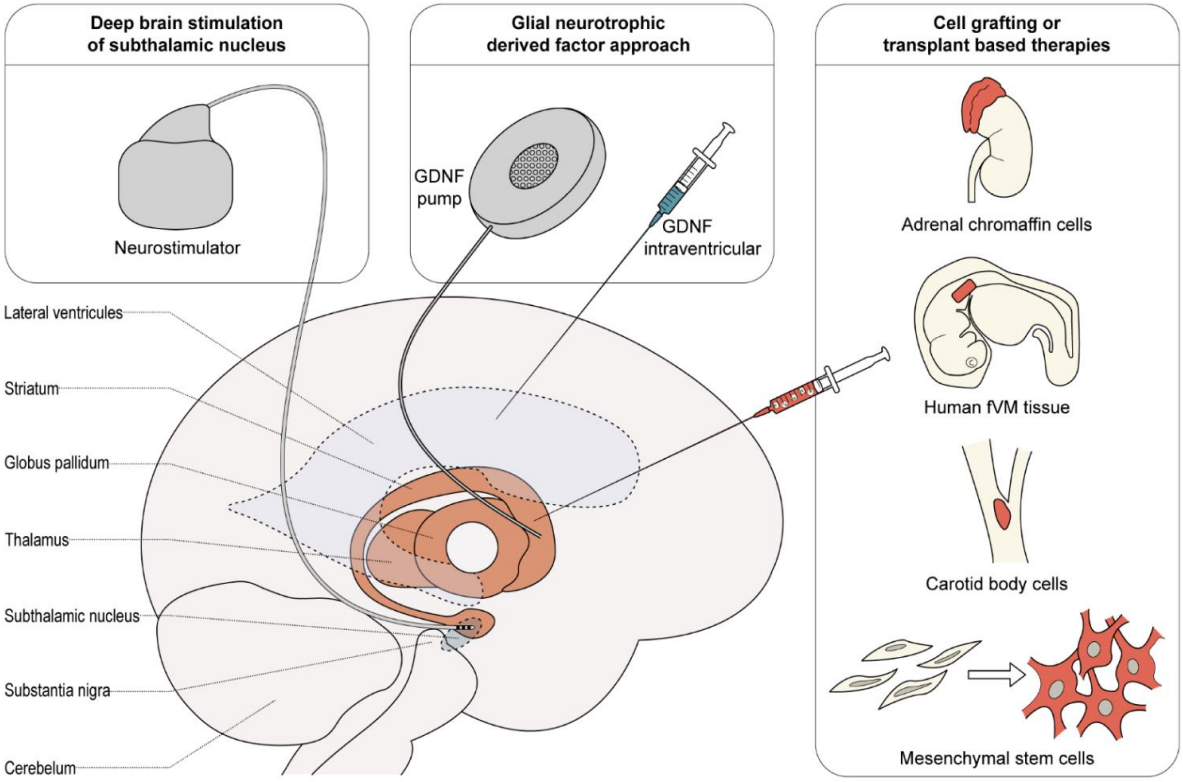

Figure 3.5 Surgery in PD

3.10 Lifestyle and home remedies

If you've been diagnosed with Parkinson's disease, you and your healthcare provider will need to collaborate closely to determine the best course of action to alleviate your symptoms. And if you're living with Parkinson's, you might find that some changes to your routine help. [36]

3.11 Healthy eating

Foods may help ease some symptoms of Parkinson's disease, but no single food or combination of foods has been proven to help. Constipation is a common symptom of Parkinson's disease and can be alleviated by taking measures such as increasing your fiber intake and drinking enough fluids.[36] People with Parkinson's disease may benefit from the nutrients found in a well-balanced diet, such as omega-3 fatty acids.

3.12 Exercise

Physical activity has been shown to improve muscular strength, range of motion, and equilibrium. Depression and anxiety are two of the many mental health issues that may be ameliorated by exercise.

Your doctor may recommend seeing a physical therapist in order to develop a personalized fitness plan. You may also try stretching, water aerobics, dancing, gardening, walking, and other forms of exercise.

The loss of equilibrium caused by Parkinson's disease might make it difficult to walk normally. There's some evidence that regular exercise may improve balance. You might also try these other ideas:

- Try not to move too quickly.
- Aim for your heel to strike the floor first when you're walking.
- If you notice yourself shuffling, stop and check your posture. It's best to stand up straight.
- Look in front of you, not directly down, while walking.
-

3.13 Avoiding falls

This disease can make you more clumsy as it progresses. Just a slight prod or bump could be enough to throw you off your feet.The following suggestions may help:

- Make a U-turn instead of pivoting your body over your feet.
- Distribute your weight evenly between both feet, and don't lean.
- Avoid carrying things while you walk.
- Avoid walking backward.

3.14 Daily living activities

People with Parkinson's disease may have trouble with routine tasks like getting dressed, eating, bathing, and writing. An OT can instruct you on how to implement various strategies that will facilitate your progress toward greater independence in your daily tasks.

3.15 Alternative medicine

Pain, fatigue, and depression are just a few of the complications and symptoms of Parkinson's disease that can be alleviated with supportive therapies. [37,38] These therapies, when performed in addition to your treatments, may enhance your quality of life:

Table 3.1 Alternative medicine for Parkinson's disease

Massage	Muscle tension can be alleviated and stress can be lowered with a massage. Unfortunately, health insurance plans almost never cover this type of treatment.
Tai chi	Tai chi is an ancient Chinese type of martial art and exercise that emphasizes slow, fluid movements that may improve mobility, stability, and strength. The practice of tai chi has been linked to a decreased risk of falling. There are variations of tai chi that are adapted to the needs of persons of varying ages and abilities. A research found that tai chi was more effective than stretching and weight exercise in helping persons with mild to moderate Parkinson's disease improve their balance.
Yoga	Stretching postures and motions in yoga may help improve flexibility and equilibrium.

	Most positions may be adapted to suit your level of flexibility and strength.
Alexander technique	Muscular tension and soreness may be alleviated by practicing this method, which emphasizes proper muscle posture, balance, and awareness of how muscles are used.
Meditation	Meditation entails contemplation and concentration on a single thought or image. There is some evidence that meditation can help with all three of these issues.
Pet therapy	Having a pet, such a dog or cat, may do wonders for your mental and physical well-being.

3.16 Coping and support

The ups and downs of dealing with a chronic condition may be overwhelming, and it's common to experience negative emotions like anger, depression, or discouragement. Parkinson's disease in particular is very aggravating since it makes even the simplest of tasks, such as walking, talking, or eating, extremely challenging and time consuming.

People with Parkinson's disease are prone to depression. But if you're feeling continuously gloomy or hopeless, talking to your doctor about antidepressant medicines may help.

Even if they might be your strongest supporters, friends and family can be even more useful when they have experienced something similar to what you are. Not everyone benefits from attending a support group. Still, many individuals living with Parkinson's and their loved ones find that a support group is helpful when looking for knowledge regarding the disease's practical aspects. [17]

In addition, organizations are a great way to connect with others who may relate to your experiences and give encouragement.

Consult your physician, a social worker specializing in Parkinson's disease, or a public health nurse in your area to find out more about local support groups. Another option is to get in touch with the Parkinson's Foundation or the American Parkinson Disease Association.

You and your loved ones could also benefit from meeting with a mental health expert, such as a psychologist or social worker who specializes in helping those who are living with long-term illnesses.

[39]

3.17 Preparing for appointment

Primary care physician visits are the norm. It's possible, however, that you'll be directed to a specialist in nervous system problems (neurologist). It's best to be well-prepared for your scheduled visit since there's usually a lot to cover. Read on for details that can help you prepare for your doctor's visit and understand what to anticipate. [40]

- **Write down any symptoms you're experiencing,** including any that may seem unrelated to the reason for which you scheduled the appointment.

- **Write down key personal information,** including any major stresses or recent life changes.
- **Make a list of all medications,** vitamins and supplements that you're taking.
- **Ask a family member or friend to come with you,** if possible. Sometimes it can be difficult to remember all of the information provided to you during an appointment. Someone who accompanies you may remember something that you missed or forgot.
- **Write down questions to ask** your doctor.

Time with the doctor is limited, so preparing a list of questions ahead of time will help you make the most of your time together.[41,42] For Parkinson's disease, some basic questions to ask your doctor include:

- What's the most likely cause of my symptoms?
- Are there other possible causes?
- What kinds of tests do I need? Do these tests require any special preparation?
- How does Parkinson's disease usually progress?
- Will I eventually need long-term care?
- What treatments are available, and which do you recommend for me?
- What types of side effects can I expect from treatment?
- If the treatment doesn't work or stops working, do I have additional options?
- I have other health conditions. How can I best manage these conditions together?
- Are there any brochures or other printed material that I can take home with me? What websites do you recommend?

In addition to the questions that you've prepared to ask your doctor, don't hesitate to ask questions that occur to you during your appointment.

Your doctor is likely to ask you a number of questions. Being ready to answer them may reserve time to go over any points you want to spend more time on. Your doctor may ask:

- When did you first begin experiencing symptoms?
- Do you have symptoms all the time or do they come and go?
- Does anything seem to improve your symptoms?
- Does anything seem to make your symptoms worse?

3.18 Non-motor complications

With the progression of the disease, there are a number of non-motor complications in PD that are often seen. In many cases, these are not directly related to involvement of dopaminergic pathways and may therefore develop even in patients where motor symptoms are well controlled.[22,43]

3.18.1 Sleep and PD

Parkinson's disease is characterized by a variety of sleep disturbances. This results in a lack of sleep throughout the night as well as excessive tiredness during the day. Sixty percent to ninety eight percent of patients have trouble falling or staying asleep at night, and this percentage tends to rise as the disease progresses and as the patient takes more levodopa. It is important to rule out other potential causes, such as medication-related sleep disturbances (such as off-dystonia), depression, obstructive sleep apnea, REM sleep behavioural disturbance (RBD), periodic limb movements during sleep, and restless leg syndrome, even though Parkinson's disease (PD) itself may play a role. Other potential causes include periodic limb movements during sleep (PLMs), which occur when the legs move involuntarily while the person is sleeping. Parasomnia RBD is becoming more well recognized in people with neurodegenerative illness, specifically the synucleinopathies, and is characterized by the absence of normal skeletal muscle atonia during REM sleep with substantial motor activity accompanying dreaming. This condition is more common in people who have synucleinopathies. There is a correlation between the onset of this symptom and an increased risk of cognitive decline in Parkinson's disease patients who do not have dementia. If it's something that keeps you up at night, a low dose of clonazepam before bed might be able to help. [24]

Additionally, those who have PD are more likely to fall asleep at inappropriate times throughout the day. In its most extreme form, this might present itself as uncontrollable episodes of drowsiness that come on with no warning in advance. Patients receiving levodopa monotherapy have also reported experiencing these episodes, despite the fact that dopamine agonists, in particular ropinirole and pramipexole, are more likely to be the culprits. When a patient exhibits these symptoms, it is imperative that they be counseled to immediately stop driving and refrain from using any machines. These symptoms will go away on their own as soon as the chemical that caused them is eliminated from the body. [44]

3.18.2 Cognition in PD

It would seem that cognitive engagement in PD is rather widespread. Dementia affects a significant portion of people living with Parkinson's disease (PD), often developing at least ten years after the beginning of motor symptoms. The incidence of overt dementia varies from research to study according on the diagnosis, techniques of cognitive testing, and demographic variables; nonetheless, the frequency of overt dementia is on the order of 40% for all PD patients. Even in the early stages of Parkinson's disease, patients often have more modest cognitive disturbances, notably in their executive function. [45]

It is possible that dementia in PD is connected to a number of different illnesses. On the other hand, it seems that the pathology associated with the formation of cortical lewy bodies and/or Alzheimer's disease is the most significant. It has been demonstrated in open studies that the cholinesterase inhibitors rivastigmine, donepezil, and galantamine have a modest benefit in cognitive function and in the amelioration of hallucinations and psychosis in patients with PD-related dementia. However, the robust evidence-based data are strongest at this time for rivastigmine and to a lesser extent for donepezil. [45,46]

3.19 Dementia with lewy bodies or Parkinson's disease with dementia

The distinction between dementia-like symptoms caused by Parkinson's disease (DLB) and Parkinson's disease with dementia (PDD) has been the subject of much debate. When dementia arises either before or simultaneously with parkinsonism, a diagnosis of DLB might be made. It is common practice to use an arbitrary cutoff known as the "1 year rule," which states that a diagnosis

of PDD is made if extrapyramidal motor symptoms have been present for at least a year prior to the onset of dementia, whereas a diagnosis of DLB is made if the onset of dementia occurs before or within a year of the onset of parkinsonism. There has just been a publication of revised criteria for the clinical diagnosis of DLB. These depend on the existence of a dementing process with other basic qualities including fluctuating cognition and change in attention and alertness, as well as parkinsonian signs and recurring visual hallucinations. There is a correlation between the degree of dementia in DLB and the presence of Parkinsonian symptoms. Myoclonus, the lack of rest tremor, a poor response to levodopa, and strong neuroleptic sensitivity are some of the characteristics that may help differentiate DLB from PD. [27,47] Both DLB and PDD are characterized pathologically by the presence of lewy bodies; however, in patients with PDD, there is greater neuronal loss within the substantia nigra, whereas in patients with DLB, there is greater cortical beta-amyloid deposition. Both of these diseases are characterized pathologically by the presence of lewy bodies. The dementia that causes DLB is characterized by a significant deficit in visuospatial and executive function, as well as vivid visual hallucinations and variable attention. DLB patients are frequently less levodopa-responsive. It is essential to keep in mind that dopaminergic medications may significantly increase symptoms of disorientation as well as visual hallucinations in patients suffering from any of these diseases. Cholinesterase inhibitors are effective treatments for both disorders. Please refer to the review done by McKeith for the most current information available on the differences between PDD and DLB. [27,49]

3.20 Mood disturbance and PD

Depression is the most prevalent mood disorder that is associated with Parkinson's disease, with a frequency of up to 50 percent and the ability to arise at any stage of the illness. Patients should be tested for underlying metabolic disorders such as hypothyroidism, which is frequently mistaken for a depressed disease and should be included in the differential diagnosis of depression. Alterations in mood are more prevalent in more advanced stages of the illness and have a greater association with alterations in motor function. [51]

Cognitive behavioral therapy and antidepressants, such as tricyclics and short-acting serotonin uptake inhibitors, are both viable treatment options for patients who have been clinically diagnosed

with depression (SSRIs). There is evidence that pramipexole has a significant antidepressant action.

3.21 Psychosis and confusion in PD

Up to thirty percent of those who have Parkinson's disease may develop psychosis. It often manifests itself with hallucinations, which are typically visual, along with delusions, agitation, and even aggressive behavior. Patients could develop paranoia, especially with regard to their spouses or other members of their families. Loss of dopaminergic neurones, in particular those located in the nigro-mesolimbic projections, has been hypothesized to have a role in the pathogenesis of psychosis. It is often seen in patients who go on to develop PDD or DLB.

It is strongly recommended that you stay away from most of the older antipsychotic drugs since they have a tendency to significantly exacerbate motor symptoms. The more recent 'atypical' antipsychotic medications, such quetiapine and clozapine, are more efficacious and easier to take than their older counterparts. Because of the 1% risk of agranulocytosis associated with clozapine, patients need to have their white cell counts carefully monitored. It is possible that acetylcholinesterase inhibitors might help people with Parkinson's disease have less hallucinations and delusions. [52]

Chapter Four
Conclusion

Conclusion

Parkinson's disease (PD) is a prevalent form of neurodegeneration. It is believed that both hereditary and environmental variables are involved in the process that results in aberrant protein aggregation within certain groups of neurons, which subsequently leads to malfunction within the cells and ultimately death of those cells. The diagnosis is still made on a clinical level, and a high index of suspicion need to be maintained in order to rule out other possible causes of Parkinsonism. Treatment options for early and late consequences of Parkinson's disease (PD) currently include a wide variety of different medicines in addition to surgical treatments. When Parkinson's disease reaches its severe stage, providing care for patients becomes more difficult. It may be necessary to take additional drugs to treat deteriorating sleep issues, gastrointestinal dysfunction, and a myriad of other challenges when the side effects of years of using PD meds begin to take their toll. The diagnosis and management of non-motor problems associated with PD are receiving an increasing amount of focus as of late. The goal is to identify what causes Parkinson's disease as well as medicines that may halt the progression of the condition. For the time being, medical professionals need to keep educating themselves on the therapies that are now on the market while keeping their fingers crossed for the development of more effective alternatives in the not too distant future. Therefore, it is expected that future breakthroughs in Parkinson's disease will center on the idea of disease-modifying medications that also provide neuroprotection.

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