Parkinson’s Disease: An Overview of Various Treatments

Tanvi Dasharath Choukekar¹, Shilpa Laxman Mestry², Akanksha Prakash Phondke³, Akhil Kanekar⁴

¹,²,³ Final Year Student of Shree Saraswati Institute of Pharmacy, Tondavali, Kankavali. Dr. Babasaheb Ambedkar Technological University, Lonere, Raigad.
²Assistant Professor in Shree Saraswati Institute of Pharmacy, Tondavali, Kankavali. Dr. Babasaheb Ambedkar Technological University, Lonere, Raigad.

Corresponding Author: Tanvi Dasharath Choukekar

ABSTRACT

Parkinson’s disease is a chronic progressive neurological disease that slowly damages the central nervous system characterized by rigidity, tremor and hypokinesia with secondary manifestations like defective posture and gait, mask like face and sialorrhoea; dementia may accompany. There is no known cure to prevent or delay the disease progress. The prevalence of Parkinson’s disease increases with age. Various therapies have been discovering to relieve the symptoms and to prevent the progress of disease. That comprising deep brain stimulation, coffee therapy, stem cell therapy, gene therapy, shark therapy. The goal of this review is to emphasize the development of various therapeutic approaches. This article highlights the newer therapeutic methods for the treatment of Parkinson’s disease such as deep brain stimulation, stem cell therapy, gene therapy etc.

Keywords: Parkinson’s disease, hypokinesia, deep brain stimulation, coffee therapy, gene therapy, mesenchymal cells, squalamine.

Parkinson’s disease

In 1817, Parkinson’s disease (PD) was first described by Dr. James Parkinson as an essay “Shaking Palsy”. [1] It is a chronic, progressive, neurodegenerative disorder characterized by both motor and non-motor features. [2, 3] The pathology of PD involves extensive regions of the nervous system, various neurotransmitters and protein aggregation other than just Lewy bodies.

Figure 1: Brain of Parkinsonian patient [49]
Etiology of Parkinson’s Disease

Parkinson’s disease caused by degeneration of nerve cells in the part of the brain called substantia nigra, which controls movement. This leads to the inability to produce an important chemical called dopamine. It may be also caused from a complicated interplay of genetic and environmental factors. Genetic factors including genetic mutation and environmental factors including age, sex, NSAID use, blood urate level, head trauma, anxiety disorder etc.

The motor symptoms of PD include four cardinal features; bradykinesia, rest tremor, rigidity, postural instability and gait impairment. Non-motor symptoms include autonomic disturbance, sensory, skin, sleep, visual, neuropsychiatric dysfunctions, olfactory dysfunction. Impulse control disorders and apathy are recognized as important neuropsychiatric syndrome associated with PD. Most therapies are oriented towards symptomatic relief which slow or even terminate neurodegeneration and that causes slow progression of the disease.

Therapies for Parkinson’s disease:

1) Deep Brain Stimulation

It is a treatment that helps to relieve the motor symptoms of PD as well as some of the non-motor symptoms. It is called as symptomatic therapy; it does not change disease progression. The DBS system contains 3 components:

1) The lead is a thin, insulated coiled wire with 4 electrodes at the end inserted through a small opening in the skull and implanted in the brain.

2) The internal pulse generator (IPG) is neurostimulator usually implanted under the skin near the collarbone. In some cases it may be implanted in the chest or under the skin over the abdomen.

3) The extension is an insulated wire that is passed under the skin of the head, neck and shoulder and connects a lead to the IPG.
problems that have been resulted from using the medication for a long time.\cite{24} It has potential to improve tremor, motor fluctuation, rigidity, bradykinesia, dyskinesia, walking and balance.\cite{25-29}

ii) Subthalamotomy:
When a tiny heated probe is inserted into the subthalamic nucleus of the brain to destroy tissue, the process is known as the subthalamotomy.\cite{30} It can provide the same type of effects as pallidotomy. It can be performed on the both sides of the brain.\cite{31,32} A few subthalamotomy patients have developed a side effect called hemiballism (the appearance of flailing, ballistic, undesired movements of the limbs), but in most of the cases it is a transient adverse effect.\cite{33-36}

iii) Thalamotomy:
It is the precise destruction of a tiny area of the brain called the thalamus that controls some involuntary movement with the help of heated probe.\cite{37} It is used to treat severe tremor on one side of the body that does not respond to medicines.\cite{37,38} Surgery on one side of the brain affects the opposite side of the body. If the patient have tremor in the right hand then the left side of the brain will be treated.\cite{39}

It is used less often than pallidotomy and subthalamotomy because they both can improve a broader range of symptoms.\cite{40} Thalamotomy can reduce tremor,\cite{41} but it does not have a strong effect on other symptoms like bradykinesia, speech problem, walking difficulties and dyskinesia.\cite{42}

<table>
<thead>
<tr>
<th>DBS surgery</th>
<th>Effects of surgery</th>
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<tr>
<td>Pallidotomy</td>
<td>Reduces tremor, rigidity, bradykinesia, gait problems, dyskinesia</td>
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<td>Subthalamotomy</td>
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</tr>
<tr>
<td>Thalamotomy</td>
<td>Reduces tremor but no other symptoms of PD</td>
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2] Gene therapy
The treatment of Parkinson’s disease required dopamine replacement therapy. Now a day a new treatment uses a virus to deliver gene in the brain and it is known as Gene therapy.\cite{43} In 1972, it was first described as a means to “replace bad DNA with good DNA”.\cite{44,45} Gene therapy affects an enzyme called AADC (Aromatic amino acid decarboxylase). This enzyme helps to transform levodopa into dopamine in the brain.\cite{46} Gene therapy is not a cure for disease, but it may allow more effective management of symptoms.\cite{47}

Typically gene therapy introduces a working version of gene into cells to create key proteins or enzymes. Then these genetic instructions delivered to the cells using viral or non-viral vectors.\cite{47} Vectors are derived from viruses because they have ability to enter into the cells to deliver genetic material such as DNA, mRNA, small interfering RNA (siRNA), microRNA (miRNA) or antisense oligonucleotide.\cite{48}

To provide a safer approach for gene delivery various non-viral vectors have been developed, including liposomes, polymerase, nanoparticles and peptides.\cite{49} Due to short duration of gene expression, non-viral techniques are insignificantly used for the treatment of PD. Viral vector technology is the most commonly used method for gene transfer in the CNS.

It causes long lasting gene expression via DNA integration or episome formation into the host genome.\cite{50} Based on the criterion of safety, stability of gene expression various viral vectors are developed to transfer foreign gene. Recombinant Adeno-Associated Virus (rAAV) and lentivirus vectors are most commonly used.\cite{51}

All viral genes are removed and the vector is modified to only deliver therapeutic genes into cells. For PD, gene therapy deliver a vector that has functional gene to help cells to create enzymes or neurotransmitters which work together with existing PD medications to create better result.

As the disease progresses, not only brain create less dopamine, it also creates less AADC enzyme. The AADC enzyme helps the brain cells to convert L-DOPA to dopamine.\cite{45} L-DOPA is naturally
occurring or can be provided via Parkinson’s medication. Gene therapy delivers the dopa decarboxylase (DDC) gene via vector to increase the production of AADC enzyme. Then DDC gene helps to create more AADC enzymes. It effectively regulates level of dopamine in the brain.

Viruses used to delivered gene:

1] Adenovirus

Adenovirus was first viral vector contains a 36kb genome and comprised of double stranded DNA in animal models of PD. Gutless adenovirus vectors have higher capacity to achieve transgene expression and reduced toxicity.

2] Adeno-associated virus

AAV comprise two genes: 1) encoding capsid (cap) 2) viral replication (rep) proteins and required other viruses (adenovirus) for replication. These includes long term gene expression formation hence AAVs are suited to gene therapy for PD. AAV-2 derived vectors are frequently utilized serotype in gene therapy. AAV-2 transduced only neurons within CNS after local administration. The basal ganglia neurons are high efficiently and in specific manner able to transduce by AAV-1, AAV-5 and AAV-8 in nonhuman primate. Hence they can use in future gene therapy.

In recent studies, use of erythropoietin as a therapeutic agent for PD delivered in the gene to striatal neurons using AAV-9 in rodent model.

3] Lentivirus (Retrovirus)

Lentiviral vectors are based on HIV. HIV-1 derived vectors incorporate a transgene between the long terminal repeats (LTRs) for integration into the host genome. They infect dividing and non-dividing cells.

4] Herpes Simplex Virus (HSV)

It is a 150kb double stranded DNA virus. HSV-1 has infected neuron. HSV-1 vectors divided into: a) Recombinant viral b) Amplicon vector

3] Stem cell therapy

Stem cell therapy (now commonly referred as cell replacement therapy (CRT)), promotes the repair response of diseased, dysfunctional / injured tissue using stem cells or their derivatives. This therapy works by the infusion or transplantation of whole dopamine producing cell into the part of the brain where the lead cells used to release DA. The numerous pre-clinical studies have shown that transplanting dopaminergic neuron improves motor symptoms in animals with Parkinson’s disease.

CRT is performed by using stem cells. Stem cells are the body’s raw material cells from which all other cells with specialized functions are generated. They divide to form more cells. These daughter cells either becomes new stem cells (self-renewed) or become specialized cells (differentiation) with a more specific function such as, bone cells, heart muscle cells, blood cells and brain cells. The ability of stem cells to multiply and differentiate into any other cell type with specialized function is known as pluripotency. Due to two distinct properties i.e. differentiate and multiply stem cells can serve as an internal repair system, dividing without limit to replenish other cells. The two main sources of stem cells are embryos (embryonic stem cells) and adult tissue (adult stem cells). These cells are generally characterized by their potential to differentiate into particular cell types such as skin, muscle and bone.

Following are the sources of stem cells:

i) Human embryonic stem cells (hESCs):

In 1981, embryonic stem cells (ESCs) were first isolated from mouse blastocysts. The pre-clinical study showed some gradual but significant improvement of symptoms in rats with ESC-derived dopaminergic neurons. This study also highlighted some unfavorable

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side effects. It involves a high rate of tumor formation and graft failure. The study showed some positive results, the high incidence of tumor formation indicates some risks involved in transplantation highly proliferative tissue.

Another study looked at stimulating the differentiation of ESCs into dopaminergic neurons in vitro before transplanting these into an animal model of PD. It showed that the grafted ESC-derived neurons survived and proved to be functional but the study also agreed that tumor formation was an unacceptable complication associated with ESC grafts so that the further animal studies were required to understand safety and efficacy of these transplants.

In 1998, human embryonic stem cells (hESCs) were first isolated by Thomson. These cells are harvested from the blastocysts and a number of human embryonic stem cell lines have been generated from excess embryos from in-vitro fertilization procedures. The blastocysts consist of inner cell mass (ICM) and trophoblast cells (trophectoderm). ICM cells are totipotent, so they can give rise to a complete human being. Once ICM cells have been removed from the intact blastocyst they become embryonic cells. Embryonic cells are pluripotent. Human embryonic stem cell research remains at the pre-clinical stage and early work showed that ESCs could alleviate neurochemical and behavioral problem in animal model of degenerative disease. One of the limitations of embryonic stem cell use is caused by their immunological rejection phenomena.

ii] Human induced pluripotent stem cells (hiPSCs)

A new technique of deriving human pluripotent stem cells has been evolved in 2007 which is concurrent to the development of “disease specific” hESC lines. The generations of hiPSCs have been shown ESC like properties. These cells have been generated from adult somatic cells such as skin fibroblasts or peripheral blood mononuclear cells (PBMCs) by genetic reprogramming process.

The reprogramming of mouse and human somatic cells to a pluripotent state has been performed by viral transduction of four transcription factors. The transcription factors used were OCT4, KLF4, SOX2 and c-MYC.

In the mouse system, it has been demonstrated that induced pluripotent stem cells (iPSCs) develop tumors resulting from reactivation of the c-MYC. When reprogramming has been achieved in the absence of c-MYC, it was shown longer latency with reduced efficiency. A major limitation of hiPSCs in the clinical application is the presence of viral vectors used for transduce the reprogramming factors. To avoid the integration of vector and transgene sequences into the cell genomes different vectors were used such as adenoviral vector, sedai virus, episomes, plasmids, transposons, synthesized mRNAs and proteins.

The process by which somatic cells are converted to iPSCs is not fully understood. They represent an endless source for patient- specific stem cells because they overcome the ethical aspects related to embryonic stem cell production. They also have tremendous potential applications in regenerative medicines, drug development, toxicity tests and disease modeling.

iii] Adult stem cells

The common type of adult stem cells are Mesenchymal Stem Cell (MSCs). MSCs present in adult bone marrow normally provide structural and functional support for hemopoiesis. The mesenchymal stem cell therapy is an attractive research field for scientist because these cells are free from ethical and immunological problems. MSCs have capacity for multipotency and differentiating under appropriate condition into chondrocytes, skeletal myocytes and neurons.
According to recent studies, it was found that human mesenchymal stem cells produce neurotrophic factors (NTFs), such as vascular endothelial growth factor (VEGF), nerve growth factor (NGF), brain derived neurotrophic factors (BDNF), ciliary derived neurotrophic factors (CDNF), glial cell line derived neurotrophic factors (GCNF), which are neuroprotective molecules, but the source and the donor influence the synthesis rate.\(^{[105, 106]}\) CD29 (B-1 integrin), CD90 (Thy-1), CD54 (intracellular adhesion molecule), CD44 (homing associated cell adhesion molecule), CD71 (transferrin receptors), CD105 (SH2, SH3, Stro-1, and CD13 are mesenchymal markers by which MSC’s are express, but they do not express markers typical of hematopoietic and endothelial cell lineages, such as CD11b, CD14, CD31, CD33, CD34, CD133 and CD45.\(^{[107, 108]}\)

NTFs are essential for the development and maintenance of normal neuronal function in adults and also for neuronal survival and differentiation.\(^{[99]}\) According to experimental studies, NFTs slows the progression of degeneration, enhance the activity of remaining neurons, induce regeneration, support the survival of transplanted dopaminergic cells and induce proliferation and differentiation of neural stem cells. Thus, the use of this therapy is increased due to the effectiveness of NTFs in protecting or restoring dopaminergic neurons.

In vitro studies have shown that MSCs can not only inhibits nearly all cells participating in the immune response cell-cell-contact-dependent mechanism but can also release various soluble factors that might be involved in the immunosuppressive activity of MSCs, but the exact mechanism is unclear.\(^{[99, 109, 110]}\)

The in-vivo and in-vitro studies have shown that MSCs exert tissue protective effects via anti-inflammatory action.\(^{[111, 112]}\) These studies have shown that MSCs increased the expression of the anti-inflammatory cytokines IL-6, IL-10 and transforming growth factor beta (TNF-beta) and decreased the number of activated forms of microglia.\(^{[113]}\) MSCs also increased the production of TNF-alpha and inducible nitrous oxide synthase (iNOS) from microglia stimulated by lipopolysaccharide (LPS).\(^{[114]}\) Thus, by this anti-inflammatory mechanism MSCs show neuroprotective effects against dopaminergic neurons death.

The major advantage of MSCs in clinical application is their neuroprotective properties which have therapeutic implications for Parkinson’s disease.\(^{[115]}\)

4] Physical therapy

Physical therapy is not a cure for PD, because neurological damage cannot be reversed.\(^{[116]}\) It focuses on mobility-related activity limitation, includes physical capacity, transfers, manual activities, balance, gait and an important target for PD treatment is posture.\(^{[117, 118]}\) This therapy includes support to patients for participation in movement related activities and self-management and also helps to build strength, balance, flexibility and coordination. The aim of this therapy is to increase general fitness, movement quality and functional independence. It deals with anatomy and person’s strength, capacity and motor progress.\(^{[119]}\) In this treatment, first appointment is for evaluation and recommendations for exercise and further appointments are for checking patient’s progress.

Physical therapist teaches exercise and other techniques such as-
- Get in and out of bed
- Muscles stretching to improve range of motion
- Avoid fall
- Smooth walk
- Go up and down from stairs\(^{[120]}\)

Physical therapists used cues to improve gait.\(^{[121]}\) Cues are classified as auditory (using music),\(^{[122-126]}\) visual (stepping over stripes on the floor),\(^{[122-128]}\) tactile (tapping on the hip or leg)\(^{[122, 123]}\) and cognitive (using a mental image of the appropriate length of a step).\(^{[128]}\) In PD
patients, visual or auditory cues have been applied to improve gait during active training. But how cues improve movement is not yet clear.

**Types of physical therapy:**

1) **Amplitude Training**
   This is a specific type of physical therapy for PD and it is called as LSVT BIG training (LSVT- Lee Silverman Voice Treatment). LSVT LOUD therapy is to amplify the voice. It involved a way to retrain the muscles and slow down the progression of hypokinesia.

2) **Balance**
   For patients with Parkinson’s disease, when balance training combined with walking training exercise, muscle strengthening and the range of movement is more effective than balance exercise alone.

3) **Exercise**
   It consists of repetitive and planned physical activity. Exercise performed with three different goals. First, improve physical capacity and functional mobility including balance, transfers and gait. Second, it works as a symptomatic treatment for suppression of motor symptoms. Third, it improves non-motor symptoms such as depression, apathy and fatigue.

4) **Strength Training**
   For patients with Parkinson’s disease muscle weakness is a bigger problem. Physical therapists guided people to strengthen their muscles using exercises that use light weights (light dumbbells) or a resistance band (a kind of thick rubber band).

   Physical therapy cannot stop Parkinson’s disease. It can help to improve a patient independence. Also, increase quality of life by improving cardiovascular health, strength, movement range and relieving pain.

5) **Occupational therapy**
   Occupational therapy (OT) is a multidisciplinary treatment. Several multidisciplinary rehabilitative treatments have been shown to be effective for Parkinson’s diseases patients in reducing PD symptoms and improving motor function. This focuses on enabling the person to engage in daily activities. Also, deals with rehabilitation and motion. The aim of this therapy is to help people with Parkinson’s disease to stay active in their daily life by improving skills, showing different ways to complete tasks. For this, therapists combine design exercise and mental health with physical aspects. Modifications of occupational therapy with PD:

   - Changing the time, nature and duration of an activity.
   - To reduce situations, arranging items.
   - To reduce the risk of falling, environment structuring.
   - Activities simplification by breaking complex action into simple task.

   Occupational therapy teaches way to help you accomplish daily tasks more easily, confidentially and safely. This therapy can reduce the high level of disability and improve the quality of life. This therapy also improves the performance and engagement in activities within the community. This therapy is different for each patient. In this therapy, first appointment includes evaluation and recommendations. The following appointments are for checking progress and review of patients. This therapy used along with other treatment to tackle with motor and non-motor symptoms of PD.

   Occupational therapy focuses on adapting the environment through modifying the task, teaching skills and educating the person. For this, the training and advices are given to patients with PD by therapists. Occupational therapist encourages their patients with PD engage in their regular physical activity.

   Following are some things that therapists can teach patients:
• How to use a walker?
• How to keep balance while working?
• How to get in and out of bed easily?
• Tricks to do other self-care tasks.
• Easy tips to make daily activities e.g. eating, cooking.

In occupational therapy some recommended areas are:

1] Mobility:
This includes help to the patient with PD to concentrate on walking avoiding other non-essential talking.\[138\]

2] Prevention of fall:
This includes people with PD concentrate on walking with full attention.\[138\]

3] Sit-to-Stand transfers:
It involves practice of sit to stand transfers from chair with full attention without falling down.\[138\]

4] Domestic skills:
It includes practice of some work which is affected due to loss of coordination and balance.\[138\] E.g. Meal preparation

5] Fatigue management:
In this, therapists introduce regular resting period to patients because PD patient’s feels tired more quickly due to inefficient movement.\[138\]

6] Handwriting:
People with PD tend to have handwriting where small letters are sloping towards page corners instead of straight across.\[138\]

Occupational therapists serve as a link between a patient and the workplace. They promote the maintenance of normal roles, daily routines and social habits.

6] Dogfish Shark Therapy
A recent study suggest that a chemical compound derived from dogfish shark is may be the key to treat PD. Proceeding of the National Academy of sciences was published that the “Squalamine” derived from dogfish sharks reduced the creation of α-synuclein. These results were seen in both human neurons cells and in roundworm models of PD.\[141-143\]

“Alpha-synuclein” is a small protein (140 amino acid), which is encoded by the SNCA gene and it is the best isoform of the synuclein protein family.\[144\] Its physiological role is still not fully understood but there is growing experimental evidence for a causal role of α-synuclein in neurodegenerative disease like PD.\[141\] The abnormally aggregated alpha-synuclein is the major component of lewy bodies and lewy neurities, which are characteristic of PD.\[145,146\]

In 1993, Michael Zasloff discovered squalamine from the liver of dogfish shark of the genus squalus.\[141\] Squalamine is a steroid-polyamine conjugate, naturally occurring compound. It is having broad spectrum of anti-microbial activity and anti-angiogenic activity. Zasloff has been studying for more than 20 years.\[146\] He explained that squalamine is a positively charged molecule which having a high affinity for negatively charged molecules. When it enters in a cell, it fits on a particularly negatively charged membrane present in that cell and kicks off proteins (alpha-synuclein) that are stuck on. It also helps to prevent aggregation of alpha-synuclein.\[141\]

Zasloff studied by using animal model of worm. These worms have been genetically engineered to produce human alpha-synuclein in their muscles. As the worms grown alpha-synuclein protein accumulated, they experienced that begin to damage their functional activity. When squalamine given to these worms, there is an inhibition of the aggregation and complete rescued of the animals from damage.\[147\]

In in-vitro models squalamine was first tested to establish how it interacts with alpha-synuclein and lipid vesicles, which are known to cause a build-up of the protein in brain cells. The investigators found that protein aggregation was successfully
inhibited with the help of squalamine by stopping alpha-synuclein binding to negatively charged lipid vesicles.\[^{142}\] Then squalamine was tested in Caenorhabditis elegans because they share approximately 40% of their genes with humans. When squalamine was orally administered by C. elegans, it was found that the shark derived compound inhibited alpha-synuclein aggregates and prevented the toxic effects of the protein.\[^{142, 147-149}\]

The researchers said that further studies should be required to determine whether squalamine can reach the specific parts of the brain where the process determining Parkinson’s take place.\[^{146}\]

7] Coffee Therapy

There is no known cure to prevent or delay the Parkinson’s disease progression. Now, coffee therapy has been developed to treat PD because active compound in coffee possess therapeutic effects for treating Parkinson’s disease. The most effective drug being used to treat symptoms of PD is L-DOPA.\[^{150}\] Current studies have shown that coffee consumption increases the effects of L-DOPA and has an effective role in both the onset and progression of PD.

Coffee is one of the most consumed beverages around the world. There are so many compounds found in coffee but mainly it contains caffeine.\[^{151}\] Caffeine has important role in prevention of PD development. Caffeine antagonizes and blocks adenosine A2A receptors in the striatum. The blockade of receptors improves motor functions\[^{152, 153}\] It indicates that coffee as A2A receptor antagonist in potential symptomatic treatments for PD. Increasing consumption of coffee has been correlated with a lower risk of PD development.\[^{154, 155}\]

Active compounds in coffee are able to penetrate blood brain barrier (BBB). After entering the CNS, L-DOPA converted into dopamine (DA) via enzyme aromatic L-amino acid decarboxylase.\[^{156}\] Caffeine behaves as a competitive inhibitor for enzymes that participates in converting L-DOPA to DA. Studies have confirmed that caffeine is metabolized by isoforms of CYP.\[^{157, 158}\] The conversion is occurring via different enzymes. Caffeine acting as an inhibitor which enhances the effects of L-DOPA in treatment of PD. L-DOPA has a half-life of 60-90 minutes.\[^{159}\] Caffeine extends the time of L-DOPA present in body before its conversion into DA. DA is the neurotransmitter which binds to DA receptors in central nervous system (CNS). DA receptors have five subtypes; D1, D2, D3, D4 and D5.\[^{160}\] The loss of D1 and D2 receptors are associated with onset of PD.\[^{161}\] D1 receptors activate adenylate cyclase whereas D2 receptors inhibit it.\[^{162}\] These both receptors have opposite roles.

The coffee compounds also have been shown to stimulate production of G-CSF via immune cells.\[^{150}\] G-CSF binds to receptors on the cell membrane. The nucleus and relay chemical signals prevent the apoptosis and extend the cells. Mechanism is also applying to cells other than neurons, in particular those of the immune system. Immunity suggested as a significant catalyst in a variety of disorders such as PD. There is a benefit to coffee drinkers that many of the coffee compounds have been shown therapeutic effects. So, it is still necessary to continued research on coffee to find many more uses of it.\[^{150}\]

CONCLUSION

There is no known cure for Parkinson’s disease. There are many modern therapies have been developed for the treatment of PD, including DBS, stem cell therapy, gene therapy, coffee therapy, etc. But all of these therapies have some merits and demerits. Many PD patients goes for surgical therapies due to inadequate symptomatic relief on medication or because they suffer from medication-related side effects. DBS helps to relieve motor as well as some non-motor symptoms of PD. Pallidotomy and subthalamotomy improve tremor, motor fluctuation, rigidity, bradykinesia, dyskinesia, walking and balance, but it can not a cure disease. Gene
therapy is not a cure for PD, but it may allow more effective management of symptoms. Stem cell therapy also improves symptoms of PD. Current treatment showed only slowing down the progression of PD. Hence further preclinical and clinical studies are required to determine whether stem cell-based therapies can be useful in treating disorders.

Physical and occupational therapy are not cure but care for PD. It increases patient’s strength, balance and may help to relieve pain. It also improves quality of life of patients. Recently coffee therapy has been developed to treat PD. Active compounds in coffee therapy have ability to penetrate BBB but there is a need of further research to find its effectiveness. A recent study suggest that a chemical compound derived from dogfish shark is may be useful to treat PD, but still it is necessary to continued research on Shark therapy.

We have found that there is no proper cure for PD. Hence there is a need of more research to develop a permanent therapy for PD.

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