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A futuristic perspective in subsiding the symptoms of Parkinson's Disease

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder that primarily impinges the dopaminergic neurons in a particular region of Brain termed as Substantia Nigra. The disease affects more than 1900 people per 100,000 aged 80 years and above. Furthermore, men are 1.5 times more prone than their counterpart. Potential biomarkers escalated the precise diagnosis and helped to initiate treatment to limit its adversity. The current therapeutic schemes are focused on administration of Dopamine precursor, Dopamine agonist, Monoamine oxidase (MAO) inhibitor, Catechol-o-methyl transferase (COMT) inhibitors and deep brain stimulation. The CNS delivery focuses mainly on increasing the dopamine level in the brain. CNS drug delivery faces a crucial challenge of crossing Blood Brain Barrier. Blood-Brain Barrier Penetration can be attained by several techniques. Conventional drug therapy yields harmful affects to the patients without much therapeutics. It is visible that crossing BBB is quite strenuous process. It is mandatory for developing a novel approach untangling these situations. Nanotechnology-based formulations like nanosuspensions, nanotubes etc. promotes the penetration of drug across the sophisticated barrier without creating any deterioration to cells or organs. Several novel routes for drug administration reduce dose intake with increased and precise pharmacological action. Nanoformulations and Novel routes of drug administration are a promising tool to enhance the action of drug which helps to abate the symptoms of the Disease and assist in the betterment in treatment.

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INTRODUCTION

Parkinson's disease (PD) is a chronic, second most common neurodegenerative disorder following Alzheimer's disease. PD was first described by James Parkinson, an English Surgeon in 1817 in his book "An essay on the Shaking Palsy" (Pearce, 1989). It affects 0.5 – 1% of population with 65-69 years and 1-3 % of the population above 80 (Tanner and Goldman, 1996). It has been evaluated that 10 million or more individuals worldwide have been affected by this ailment. It adversely affects the normal body movements (Davie, 2008). Early onset of Parkinson's is often inherited or is linked with mutation of a specific gene. The Parkinsonian symptoms may appear in very rare cases in people aged below 20. This condition is termed as juvenile Parkinsonism.

PD is characterised by the progressive degeneration of Dopaminergic neuron of Substantia Nigra, which causes Dopamine (DA)loss (Michel *et al.,* 2016). The paucity in Dopaminergic neurons blocks various motor functions as well as non-motor functions. Moreover, it is indicated with the four cardinal motor symptoms that are;

- Bradykinesia: It is the slowness in performing voluntary movements or an incapability to

move body swiftly. It is an authentication of basal ganglia disorders, and it circumscribes with the inability in planning, initiating and executing movement and other tasks. (Berardelli *et al.,* 2001)

- Rigidity: Stiffness in limbs or other body parts that stops the muscles from stretching and relaxing which results in inflexible muscles, pain, and cramps. Rigidity may be bound with pain, painful shoulder and is one of the most recurring initial manifestations of PD even though it may be misdiagnosed as Arthritis, Bursitis or Rotator cuff injury (Riley *et al.,* 1989, Stamey *et al.,* 2007).
- Tremor: Involuntary and Intractable movement of body parts specifically limbs even at rest. Certain patients may have internal shaking which is not visible (Shulman *et al.,* 1996)
- Postural instability-problems with standing, walking or impaired balance and coordination caused due to loss of postural reflex.

Various non-motor functions are also affected which includes Olfactory (Ansari and Johnson, 1975). Or potentially autonomic dysfunction, cognitive debilitation (Emre, 2003) mental indications, sleep disorders (Garcia Borreguero, 2003), pain, and fatigue. These conditions substantially deteriorate the quality of life of the diseased and his companion. One of the usual psychiatric disorder associated with PD is Depression (Burn, 2002). But it is under diagnosed and under treated that results in worsening of symptoms. Two important neuropsychiatric syndromes associated with PD are Impulse control disorders (ICDs) and apathy (Pluck, 2002) which may have a major effect on patients with PD and their carriers and are also associated with severe psychiatric morbidity.

Risk factors associated with Pd

Several factors are responsible for any diseases. Higher risk for PD is associated with various parameters that are enlisted in Table 1.

Pathophysiology of PD

The cause of Parkinson's disease is still considered largely idiopathic. It likely involves the interaction of host vulnerability and environmental factors. Pathophysiologically, the symptoms associated with Parkinson's disease are due to loss of a number of neurotransmitters, primarily Dopamine. Various causes for neuronal cell death that in turn results in the disease condition are shown in Figure-1. Abnormal turnover of cellular constituents somehow contribute to the stage for development of PD. Parkinson's is usually termed as a complex neurodegenerative disease with a series of progression. It first affects the dorsal motor nucleus of

the vagus nerve and the olfactory bulbs and nucleus (Hawkes *et al.,*1999), then the locus caeruleus, and eventually the Substantia Nigra. Cortical areas of the Brain are affected at a later stage (Braak *et al.,* 2003). However, the two main neuropathologic inference in Parkinson's disease are Loss of pigmented Dopaminergic neurons in the Substantia Nigra (Forno, 1982) region and presence of Lewy bodies and Lewy neurites. (Forno, 1996, Kovari *et al.,* 2009).
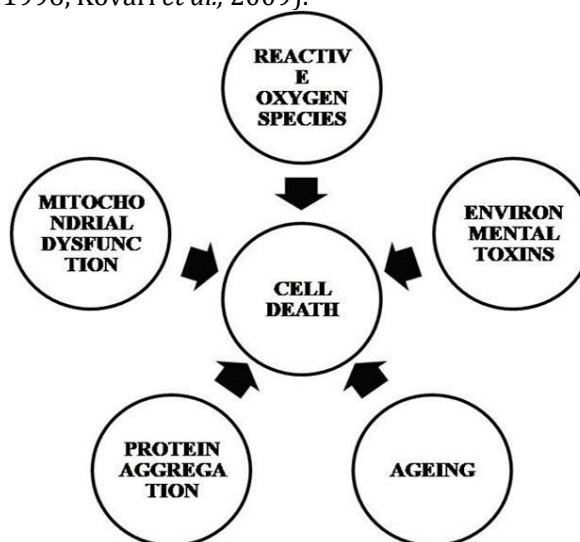

Figure 1: Pathophysiology of PD

The Environmental hypothesis of PD is based on observation of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). MPTP is found as a contaminant in illegally synthesised batches of opioid meperidine. MPTP exerts its action indirectly by getting converted to toxic MPP+ ion by enzyme MAO type B. MPP+ is toxic to neurons by obstructing the mitochondrial metabolism. The free radicals generated by auto-oxidation of dopamine & MAO metabolism may damage the mitochondria & cell membrane (Zhang, 2010). Dopaminergic neurons are degraded in oxidative Deamination by Monoamine Oxidases A&B. The action of MAO is age-related. In seniors, MAO action increases while dopamine level gets depleted which is accompanied with release of many reactive oxygen species. Non-enzymatic reaction of Dopamine neurons with oxygen form Quinines and Semiquinones with production of Superoxides, Hydroxyl ions and Hydrogen peroxide which in presence of iron deposits in Brain and may lead to Lipid Peroxidation and Neurotoxicity by interfering with Mitochondrial Oxidation metabolism. Increased production of hydrogen peroxide due to oxidative deamination by MAO is closely associated with increased oxidative stress (Mary and Gerald, 1989). Due to loss of Dopaminergic neurons from Substantia Nigra (Hornykiewicz, 1982), the nerve cells fails to release Dopamine to the Dopamine receptors D1 & D2 over the Striatum. Thus, the receptors get deactivated. This hinders the transmission of signals

from Striatum to Thalamus, which in turn cause decreased Motor output (Beaulieu and Gainetdinov, 2011). As a result, Bradykinesia, Tremor, Rigidity, Dyskinesia occurs that marks the presence of Parkinson's Disease (Poon *et al.,* 2005).

In Autosomal Dominant PD two mutations have been found in the gene coding for α- synuclein on chromosome 4q (Conway *et al.,* 2000) Abnormal folding of this protein leads to impaired cellular processing called Ubiquitination, which further leads to accumulation of Lewy bodies and Lewy neuritis (El-Agnaf. *et al.,* 2002)*.* Lewy bodies are concentrically laminated, eosinophilic, intracytoplasmic inclusions composed of aggregates of α-synuclein, neurofilaments and ubiquitin. α-synuclein is an abundant lipid binding protein associated with synapses(Gibb and Lees, 1988). It is involved in mitochondrial targeting, so any alteration in the gene coding for a-synuclein leads to mitochondrial dysfunction (Devi *et al.,* 2008, Baba *et al.,* 1998) In a PD patient, Lewy bodies are first observed in medulla oblongata, olfactory bulb, pontine tegmentum. Mitochondrial dysfunction produces increased oxidative stress which in turn cause defect in mitochondrial complex-1. Thus, ATP synthesis get reduced leading to neurodegeneration in PD. Mitochondrial dysfunction is due to mutation in gene that encodes DJ-1, PINK1 and Parkin (Dawson and Dawson, 2003). DJ-1 is an oxidative stress protein, and its loss leads to neurodegeneration (Vincenzo *et al.,* 2003). PINK-1 is a kinase that is degraded in mitochondria under normal circumstances, but with mitochondrial dysfunction, Parkin gets replenished. Parkin plays a role in protein degradation, and it is an E3 Ubiquitin Ligase. In normal case combination of PINK1 and parkin cause clearance of dysfunctional mitochondria (Jessica *et al.,* 2003). In case of PD, dysfunctional mitochondria get accumulated causing disruption in autophagy. Mitophagy is selective autophagy of mitochondria in which damaged or excess mitochondria is eliminated. Defective mitophagy leads to decreased ATP production thereby leads to mitochondrial destruction and finally neurodegeneration (Ding and Yin, 2012). Mutation in gene encoding LRRK2 cause autosomal dominant PD. LRRK2 is a cytoplasmic kinase. Pathogenic mutation increases the kinase activity of LRRK2 causing mitochondrial fragmentation and decreases mitochondrial fusion producing defective mitochondria (Nuytemans *et al.,* 2010, Subramaniam and Chesselet, 2013).

Biomarkers in PD

Biomarker is defined as a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention". A biomarker acts as a tool to track the diseases by confirming a diagnosis, diseases progressions and response to treatment. Several studies helped in identifying numerous biomarkers in PD. These include clinical, genetic, blood, cerebrospinal fluids and neuroimaging biomarkers.

Clinical Biomarkers

PD is characterised by certain motor symptoms which acts as a key biomarker for the pathologic condition (Berardell *et al.,* 2013) the Dopaminergic loss. These symptoms progress at various rates in each individual. Some cases are unexplained regarding the symptoms as these are seen at different stages of may even be absent in a PD patient. Visibility of these symptoms depicts the degree of disease progression. Apart from these clinical signs including symptomatic therapy, there exists a limitation to separate symptomatic from neuroprotective action.

Various non-motor features including REM sleep behaviour disorder, olfactory impairment, depression, bowel problems are also characterised along with the motor symptoms.REM sleep behavioural disorder is specifically associated with higher risk of Parkinsonism (Boeve, 2013) and dementia. Depression, ability to experience things is lacked in PD patient. Over 90% of diseased posses olfactory impairments which can be detected by smell testing.

Genetic Biomarkers

It has been stated earlier the aetiology of PD is idiopathic, but a certain mutation in the genes are correlated with PD. Mutation of genes like - a-synuclein (SNCA), Parkin, PTEN-induced kinase (PINK1), DJ-1, and Leucine-rich repeat kinase 2 (LRRK2) accounts for 2% with PD and is tantamount with idiopathic one. Mutation in the gene for glucocerebrosidase too results in depicting Parkinsonian features (Beavan *et al.,* 2015). Genetic causes of PD sustain in one's body for years or maybe for decades before the appearance of symptoms. In this case, one can detect numerous misregulated genes, and their messenger RNA or protein expression allows in the Characterisation of networks of interacting proteins that manifest the root of disease process.

Biochemical Biomarkers

It has been identified that certain potential biomarkers are present in blood, saliva, CSF that helps in the detection of the ailment. α-synuclein first gene discovered which was found to cause PD and could be detected from patients CSF, serum, urine and even in Gastrointestinal tract(Malek *et al.,* 2014). DJ-1 also accounts as a biomarker in PD

after mutations in the gene encoding this protein were identified in familial PD, but only in rarest cases(Bonifati *et al.,* 2004) Like a-synuclein, CSF DJ-1 can also be a PD diagnostic markers (Hong *et al.,* 2010).

Elevation in Oxidative stress is common in PD but not specific to this condition. 8-OHdG(8-hydroxy-2'-deoxyguanosine), nitrotyrosine, and reactive oxygen species may act as biomarkers for tracking disease progression, because as mentioned earlier; markers of oxidative stress increase as PD progresses (e.g., urinary 8 OHdG) (Sato *et al.,* 2005). It has been discovered that hydroxyl radical levels in the plasma of PD patients were higher and helps to correlate with disease duration (Ihara *et al.,* 1999).

Neuroimaging Markers

Various neuroimaging techniques are quite available and has been widely used for the diagnosis of PD (Pavese and Brooks, 2009). Positron Emission Tomography (PET), Single Photon Emission Tomography (SPECT), Magnetic Resonance Imaging (MRI) and Transcranial Sonography (TCS) are a non-invasive technique for tracking of molecular targets of importance in neurodegeneration. MRI and TCS can examine the structural changes in the brain that may indicate increased risk for PD, while PET and SPECT in synchrony with radioactive metabolic tracers computes function, and may support the diagnosis as well as monitor the severity of disease and its progression. PD is associated with dopamine loss in the Substania Nigra region; therefore, a felicitous biomarker in neuroimaging of the dopamine system is essential. Radiotracers like 18-Fluorodopa, Dihydrotetrabenazine, 2-beta- carbomethoxy-3-beta-4-fluorophenyltropane reflects the activity of dopamine transporter (DAT) or vesicular monoamine transporter type 2 that accounts for the status of the disease (Delenclos *et al.,* 2016).
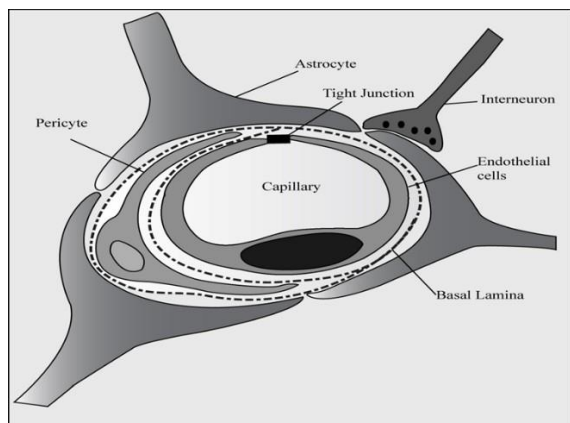
Blood-brain barrier (BBB)

Figure 2: Blood-Brain Barrier

Every organism with well-defined CNS possess a Blood Brain Barrier (BBB) (Abbott, 2005) It is a functional vascular endothelium that comprises of astrocytes, neurons, tight junctions, adherent junctions and pericytes (Hawkins and Davis, 2005). Diagrammatically it can be represented as in Figure 2. It guards the Brain from particles in the systemic circulation. Under normal physiology, BBB helps in oxygen supply to the Brain cells and initiate inflammatory response near the brain and associated areas. Neurons should be alienated from the rest of our body for an explicit communication among them and this is attained by BBB (Bradley *et al.,* 2011) Continuous supply of oxygen and nutrient is an essential parameter and moreover the brain homeostasis should be maintained as neurons are sensitive to numerous compounds and varies its concentrations(Yuri *et al.,* 2006). To overcome these requirements, brain vessels are recast sculpting the BBB. Unlike other barriers BBB lacks fenestrations, and tight junctions are abundant (Abbott *et al.,* 2010) BBB composed of blood vessels built up by specialized endothelial cells, Astrocytes encasing the vessel has a role in neuroinflammation (Clarke and Barres, 2013), Pericyte forming a Basal lamina which is made of mesenchymal cells and plays an important role in maintaining BBB integrity and promotes angiogenesis. Pericytes also posses multipotent stem cells (Armulik *et al.,* 2011). A number of factors influence the integrity of the complex barrier. These are tight junction and adherent junction, impediment of fenestrae, pinocytosis, transcytosis of bulk drugs, and moreover the inhibition of Leukocyte Adhesion Molecule (Obermeier *et al.,* 2013). Major functions of BBB components are described in Table 2. In order to cross the barrier, several transport mechanisms can be adopted. These mechanisms are tabulated in Table 3.

Apart from its specific functions, BBB possess various vital functions. It helps in the maintenance of ionic composition; it separates central and peripheral transmitter (Bernacki *et al.,* 2008) prevention of macromolecule from entering the brain; as certain macromolecules such as Albumin, Prothrombin, and Plasminogen leads to Cellular Apoptosis. (Gingrich and Traynelis, 2000, Nadal *et al.,* 1995), shields the CNS from neurotoxins and provides brain nutrition by specific transport mechanism. In general, it serves a stable fluid microenvironment and protects the brain from toxins and other damages.

In order to exhibit definite pharmacological action, it should cross the Barrier (Krishnapriya *et al.,* 2017). This task is quite laborious. It has been identified only negligible amount of large-sized and small-sized molecule can cross the barrier. Numerous *In-vitro* studies are carried to recognise a significant material to enhance BBB penetration.
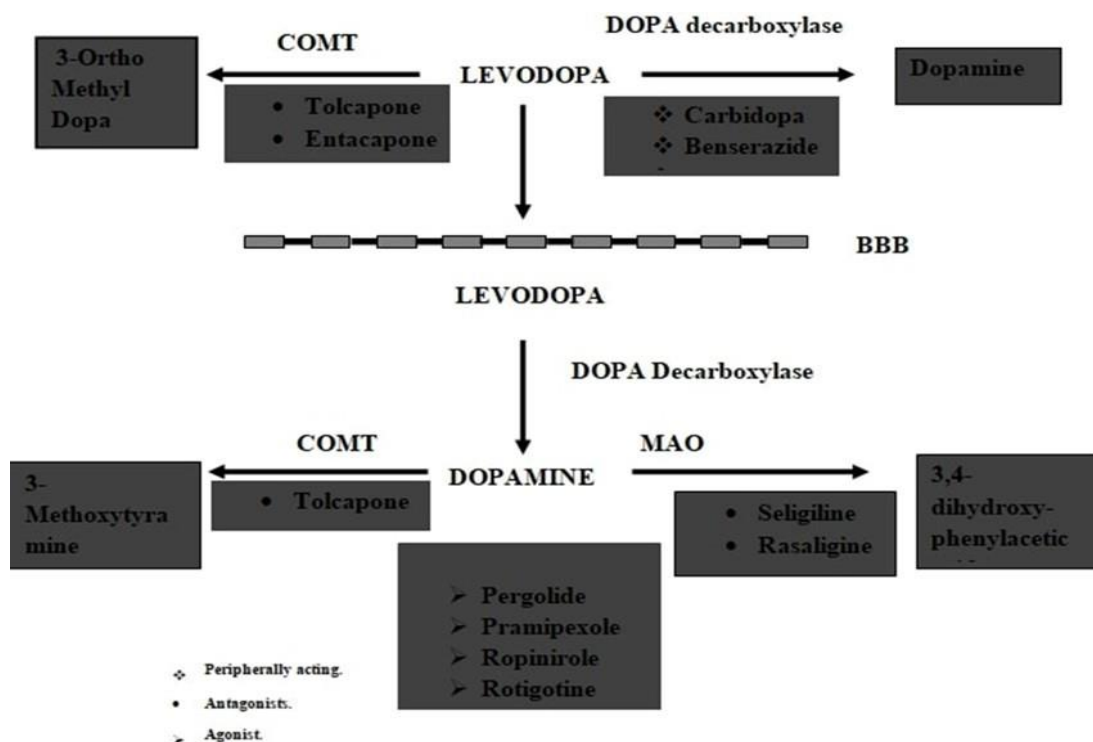
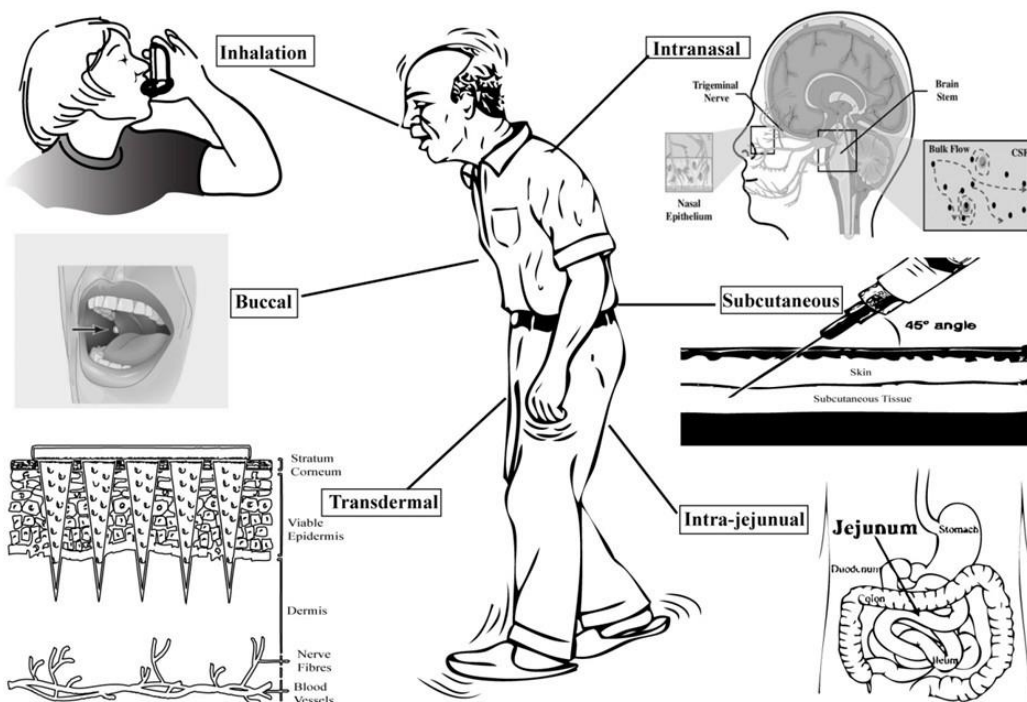**Figure 3: Pharmacological approach for treating PD**

Figure 4: Representation of possible routes for drug administration in PD

When considering the case of a drug molecule, there are several physicochemical parameters should be considered which includes the lipophilicity of the drug, size, plasma drug-protein binding etc. Another issue is the inability of the drug to reach BBB with sufficient concentration to elicit the Therapeutic action. Conventional Oral Administration undergoes presystemic metabolism that deplete the drug molecule and eventually affect its action, even on administration of sufficient dose. One of the best ways is Nanotechnology-based Drug Delivery. Upon adopting this strategy, it is easy to reach the CNS target. Initially, the drug should reach systemic circulation by various routes from which it crosses the barrier. One of the merits for using Nanoparticle in contrast with current method is that it does not cause any destruction of BBB (Jain, 2007). Nanoformulations to en-

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hance BBB penetration and various routes to elevate drug in systemic circulation are discussed below.

Current treatment strategies for PD: The practice of giving drugs which reduces the severity of the disorder is more common in case of neurodegenerative diseases like Parkinson's, Alzheimer's etc. where the complete cure is not desirable. In consideration with PD, the drugs which induce the production and release of dopamine neurotransmitters help in reducing the risk of the disease. The medications like levodopa, MAO inhibitors, COMT inhibitors are most prominent medications which are widely used. Current Drug therapy for PD is shown in Figure 2.

Levodopa therapy: This includes the administration of the drug which increases Dopamine level by the conversion of the levodopa- the precursor of Dopamine into Dopamine by the action of the enzyme amino acid decarboxylase. The amino acid precursor is taken up in the gastrointestinal tract by a facilitated transport mechanism. When the levodopa enters into the brain through systemic circulation, it rapidly gets converted into dopamine in the nerve terminals of Substantia Nigra. The revival of the neurotransmitter helps in promising changes in the disease over few decades. The levodopa therapy though helps in improving the condition of patients but provides adverse side effects including Nausea, Depression, Tachycardia, Anorexia etc. (Olanow *et al.,* 2004).

Along with these effects, the administered drug elicits an action of conversion into dopamine in the peripheral tissues. This conversion decreases the dose of the levodopa entering the Blood-Brain Barrier which in-turn results in neurodegeneration. Various study states that levodopa administration produces Apoptosis in PD patients through the activation of Apoptosis signalling kinase 1. Hence, the combination of the drug by targeting the kinase leads to better therapeutic action (Fahn *et al.,* 2004).

Levodopa is combined with carbidopa (Papavasiliou *et al.,* 1972) or benserazide (Birkmayer and Mentasti, 1967) which prevents aromatic amino acid decarboxylation in peripheral tissues. This helps in the transport of the increased dose of drug into the blood-brain barrier where it can be converted into dopamine. This combination of the drug declines the symptoms in patients with PD.

Levodopa is available as different dosage forms in different brand names. These are formulated as tablets (disintegrating, extended release), capsules, enteral suspensions etc.;

DOSE**:** Standard release preparations: 25/100 or 25/250mg tablets.

Extended-release preparations: 25/100 or 50/200mg

MAO Inhibitors: The Monoamine Oxidase inhibitors mainly includes Selegiline, Rasagiline etc. The MAO inhibitors are helpful in preventing the degradation of dopamine which enhances the dopamine level. Comparatively, the MAO inhibitors elicit less effective than levodopa. Selegiline inhibits the enzyme MAO-B which promotes the dopamine level in the synaptic terminals of the nerve (Ives *et al.,* 2004). Selegiline is also administered in combination with levodopa so that it provides a pharmacological effect. The combination is given in low dose so as to avoid complications such as hypertension when upgrading the quantity of dose.

Rasagiline is also an inhibitor of MAO-B which has been newly identified for the therapy of PD. It is an effective mono treatment that cures the early symptoms of the disease (Parkinson Study Group, 2002, Parkinson Study Group, 2005). But Selegiline is mostly preferred than Rasagiline due to the cause of insomnia while combined administration of the drug. Rasagiline is available as tablets whereas Selegiline as both tablet and capsule.

COMT Inhibitors: The main function of Catechol-O-methyl transferase enzyme is it inactivates the catecholamine Neurotransmitters like dopamine transmitters by degrading the catechol structure. When the administration of levodopa takes place, it increases the risk of the conversion into 3-O-methyl dopa by COMT enzyme which actively competes with the drug during the transport through a blood-brain barrier. This minimises the active transport of the drug into the blood-brain barrier. (Thorogood *et al.,* 1998) The COMT inhibitors including Tolcapone and Entacapone widely involves in decreasing the risk of the disease. The administration of drug produces less effective when compared with the prominent drug levodopa. The action of Tolcapone and Entacapone initiates at the peripheral tissue where the COMT enzyme actively converts the drug into 3-O-methyldopa. It blocks the conversion of levodopa which results in the transport of the drug into the CNS. The drug thus transferred is converted into dopamine where the level is balanced by the COMT inhibitors which prevents the degradation of dopamine to 3-methoxytyramine (Schrag, 2005). Tolcapone use in PD is limited due to the toxic effects on liver. This can be determined by plasma monitoring liver function and terminating the use if necessary. (Olanow and Tasmar, 2000)

DOSE: 200mg tablets per unit dose of levodopa

Dopamine Agonist: Dopamine agonists elicit their effect by acting on the receptors of dopamine. It

Table 1: Risk factors associated with Parkinson's disease

Sex
- Men are 1.5 times more susceptible

Race
- Whites

Genetic
- Family history of PD.

Elevated cholesterol level

Life Experiences
- Head trauma

Environmental Exposures
- Carbon disulfide
- Cyanide
- Pesticides: rotenone
- Fungicide: benomyl
- Herbicide: paraquat, roundup
- Neurotoxins: 1-methyl-4-phenyl-1,2, 3,6-tetrahydropyridine and its analogues.
- Metals: manganese, lead, mercury.

Methamphetamine/amphetamine abuse

Dietary factors
- Animal fat consumption.
- Dairy products.

Melanoma

Table 2: Components of Blood-Brain Barrier with its function

Cells	Functions
Endothelial cells	Micro and macronutrient transport
	Receptor-mediated signalling
	Leukocyte trafficking
	Osmoregulation
Pericyte**s**	Regulate endothelial cell proliferation
	Migration
	Differentiation
	Vascular branching
Astrocytes	Enhance endothelial tight junction
	Reduce gap junction area
The extracellular matrix	Increases permeability

includes two types of agonists. They are ergot agonist and non-ergot agonist. The derivatives of the dopamine agonist include Pramipexole, Rotigotine, Apomorphine, and Ropinirole which are used in decreasing the risk of Parkinson's disease. Initially, the Dopamine agonists were administered to reduce the on-off fluctuations and Dyskinesia. Later the use of a drug in late PD played a major role in reducing the off periods (Whone *et al.,* 2003). The dopamine agonists are administered along with levodopa due to various other symptoms like hallucination, nausea, hypotension etc. when administered separately (Parkinson Study Group, 2002). The ergot derivatives of the dopamine agonists are administered less because they produce fibrosis and lung diseases.

Amantadine

Amantadine is the organic derivative which consists of an adamantine backbone that has an amino group substituted at one of the four methylene position. It is an antiviral agent with moderate therapeutic effects. Currently, it is also administered with levodopa for reducing the symptoms like tremor and rigidity (Hely *et al.,* 2005). It decreases Dopamine reuptake and release.

Deep Brain Stimulation

Deep Brain Stimulation (DBS) proceeds with the implantation of electrodes in a specific region of the brain, and electric signal are transmitted in treating movement disorders. DBS involves symptomatic treatment of PD. In PD treatment; stimulation of Globus Pallidus (GPI) provoked a positive impact by decreasing the motor symptoms. Stimulation of Gpi reduced painful cramps and sensory symptoms when the levodopa administration is lowered in a PD patient (Loher *et al.,* 2002). Subthalamic nucleus (STN) stimulation also showed a decrease in motor symptoms (Benabid *et al.,*

Table 3: Various transport mechanisms for crossing Blood-Brain Barrier

Transport system	Materials
Channels	Small ions and water
Membranes	Small lipophilic molecule
	Anaesthetics, barbiturates
	Ethanol
	Nicotine
	Caffeine
Carrier-mediated	Energy transport system
	Glucose(glut-1)
	Monocarboxylates,lactate,pyruvate(mct1)
	Creatine(CRT)
	Amino acid transport system
	E.g. Large neuter amino acid (lat10
	Organic anion/cation transporters: (e.g. oatp1a2)
	Nucleoside
Receptor-mediated transcytosis	Insulin,transferrin,leptin,igg,tnfα
Adsorption mediated transcytosis	Histone, albumin
Tight junction modulation	Polar solutes.

Table 4: List of Polymers, Drugs and their Route of administration

Drug	Type	Polymer	Administration route
Dopamine	Np	Chitosan	Intraperitoneal
Levodopa	Np thermoreversible gel	Chitosan	Intranasal
Apomorphine	Solid lipid nanoparticle	Tripalmitin hydrogenated Soybean	Oral
Levadopamethylester+ benserazide (decarboxylase inhibitor)	Np	Plga	Subcutaneous
Bromocriptine (agonist and antagonist)	Np	Chitosan	Intranasal
Tempol (antioxidant)	Np	Plga	Intraperitoneal
Urocortin	Np	Peg –plga	Intravenous
Urocortin	Np	Peg –plga	Intranasal
Ngf	Np	Polybutyl	Intravenous
Ropinirole	Nanoemulsion	Cyanoacrylate	Transdermal
Gdnf	Np	Panam/peg	Intravenous

GDNF - Glial Cell Line-derived Neurotrophic Factor; NP -NanoParticle; PANAM - poly(amidoamine); PEG - polyethylene glycol; PLGA – poly (lactic-co-glycolic acid)

1991). The benefit is that intake of medication, and its unwanted effects can be avoided (Jaggi *et al.,* 2004). The effect of DBS may last for about a few years and improves the quality of life.

A Nano technological approach in formulating drugs for PD

Nanoparticles: The drug delivery by Nanotechnology is discussed here. These include Polymeric Nanoparticles, Nanocapsules and Nanospheres (Nikalje and Anna, 2015). The size range of Polymeric nanoparticles and nanocapsules is from 10-1000 nm (Suri *et al.,* 2007) that possess efficient drug loading capacities and preserves the encapsulated drugs against degradation and hence the drug can achieve the target site predominantly. Furthermore, they are stable, and their surface properties can be engineered in such a way that it helps to abscond macrophage recognition. Nanospheres are dense polymeric matrices in which drug is dispersed. Nanospheres are prepared using Micro Emulsion polymerisation method (Muller *et al.,* 2004). Nanospheres are nanoparticle systems constituted by a solid core with a dense polymeric matrix whereas nanocapsules are of this polymeric envelope surrounding an oil-filled cavity (Kreuter *et al.,* 2003).

Drug-Loaded Nanoparticle: Dopamine -loaded Chitosan nanoparticle enhanced Dopamine transport across the BBB (De Giglio *et al.,* 2011). *In-vitro* studies proved that Free-drug is more cytotoxic than Dopamine (DA) loaded chitosan Nanoparticle. After few hours, it showed an elevation in DA transport across the cells and reduction in the

reactive oxygen species was observed. The key reason for the selection of Chitosan is due to its high loading and good delivery capacity (Kulisevsky *et al.,* 2013). These nanoparticles are a solid matrix which is analogous with colloidal particles which are composed of polymers or lipids. These formulations are mainly administered through Intravenous route and prominent in targeted delivery of therapeutic agents. Chitosan nanoparticle for intranasal delivery for Bromocriptine was designed (Md S *et al.,* 2013). Sharma et al. formulated a Levodopa encapsulated in Chitosan nanoparticle which was then incorporated into an intranasally deliverable Pluronic F127 gel (Sharma *et al.,* 2014).

Polymeric Nanogels and Nanosuspensions: Nanogels are nano scalar networks of cross-linked polymers that often comprises of ionic and non-ionic polymeric chains and are prepared using an emulsification solvent evaporation approach (Kreuter *et al.,* 2002, Bronich *et al.,* 2006). Nanogels absorbs water when placed in an aqueous medium and are incorporate molecules such as Oligonucleotides, siRNA, DNA, proteins, and low molecular mass drugs. The size ranges of Nanogel is between 100nm -700nm and are able to escape Renal Clearance and possess prolonged Serum Half-life. The drug-loading capacity is up to 40–60%. *In-vivo* studies suggested the increased brain uptake of oligonucleotides through nanogels while decreasing uptake in the Liver and Spleen. So, it could be a promising carrier for CNS delivery. Nano Suspensions are biphasic consisting of pure drug particles are suspended in aqueous vehicles whose diameter of a suspended particle is less than $1\mu m$. Drug-loaded Nanosuspensions are crystalline drug particles stabilised by non-ionic surfactants or mixtures of lipids (Vinogradov *et al.,* 2005, Kumar and Sameti, 2003). Major advantages of Nanosuspensions include their simplicity, high drug-loading capacity, and applicability to numerous drugs for CNS delivery. An example includes a Ropinirole Transdermal Delivery which is a Nanoemulsion gel, showed improved drug delivery, drug absorption and improved bioavailability compared to the conventional oral tablets and conventional gels (Zhang *et al.,* 2013).

Polymeric Nanomicelle

Polymeric Nano micelles possess a core-shell structure composed of a hydrophobic core and a shell of hydrophilic polymer blocks. About 20-30% w/w of poorly water-soluble drugs can be subsumed into the core. This helps in preventing premature release and depletion of drugs. The shells mainly possess two functions that is: it can stabilise the Nano micelles and protects the drug from interaction with serum proteins and non-targeted cells. On reaching the site of action, the drug is liberated by diffusion. Polymeric Nano micelles are versatile and certain *In-vitro In-vivo* studies showed efficient delivery of DNA molecules but until no CNS delivery has been discovered (DuToit *et al.,* 2007).

Polymeric Nanoliposomes

Nanoliposomes or sub-micron bi-layer lipid vesicle are vesicular structures which consist of uni or multilamellar lipid bilayers encircling internal aqueous compartments (Oishi *et al.,* 2007). A large proportion of drug can be incorporated either into its aqueous compartments or into the lipid bilayers. Nanoliposomes formulations may have prolonged action as systemic circulation is augmented due to modified surfaces that reduces opsonisation in plasma and reduce its identification and elimination by the liver as well as spleen (Shi *et al.,* 2001). Several studies are done focussing on the application of Nanoliposomes for targeted drug delivery to the CNS (Mora *et al.,* 2002).

Nanofibers as Stem Cell Therapy in PD

Polymer-based biodegradable Nanofibers having scaffolds releases the stem cells that can repair damaged neurons (Yurek, 2007). This process can be achieved through electrospinning and customising the Nanofibers structure into a scaffold and are injected into the body. This structure is installed into the target site followed by implanting the stem cells into the Nanofibers. Nerve cells are attached to the scaffold and form a bridge between the Brains. As time passes, scaffold erodes and is eliminated from the body leaving the newly regenerated nerve intact which helped in enhancing the treatment progress. Scientists identified that genes that initiate and control Dopamine was identified and were able to develop embryonic stem cell Dopamine producing cell (Nisbet *et al.,* 2008). However, it faces a crucial challenge; since a pure Dopamine producing stem cell has not yet identified.

Carbon Nanotubes: Apart from spheres, tubes that are" bio-nanotubes" of tubulin coated with lipids could enclose a drug (like Levodopa), and use electrical charge for the release of the drug, at the desired site within the body. Nanotubes are both strong as well as flexible. First Carbon Nanotube was designed by Jun Li et al. which was capable of monitoring Dopamine loss and initiate the activities of neurons and neuritis (Lindvall and Hagell, 2002). Another type is Nanodiamonds which is an area of extensive research for drug delivery because of its larger surface area and the ability to cluster. Drugs are attached to the surface of individual, and the remaining Inactive Nanodiamonds are clustered together. On reaching the site of delivery; clusters break apart, and drugs are released.

Nanowires: Certain biosensors of carbon nanowires are developed for treating PD (Jun *et al.,* 2005). These are hollow, chemically inert structures with very high mechanical strength. It has been designed as a chip to prevent rejection by the human body and possess functions like detecting and monitoring Dopamine.

Nanotechnology for Gene Therapy

Apart from conventional therapies research has been scrutinised into various areas and more into the science of nanotechnology; particularly with respect to Gene Therapy. In Gene Therapy for PD (Parati *et al.,* 2003) initially, the DNA plasmid is incorporated into a nanoparticle which composed of standard genes that are capable of producing Dopamine which is defective in a parkinsonian patient. This was then transferred using a viral vector (Dass and Kordower, 2007). Studies were very effective in animal models to reduce the symptoms of the disease. It is expected that healthy Genes begin to adopt the malfunctioning cells by making various changes and initiate dopamine production. If this process can be achieved effectively with a very little without any complications, then this criterion could be a valid way of managing or ceasing the symptoms of Parkinson's disease.

Liposomes for Dopamine Transport: Studies by Stefano et al. (Di Stefano *et al.,* 2004) suggests that the use of dopamine prodrugs enfolded in unilamellar liposomes of dimyristoyl phosphatidylcholine and cholesterol as a remedy for controlled release of drugs for PD. This showed a positive impact by the release of dopamine in the rats' brain, manifesting the potential of such formulations (Dhanalakshmi *et al.,* 2016).

Nanoparticle for Growth Factor Delivery: Khurakhamaeva et al. (Khurakhamaeva, 2008, Khurakhamaeva, 2009) showed that nerve growth factor(NGF) adsorbed on polybutyl cyanoacrylate (PBCA) nanoparticle coated with polysorbate 80 showed an anti-parkinsonian effect. It showed a positive result by regulating the motor symptoms (like tremor, rigidity) associated with PD. Moreover, it showed an enhance transport of NGF across the BBB which was confirmed by measuring the NGF concentration in the brain (Shefrin *et al.,* 2017).

Above mentioned are some of the nanotechnological approaches for formulating drugs used in PD. Nanoformulations are done for various drugs for the treatment which is enlisted in Table 4 (Garbayo *et al.,* 2013).

Novel routes for drug administration

Various routes for administration of drugs are available. Conventional therapy possess several drawbacks and emerging studies helped in providing novel routes for the drug administration with higher efficacy and lower side effects with better patient compliance (Jayakumar, 2016). Various conceivable routes for drug administration for PD are represented in Figure 4. (Ray Chaudhuri *et al.,* 2016)

Conflict of interest

There is no conflict of interest.

CONCLUSION AND FUTURE DIRECTION

Parkinson's Disease is one of the diseases that severely affects the wellbeing of a person. Over analysis of the present scenario, patients with PD are tremendously increasing over time. Moreover, the motor instabilities decay the patient's wellbeing. As mentioned above; PD is mainly due to the degradation of the neurons that are able to produce Dopamine. The Dopaminergic neurons are anatomically positioned in the Substantia Nigra of the brain. The current strategy to render the neurological ailment mainly focuses on treating the motor symptoms by promoting the inhibition of dopamine degradants, enhancements of dopamine, and maintenance of optimum dopamine. Presently pharmacological treatments like providing Dopamine precursor, dopamine agonists, drugs inhibiting the metabolising enzymes catalysing dopamine degradation, anticholinergics are also adopted with conventional formulations. Among this levodopa; the precursor for Dopamine is mainly used for the treatment when compared to other therapeutic agents. The Dopamine as such is not an option as it can be metabolised quickly and are inefficient in crossing BBB. There are immense researches going on for the formulation for extended release of carbidopa and levodopa, sustained release levodopa prodrug, the intestinal gel of levodopa or carbidopa. It has been identified that Deep Brain Stimulation is a new approach for suppressing the motor symptom. But it possesses a various number of drawbacks and is not an authentic procedure for the treatment. Various studies unfolded different ideology to improve PD treatment. One of the great obstructions for any formulation is the permeation of the Blood-Brain Barrier. But this can be conquered by Nanotechnological approach; although some formulations are yet a promising factor to intensify the treatment. Apart from these approaches, there should be definite and reliable methods for the crossing of BBB. Biomarkers have influenced the identification of PD patient and segregate it from other pathological condition. There must be in-depth studies for the detection of highly specific biomarkers that can largely correlate with the disease. Studies should be focused on preventing further degradation of Dopaminergic neurons,

and drug targeting studies are to be done for specific targeting of Brain. It would be a remarkable achievement if it were possible in permanently replacing the defective neurons from the area it had affected. Though there are tremendous efforts happening but had not yet reached its final point. Apart from treating the disease, there should be a way of preventing the progression of the disease that helps the patients to lead a better standard of living.

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