Neurodegenerative Diseases, Symptoms and Treatment

Chapter 1

Parkinson's Disease (PD)

Sachchida Nand Rai

Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi-221005

Email: raibiochem@gmail.com

1. Introduction

Parkinson's disease (PD) is a common and complex neurological disorder. The detailed description of PD was firstly made almost two centuries ago, but the conceptualisation of the disease is yet to be evolved. Basically, PD is a neurodegenerative disease in which there is an early prominent death of dopaminergic neurons in the substantia nigra pars compacta (SNpc). The pars compacta is a portion of the substantia nigra, located in the midbrain. It is formed by dopaminergic neurons and located medial to pars reticulata. Parkinson's disease is characterized by the death of dopaminergic neurons in this region [1]. In humans, the nerve cell bodies of the pars compacta are coloured black by the pigment neuromelanin. The degree of pigmentation increases with age. This pigmentation is visible as a distinctive black stripe in brain sections and is the origin of the name given to this volume of the brain. Thus, dopamine deficiency within the basal ganglia leads to a movement disorder characterised by classical parkinsonian motor symptoms. PD is also linked with numerous non-motor symptoms, some of which head the motor dysfunction by more than a decade. The stronghold of PD management is suggestive treatment with drugs that increase dopamine concentrations or directly stimulate dopamine receptors. However, PD also involves neurotransmitters other than dopamine and regions of the nervous system outside the basal ganglia. At first, PD was thought to be caused primarily by environmental factors, but research is enlightening that the disease develops from a complicated interplay of genetics and environment. Hence, PD is now seen as a slowly progressive neurodegenerative disorder that begins years before diagnosis can be made, implicates multiple neuroanatomical areas that results from a combination of genetic and environmental factors, and is noticeable with a broad range of symptoms. Hence, clinical challenges are accompanied by these complexities of PD. In exacting, diagnostic tests which

allow for ultimate diagnosis at early stages of the disease are not known. The best standard for diagnosis of PD has been the presence of SNpc degeneration and Lewy pathology at post-mortem pathological assessment. Lewy pathology consists of abnormal aggregates of α-synuclein protein, called Lewy bodies and Lewy neurites. The association between Lewy pathology and pathogenesis of the disease is inaccurately understood. Executive strategies for many of the disabling features that occur in late stages of the disease are poor. These features comprise motor symptoms that do not respond to dopaminergic therapies or develop as complications of long-term dopaminergic drug use, as well as an array of non-motor symptoms. Disease-modifying treatments that lower the rate of neurodegeneration or stop the disease process have remained subtle and are the greatest unmet therapeutic need in PD. However, the understanding of the pathogenesis of PD is escalating and thereby helps to identify potential targets for disease modification.

PD is second most common neurodegenerative disorder after Alzheimer's disease [2]. Pervasiveness of PD seems higher in Europe, North America, and South America compared with African, Asian, and Arabic countries. The prevalence of PD ranges from 10–18 per 100 000 person-years [3]. Gender is a well known risk factor, with the male-to-female ratio being approximately 3:2 [4]. Ethnicity is also a risk factor for the disease. In the USA, the disease occurence is highest in people of Hispanic ethnic origin, followed by non-Hispanic Whites, Asians, and Blacks [3].The greatest risk factor for the development of PD is age. The prevalence and incidence of disease increase nearly exponentially with age and peak after approximately 80 years of age [5]. Thus, with an aging population and rising life anticipation worldwide, the number of people with PD is expected to increase by more than 50% by 2030 [6]. Other risk factors for PD include environmental exposures. Results of a metaanalysis [7] examining 30 different potential risk factors identified 11 environmental factors that significantly altered the risk of PD. The environmental factors that increase risk (in decreasing order of strength of association) were pesticide exposure, prior head injury, rural living, β-blocker use, agricultural occupation, and well-water drinking. Environmental factors found to be connected with a decreased risk (in decreasing order of strength of association) were tobacco smoking, coffee drinking, non-steroidal anti-inflammatory drug use, calcium channel blocker use, and alcohol consumption [7]. Risk of developing PD is clearly multifactorial, but the complex interplay between the various factors is just beginning to be deciphered.

The critical pathological feature of PD is loss of dopaminergic neurons within the SNpc. Typically, the ventrolateral tier is the most profoundly affected area of the SNpc, which contains neurons that project to the dorsal putamen of the striatum. The moderate to severe dopaminergic neuronal loss within this area is probably the cause of motor features, bradykinesia and rigidity in particular, in advanced Parkinson's disease as shown by clinical-pathological correlation studies [8]. Current findings from pathology confirm that loss of nigral neurons is also

present in early stages of the disease but also provide evidence for a population of potentially salvageable dopaminergic neurons. In PD, neuronal loss occurs in many other brain regions too, including the locus ceruleus, nucleus basalis of Meynert, pedunculopontine nucleus, raphe nucleus, dorsal motor nucleus of the vagus, amygdala, and hypothalamus. Another potential hallmark of PD is Lewy pathology. Aggregation of abnormally folded proteins has transpired as a common theme in neurodegenerative diseases, including PD. Each neurodegenerative disease is categorised according to the protein that is most abundant in the associated protein inclusions [8]. In PD, the protein was identified as α-synuclein followed by the discovery that mutations in its gene, SNCA, cause a monogenic form of the disease [9]. α-synuclein becomes insoluble and aggregates to form intracellular inclusions within the cell body (Lewy bodies) and processes (Lewy neurites) of neurons in its misfolded state [10]. Lewy pathology is not only restricted to the brain but it can also be found in the spinal cord and peripheral nervous system, including the vagus nerve, sympathetic ganglia, cardiac plexus, enteric nervous system, salivary glands, adrenal medulla, cutaneous nerves, and sciatic nerve [11]. Six stages, starting in the peripheral nervous system and progressively affecting the central nervous system in a caudal-to-rostral direction within the brain have been proposed by Braak and colleagues [12]. The Braak model [12] has gained traction because the proposed temporal and spatial progression seems to explain the clinical course of PD. Specifically, stages 1 and 2 may correspond with onset of premotor symptoms, stage3 would be when motor features present due to nigrostriatal dopamine deficiency, and stages 4–6 would occur with the non-motor symptoms of advanced disease. Association between Lewy pathology and non-motor symptoms is most convincing for cognitive impairment in PD. Findings from several pathological studies [13] have shown a strong association between dementia and severity of cortical Lewy pathology. Studies are needed to confirm the association of other non-motor symptoms with the Braak staging system 14]. Lewy pathology is hypothesised to be a biological marker for neurodegeneration in PD. However, studies over the past several years have revealed that PD pathology is more complex than neurodegeneration due to Lewy pathology alone. First, a variety of different aggregate types is now known to be formed by α-synuclein, including small dot-like or thin thread-like structures, [15] very fine presynaptic deposits [16] and soluble oligomers composed of 2–100 α-synuclein monomers [17]. These different forms of α-synuclein aggregates might play an important part in neurodegeneration in PD; in particular, certain oligomeric forms of α-synuclein could be toxic to neurons [18]. Second, pathologies dissimilar from α-synuclein aggregates, such as inclusions composed of other types of proteins, are often seen in the brains of patients with PD. β-amyloid plaques and tau-containing neurofibrillary tangles, the protein inclusions characteristic of Alzheimer's disease, can also be found in the brains of patients with PD at comparable amounts and distribution as in the brains of patients with Alzheimer's disease. Greater burden of Lewy pathology is linked to concomitant Alzheimer's disease pathology which correlates with a shorter latency to onset of dementia in PD, and occurs in up to 50% of patients with PD and dementia [13]. Another feature of PD pathology

is neuroinflammation [19]. Beginning of the neuroinflammatory cascade result from the aggregated and post-translationally modified α-Syn which leads to the progression of the PD. This aggregation causes neuronal cell death and the presence of chronically activated microglia and astroglia. These glial cells leading to the production of cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), IL-6, and enzymes such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase[20]. These changes in the microglial and astrogliyal phenotype affect the central nervous system (CNS) microenvironment by producing a pro-inflammatory milieu that speeds PD pathogenesis thus ultimately the progression of PD. Human studies also shows the evidence in support of the role of neuroinflammation which leads to neurodegeneration in PD has been seen. Greater risk for PD has been correlated with elevated plasma levels of proinflammatory cytokines, such as IL-6 [20] and the presence of activated glial cells and increased levels of proinflammatory cytokines; TNF-α, IL-1-β, IL-2, IL-6 and enzymes such as cyclooxygenase-1 (COX-1), COX-2 and inducible nitric oxide synthase (iNOS) have also been found in post-mortem tissues, as well as in the cerebral spinal fluid (CSF) [20].

The presence of an active inflammatory response in the brain mediated primarily by resident astrocytes and microglia has been long recognised, but is still somewhat unobserved, in PD. Within areas of neurodegeneration in PD, both reactive gliosis resulting from activated astrocytes and microgliosis resulting from microglial activation occurs. In clearance of extracellular debris, both the astrocytes and microglia are involved which might support in the survival of neurons. Some trophic factors are released by activated microglia, such as brain-derived neurotrophic factor and glial-derived neurotrophic factor, but they can also release harmful reactive oxygen and nitrogen species and pro-inflammatory cytokines. So, whether the balance of these actions is beneficial or harmful to neurons is not yet established [21].

2. Symptoms of PD

Since James Parkinson's initial description in the 19th century, the traditional motor symptoms of PD have been recognised as well-known components of the disease, which were later refined by Jean-Martin Charcot [22]. These parkinsonian symptoms include bradykinesia, muscular rigidity, rest tremor, and postural and gait impairment [23].Motor features in patients with PD are heterogeneous, which has impelled attempts to classify subtypes of the disease [24]. Empirical clinical observations suggest two major subtypes of PD: tremor-dominant PD (with a relative absence of other motor symptoms) and non-tremor-dominant PD (which includes phenotypes described as akinetic-rigid syndrome and postural instability gait disorder). Mixed or unspecified phenotype with several motor symptoms of comparable severity has been seen in additional subgroup of patients with PD. The Course and prognosis of disease for an additional subgroup of patients with PD differ between the subtypes; tremor-dominant PD is often associated with a slower rate of progression and less functional disability

than non-tremor-dominant PD [25]. Furthermore, the various PD subtypes are hypothesised to have distinctive aetiologies and pathogenesis [24]. Olfactory dysfunction, cognitive impairment, psychiatric symptoms, sleep disorders, autonomic dysfunction, pain, and fatigue are included in Non- motor features of PD. These symptoms are common in early PD [26] and are related with reduced health-related quality of life [27]. In PD, before the onset of the classical motor symptoms, non-motor features are also commonly present [28]. Impaired olfaction, constipation, depression, excessive daytime sleepiness, and rapid eye movement sleep behaviour disorder are the characteristic of this premotor or prodromal phase of the disease. In fact, mood disorders and constipation have both been shown to nearly double an individual's risk of subsequently developing Parkinson's disease [7]. The pathogenic process that causes PD is supposed to be started during the premotor phase, involving regions of the peripheral and central nervous system in addition to the dopaminergic neurons of the SNpc. Thus, this prodromal period provides a potential target phase during which disease-modifying therapy, once discovered, could be administered to prevent or delay the development and progression of disease [29]. Worsening of motor features is the main characteristic of progression of PD, which initially can be managed with symptomatic therapies. However, as the disease progresses, there is an appearance of complications related to long-term symptomatic treatment, including motor and non-motor fluctuations, dyskinesia, and psychosis [30].This treatment related complications are fundamental challenges in the clinical management of the advanced stage of PD. Treatment-resistant motor and non-motor features are prominent in late-stage PD and include axial motor symptoms such as postural instability, freezing of gait, falls, dysphagia, and speech dysfunction. Up to 80% of patients with PD have freezing of gait and falls, and up to 50% of patients report choking after about 17 years of disease. Common non-motor features in these late stages of PD include some autonomic symptoms, such as urinary incontinence, constipation with the need for daily laxatives, and symptomatic postural hypotension [30]. In PD patients, who have had 20 years disease duration, dementia is particularly prevalent in about 83% of them [31].

3. PD Patient care

Whether we care for someone who is newly diagnosed with PD, we are adapting to new challenges as the disease progresses or when we have been living with PD patient for a longer period of time, we should have the right and responsibility to make the care partnership most productive with the least amount of stress and conflict. As we should remember that we have dual role as a caregiver, to care for the person with PD and to take care of ourselves.

There are some important points for caregiver and PD patient:

• The incidence and severity of PD symptoms vary from day to day and even from one time of day to another. Skill and patience should be taken to know when to assist with a task and when

to simply allow the patients to do the task independently.

• Time should be taken to learn symptoms of PD as well as the often complicated medication regimens that offer the most symptom relief and improve quality of life.

• Caregivers must firmly observe the person with PD over time to detect and respond helpfully to subtle changes in motor functions and moods.

• The person we care for might not be aware of his or her changing abilities. Understanding of health risks (such as falling) may not have "caught up" to his or her actual level of risk and impairment.

• Friends and family members who have in frequent contact with the person with PD often underestimate the severity of symptoms.

• Providing physical care to someone with advanced PD, such as re-positioning or helping with bathing, can be exhausting and even cause physical injury to the caregiver. But, we can help maintain the quality of life for our loved one.

• We can educate ourselves about symptoms, treatments, and the progression of the disease.

• We can keep track of appointments with the doctor, medication schedules, and exercise.

• We can offer the love and support to the patient necessary to meet the challenges of PD. We can simplify our tasks and set realistic goals. Activities (chores, exercise, and recreation) should be planned ahead of time. Too many things should not be scheduled to be done in one day.

• Activities right after a meal should not be planned. Rest of about 20-30 minutes should be taken after each meal.

• Different tasks can be divided among family and friends.

• Extreme physical activity should be avoided. Heavy objects (more than 10 pounds) that cause strain should not be pushed, pulled or lifted. New research has found that exercise might be very valuable to people with PD, perhaps even as beneficial as medication. Exercise helps keep the muscles and joints limber and appears to promote neurological health in Parkinson's patients. In addition, physical therapy can help our loved ones maintain independence for as long as possible. We can help them by assisting in their home-exercise program or getting them to physical therapy on a regular basis.

• Many people with PD are also depressed and may deal with periods of anxiety and denial as well. Being aware of the emotional side of this disease can help us to take better care of our

loved ones.

Parkinson's patients tend to have a troubled relationship with sleep. The disease and its medication can make them incredibly drowsy during the day and then keep them up all night. Fatigue can worsen symptoms and prevent the person from focusing on their own well-being. In that case, the doctor might prescribe a sleep aid or adjust their Parkinson's medication. Also, we can help by keeping the patients active during the day and by establishing a regular bedtime routine that promotes quality sleep.

4. Gut Brain Axis in Parkinson's Disease

Sampson et al., in 2016 [32] explore that a significant contribution to neurological disorders is made by the intestinal microbiota which influence neurodevelopment and modulate behavior. However in neurodegenerative diseases the functional link between gut bacteria remains unexplored. Parkinson's disease (PD) is characterized by aggregation of the protein α-synuclein (α-Syn), also called synucleinopathies often resulting in motor dysfunction as exemplified. Gut microbiota are required for motor deficits, microglia activation, and α-Syn pathology. Postnatal signaling between the gut and the brain modulates disease. Oral administration of specific microbial metabolites to germ-free mice promotes neuroinflammation thus ultimately motor symptoms. These findings tell that gut bacteria regulate movement disorders in mice and alterations in the human microbiome represent a risk factor for PD.

Thus Sampson et al., [32] investigate that the microbiota are required for the hallmark motor and GI dysfunction in a mouse model of PD, via postnatal gut-brain signaling by microbial molecules that impact neuroinflammation and α-Syn aggregation.

5. Research happenings in PD

Though fragments of Parkinsonism can be found in earlier descriptions, but PD was first medically described as a neurological syndrome by James Parkinson in 1817, [33]. The earlier descriptions include Sylvius de la Boe¨ wrote of rest tremor, and Sauvages described festination [34,35,36].Traditional Indian texts from approximately 1000 BC and ancient Chinese sources also provide descriptions that suggest PD [37,38]. PD can be defined as: Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured. Moreover after about 50 years, Jean-Martin Charcot distinguished bradykinesia as a separate cardinal feature of the illness [39]. Describing his personal experience with 80 patients in the 1880s, William Gowers, in London, contributed an important study of PD demographics in his "Manual of Diseases of the Nervous System". He also studied about slight male predominance of the disorder and studied the joint deformities typical of the disease [40].

Further clinical descriptions and studies of the pathologic changes related to PD were predominantly reported by the French neurologic school. Richer and Meige (1895) [41] provided clinical and morphologic details of the progressive stages of Parkinsonian disability, and the former provided drawings and statues that remain among the most important pictorial documents related to PD [42]. In 1953, Greenfield and Bosanquet performed the most complete pathologic analysis of PD and the clear delineation of the brain stem lesions [43]. Hoehn and Yahr studied about the morbidity and clinical progression of PD. This system is anchored in the distinction between unilateral (Stage I) disease and bilateral disease (Stages II–V) and the development of postural reflex impairment (Stage III) as a key turning point in the disease's clinical significance [44].

The concepts of neural circuits evolved with key nuclei of importance to the clinical presentation of Parkinsonism being the substantia nigra, the globus pallidus, and the caudate nucleus and putamen (striatum). Involvement of the striatum resulting in Parkinsonism was documented in a variety of neurological disorders too. Though originally classified as a single disease, it has been merged into the larger diagnosis of multiple system atrophy as striatal-nigral degeneration was described by different researchers such as Adams [45]. Parkinsonian states associated with striatal pathology were later identified in the form of Huntington's disease, in which a Parkinsonian presentation is referred to as the Westphal variant [46] and in cases of striatal calcification, either on a hereditary basis [47] or as an acquired metabolic disorder often related to hypoparathyroidism [48].

In 1975, Richard et al [49] studied on about One hundred patients with PD, who started taking levodopa before the end of 1968 and have been assessed after 5 years. He later published that Forty-seven patients are still being followed on levodopa, and half of them are at least 25% better than at their pretreatment evaluation. However, the average functional rating is returning toward baseline from its remarkable improvement at ½ to 2 years. The major side effects were abnormal involuntary movements, rapid oscillations in motor performance, postural instability, and dementia. Thirty-two of the 100 patients have died. Life-table analysis showed an excess mortality of 1.9 compared with the U. S. population, a figure that is lower than the 2.9 reported before levodopa's use. Levodopa provides symptomatic relief for a prolonged time and it remains the single most effective medication for the illness despite of its inability to completely cure PD.

It was not until the 1980s that theory for basal ganglia function could be postulated that could explain the symptoms and signs of PD and other movement disorders [50]. DeLong, Crossman, and others proposed that in many movement disorders, the circuitry comprising direct and indirect pathways was dysfunctional, and also that parallel circuits linking cerebral cortex structures with the basal ganglia were involved in cognitive and emotional processing. A reasonable paradigm to explain many of the cognitive and emotional problems associated

with movement disorders, like the concomitance of depression and PD were provided by dysfunction in such a parallel cortico-striato-pallido-thalamic neuronal network [51]. Much research has been conducted towards elucidating the roles of the basal ganglia in PD, other movement disorders, and psychiatric illnesses within the past two decades [52,53].

Recent research focus on the efficiently specified ventral midbrain dopamine neurons from human pluripotent stem cells under xeno-free conditions restores motor deficits in parkinsonian rodents [54]. Becker et al., in 2017 [55] shown that Comparative assessment of 6-[18 F]fluoro-L-m-tyrosine and 6-[18 F]fluoro-L-dopa to evaluate dopaminergic presynaptic integrity in a Parkinson's disease rat model.

Currently the epigenetic approach is used to explore the PD research, epigenetic regulation, histone acetylation, and describes how the histone acetyltransferase (HAT) and histone deacetylase (HDAC) enzymes that mediate this process are attractive therapeutic targets for PD. It discusses the use of activators and/or inhibitors of HDACs and HATs in models of PD, and how these approaches for the selective modulation of histone acetylation elicit neuroprotective effects. Finally, it outlines the potential of employing small molecule epigenetic modulators as neuroprotective therapies for PD, and the future research that will be required to determine and realise this therapeutic potential. Recently Pezzi et al., in 2017 [56] explore how DNA methyltransferase gene polymorphism associated with PD.

An important role for autophagy impairment in Parkinson's Disease (PD) is suggested by converging evidence from genetic, pathological and experimental studies. Increased risk for developing PD, associated with Genetic studies has identified mutations in genes encoding for components of the autophagy-lysosomal pathway (ALP), including glucosidase beta acid 1 (GBA1). Observations in PD brain tissue suggest an aberrant regulation of autophagy associated with the aggregation of α-synuclein (α-syn [57].

6. Current treatments

In 1983, the discovery that the compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induces parkinsonism in humans was led by several cases of parkinsonism seen in heroin users [58].This led to the development of a primate model of parkinsonism that remains the only mammalian model to exhibit the resting tremors and drug induced dyskinesias seen in humans [59]. Metabolic marker experiments using this model showed much about activity in basal ganglia circuits alongside the electrode studies mentioned above [60]. It was shown in early 1990s that lesions made to the subthalamic nucleus of the basal ganglia in primates reversed the motor symptoms of MPTP induced parkinsonism [61,62]. Thus, this finding led to an authentic resurgence in neurosurgical treatment for PD together with the renaissance of globus pallidus lesioning surgery pioneered in Sweden in the late 1980s for movement disorders refractory to drug treatment [63,64].

Using primate models, many drugs for movement disorders have been investigated. Our understanding of levodopa has been greatly improved by primate research directed at prolonging and improving its beneficial effects and reducing side effects like dyskinesias. Such primate research continues to make possible insights into both novel pharmacological therapies, and more recently established drug treatments like dopamine agonists [65,66,67].

The progress of several therapeutic scenario for PD has been driven by advances made first in cellular in vitro studies, then non-primate mammalian research and ultimately by refinement in primate models. Neural transplantation and gene therapy for PD are the notable treatments in which clinical trials have recently been undertaken. In neural transplantation, the aim is to replace the neurons that release the neurotransmitter dopamine and connect the substantia nigra and the striatum of the basal ganglia that degenerate in PD. Porcine neural xenografts, human fetal tissue, and human stem cells are the several donor cell sources under consideration. However, several clinical trials have recently developed controversies, many centred on the development of dyskinesias after transplantation [68,69]. These dyskinesias are said to arise from changed dopamine release but the mechanisms remain debatable and some have suggested that they may only occur in certain subgroups of patients [70]. The clinical experience of neural transplantation tells about how essential it is to conduct appropriate preclinical experiments and evaluate them properly before entering clinical trials. Primate research has shown itself to be essential to progress in this regard [71,72]. For the development of gene therapy for PD, primate models have been vital. Recent clinical trials of gene therapy aim to replace either γ-aminobutyric acid (GABA), a neurotransmitter released from neurons with inputs to several basal ganglia structures, or to insert glial cell line derived neurotrophic factor (GDNF) to arrest and even reverse the degeneration of nigrostriatal neurons in the basal ganglia. The use of viral vectors is widely considered to be the most efficient, practical, and safe method to deliver gene therapy to basal ganglia structures at present alongside constant infusions of recombinant factors. In theory, viral vectors also confer the advantage of requiring only a single treatment. Rather than replacing it as neural grafts aim to do, it is suggested that neurotrophic gene therapy is in principle less likely to cause unwanted dyskinesias as it restores the patient's own neural function. The consent is that primate research is best positioned to confirm both that gene therapy is safe and that its functional restoration is lasting [73]. The introduction of enzymes required for dopamine synthesis into the striatum of the basal ganglia is one of the promising forms of gene therapy using viral vectors that may soon reach clinical trials. This method has had great success in restoring motor function in a 6-OHDA rodent model of parkinsonism [74]. However, a treatment must be validated by primate research, if anything is to be learnt from the controversies surrounding clinical trials of neural transplantation for PD. In particular, only vigorous demonstration of efficacy and safety in the MPTP primate model of PD will enable clinical trials of this treatment to be considered. As a stipulation, among all the excitement surrounding future treatments for PD it has recently been argued

that merely attempting to restore dopamine release from the nigrostriatal neurons of the basal ganglia will remain limited in the extent to which it addresses the problems caused by PD. Thus, shifts of research focus may be preferable, firstly towards halting disease progression, [75,52] and secondly towards understanding its aetiology with a view to disease prevention. As the best models of PD are currently primate models, they will continue to be crucial, both to characterising factors related to the onset and progression of neuronal degeneration in the parkinsonian brain, and in the development of preventative strategies [76].

By the standards of modern evidence based medicine, it has recently been claimed that there is little evidence that animal research benefits humans [77]. The inaccuracy of such an argument has been highlighted elsewhere, emphasising that animal research is at present best evaluated by qualitative critical reviews rather than quantitative systematic reviews that incorrectly apply methodology designed for the analysis of clinical trials [78,79].

7. Various methods of treatment

PD can’t be fully cured, but medications can help control your symptoms, often considerably. In some later cases of PD, surgery may be advised. Doctors may also recommend lifestyle changes, especially ongoing aerobic exercise. In some cases, physical therapy that focuses on balance and stretching are advised. A speech-language pathologist may help improve patient’s speech problems.

7.1 Symptomatic therapy

Levodopa, monoamine oxidase (MAO)-B inhibitors, and dopamine agonists are the medications commonly used for symptomatic benefit of motor symptoms in early PD.

7.1.1 Levodopa

The standard of symptomatic treatment for PD remains Levodopa, coupled with a peripheral dopa decarboxylase inhibitor such as carbidopa which provides the greatest antiparkinsonian benefit with the fewest adverse effects in the short term. However, long-term use of levodopa is associated with the development of fluctuations and dyskinesias. It becomes difficult to resolve once fluctuations and dyskinesias become problematic. These adverse effects are the reason to consider delaying the initiation of levodopa if other alternatives are able to control symptoms.

Levodopa/carbidopa is introduced at a low dose and escalated slowly. Allowing for greater levodopa delivery into the central nervous system, carbidopa inhibits the decarboxylation of levodopa to dopamine in the systemic circulation.

Levodopa/carbidopa immediate-release (IR) tablets (Sinemet), levodopa/carbidopa

controlled-release (CR) tablets (Sinemet CR), and levodopa/carbidopa orally disintegrating tablets (Parcopa) are the currently available levodopa preparations present in the United States. The orally disintegrating tablet dissolves on the tongue without the need to swallow it with water but is bioequivalent to oral levodopa/carbidopa IR. The orally disintegrating tablet is not absorbed in the mouth but travels in the saliva to absorption sites in the proximal small bowel (where other levodopa preparations are also absorbed).

Levodopa/carbidopa is also available in combination with a catechol-O-methyltransferase (COMT) inhibitor, entacapone. Plasma levels of levodopa are higher and more sustained than after administration of levodopa and carbidopa alone, when entacapone is given in conjunction with levodopa and carbidopa. Levodopa/carbidopa/entacapone is useful in advanced PD in patients with motor fluctuations. But, as through the STRIDE-PD (STalevo Reduction In Dyskinesia Evaluation) study, patients with early PD treated with levodopa/carbidopa/entacapone (Stalevo) developed more dyskinesia than patients treated with levodopa/carbidopa; therefore, levodopa/carbidopa/entacapone is not recommended for treatment of early disease [80].

To control clinical symptoms, Levodopa in combination with a dopa decarboxylase inhibitor is started at a low dose and slowly titrated. Most patients experience a good response on a daily levodopa dosage of 300-600 mg/day (usually divided 3 or 4 times daily) for 3-5 years or longer. Because higher doses increase the risk for the development of dyskinesia, so, doses higher than those necessary to control symptoms adequately should be avoided[81]. The levodopa dose can be taken immediately following a meal if the problem of nausea occurs. Additional measures to alleviate nausea include adding extra carbidopa or introducing domperidone. Other side effects may include dizziness and headache. Confusion, delusions, agitation, hallucinations, and psychosis may be more commonly seen in elderly patients.

7.1.2 MAO-B inhibitors

MAO-B inhibitors, such as selegiline and rasagiline, may be used for early symptomatic treatment of PD. These medications provide mild symptomatic benefit, have excellent adverse effect profiles, and may improve long-term outcomes. These characteristics make MAO-B inhibitors a good choice as initial treatment for many patients. When the MAO-B inhibitor alone is not sufficient to provide good control of motor symptoms, another medication (eg, a dopamine agonist or levodopa) can be added.

In patients being treated with levodopa/carbidopa, selegiline is indicated as adjunctive therapy (5 mg every morning; maximum, 10 mg/day) in the treatment of PD. For the treatment of the signs and symptoms of PD, Rasagiline is indicated as initial monotherapy (1 mg/day) and as adjunctive therapy (0.5-1.0 mg/day) to levodopa. Nausea, headaches, and dizziness are the Potential side effects.

7.1.3 Dopamine agonists

With fewer motor fluctuations and dyskinesias than levodopa alone in prospective, double-blind studies, initial treatment with a dopamine agonist, to which levodopa can be added as necessary, is associated. The benefit of dopamine agonists in delaying motor symptoms is due to their ability to delay the need for levodopa/carbidopa as indicated by subsequent analyses of these studies [82,83].

Pramipexole and ropinirole are the commonly used dopamine agonists. Although, dopamine agonists provide symptomatic benefit that is comparable to that with levodopa/carbidopa in early disease, but these agents lack sufficient efficacy to control signs and symptoms by themselves in more advanced disease. They provide moderate symptomatic benefit and rarely cause fluctuations and dyskinesias by themselves, but they have more adverse effects than levodopa, including sleepiness, hallucinations, edema, and impulse control disorders. However, upon lowering the dose or discontinuing the medication, these adverse effects resolve.

Dopamine agonists are commonly reserved for younger individuals (< 65-70 years) who are cognitively intact. Levodopa can be added,when the dopamine agonist (with or without an MAO-B inhibitor) no longer provides good control of motor symptoms. However, before levodopa is required, dopamine agonists may provide good symptom control for several years. The authors make a judgment based on general health and cognitive status for patients aged between 65-70 years. For patients who may be prone to adverse effects, such as hallucinations, from dopamine agonists with cognitive impairments and those older than 70 years and for those likely to require treatment for only a few years, dopamine agonist should not be used and instead depend on levodopa/PDI (peripheral decarboxylase inhibitor) as primary symptomatic therapy.

It is important to start at a low dose and escalate slowly when we are introducing a dopamine agonist. Until symptoms are controlled and the maximum dose is reached, or adverse effects emerge, the dose should be titrated upward.

Nausea, orthostatic hypotension, hallucinations, somnolence, and impulse control disorders are the most common adverse effects of dopamine agonists. Nausea can generally be reduced by having the patient take the medication after meals. A peripheral dopamine agonist, Domperidone is very helpful in relieving refractory nausea.

Patients on dopamine agonists should be routinely asked about sleepiness, sudden onset of sleep, and impulse control disorders such as pathologic gambling, shopping, internet use, and sexual activity. But, with reduction in dose or discontinuation of the medication these adverse effects typically resolve. If patients are experiencing undue sleepiness, they should

be warned not to drive. They should also be warned about the possibility of impulse control disorders and the need to let their physician know if such an effect occurs.

Dopamine agonists (DA) are therapeutic agents that are commonly used in the treatment of Parkinson's disease (PD). They can reduce undesired motor fluctuations and delay the administration of levodopa therapy. However, this drug family is associated with specific side effects that can significantly diminish the quality of life among PD patients. Some of them impose significant risks for individuals who have a history of cardiovascular diseases, psychosis, and depression, or those older patients who suffer from renal or hepatic insufficiency. Various pharmacokinetic and pharmacodynamic considerations need to be taken into account when administering DA therapy.

7.2 Anticholinergic agents

For patients who have disability due to tremor that is not adequately controlled with dopaminergic medication anticholinergic agents can be used, but these are not first-line drugs, because of their limited efficiency and the possibility of neuropsychiatric side effects. Anticholinergic medications do not meaningfully improve bradykinesia or rigidity but, provide good tremor relief in approximately 50% of patients. A second anticholinergic agent usually can be tried if the first is not successful because tremor may respond to one anticholinergic medication but not another. These medications should be introduced at a low dose and escalated slowly to minimize adverse effects, which include memory difficulty, confusion, and hallucinations. Especially in elderly persons, the adverse cognitive effects are relatively common.

Trihexyphenidyl is one of the most commonly used anticholinergic agents. The initial dose of trihexyphenidyl should be low and gradually increased. It is recommended to begin therapy with a single 1-mg dose. Until satisfactory control is achieved, dosage can be titrated by 1 mg each week or so, or until a total of 4-6 mg is given daily. Some patients may require higher doses. With an initial dose of 0.5-1 mg daily at bedtime, benztropine (Cogentin) is also commonly used. Dose can be titrated at weekly intervals in increments of 0.5 mg to a maximum of 6 mg/day.

7.2.1 Amantadine

Amantadine is an antiviral agent that has antiparkinsonian activity. The mechanism of action is not fully understood, but amantadine appears to potentiate CNS dopaminergic responses. It may inhibit the reuptake of dopamine and norepinephrine and release dopamine and norepinephrine from storage sites. In patients experiencing maximal or declining effects from levodopa, Amantadine may offer additional benefit.

Commonly, Amantadine is introduced at a dose of 100 mg per day and slowly increased to an initial maintenance dose of 100 mg 2 or 3 times daily. Confusion and hallucinations are the most concerning potential side effects of amantadine. Common side effects include nausea, headache, dizziness, and insomnia. Less frequently reported side effects include anxiety and irritability, ataxia, livedo reticularis, peripheral edema, and orthostatic hypotension.

Amantadine was found to ameliorate pathologic gambling associated with PD in a small, double-blind crossover study[84]. However, Amantadine was associated with a higher prevalence of impulse control disorders, including gambling in a large cross-sectional study [85]. Thus, to understand the role of amantadine as a treatment or cause of impulse control disorders in patients with PD, further research is needed.

7.3 Symptomatic therapy of advanced PD

7.3.1 Motor fluctuations

Stable, sustained benefit through the day in response to levodopa is initially experienced by patients. However, after several months to years, many patients notice that the benefit from immediate-release (IR) levodopa/carbidopa wears off after 4-5 hours. Over time, this shortened duration of response becomes more short-lived, and clinical status fluctuates more and more closely in performance with peripheral levodopa concentration. Ultimately, benefit lasts for only about 2 hours. The time when medication is providing benefit for bradykinesia, rigidity, and tremor is called “on” time, and the time when medication is not providing benefit is called “off” time.

Treatment of motor fluctuations in the absence of peak-dose dyskinesia is relatively easy. To provide more sustained dopaminergic therapy, several different strategies, either alone or in combination, can be used. Possible strategies include the following:

- Adding catechol-*O*-methyltransferase (COMT) inhibitor, or monoamine oxidase (MAO)-B inhibitor, i.e., a dopamine agonist.
- More frequent dose of levodopa.
- Increasing the levodopa dose.
- Switching from immediate-release (IR) to sustained-release (SR) levodopa/carbidopa or levodopa/carbidopa/entacapone.
- Continuous intrajejunal infusion of a carbidopa/levodopa enteral suspension [86].

  The FDA, in January 2015 approved a carbidopa/levodopa enteral suspension (Duopa) that is infused into the jejunum by a portable pump. In a multicenter, international

study, the efficacy of the enteral suspension to decrease off-time and increase on-time was shown. Mean off-time decreased by 4.04 hours for 35 patients allocated to the levodopa/carbidopa intestinal group compared with a decrease of 2.14 hours for 31 patients allocated to immediate-release oral levodopa/carbidopa (p=0.0015) studied from baseline to 12 weeks. Mean on-time without troublesome dyskinesia increased by 4.11 hours in the intestinal gel group and 2.24 hours in the immediate-release oral group (p=0.0059) [86].

Dopaminergic therapy should be increased until off-time is eliminated, unless limited by the emergence of peak-dose symptoms such as dyskinesia or hallucinations. Formulations of the dopamine agonists ropinirole and pramipexole are now available. Similar to the IR formulations that are administered 3 times daily, these medications appear to provide efficacy and safety [87].

7.4 Deep brain stimulation (DBS)

DBS has become the surgical procedure of choice for PD for the following reasons:

- Destruction of brain tissue is not involved.
- It is reversible.
- It can be adjusted as the disease progresses or adverse events occur.
- Bilateral procedures can be performed without a significant increase in adverse events.

Because long-term complications of levodopa therapy result in significant disability over time, DBS, a form of stereotactic surgery, has made revival in the treatment of PD largely. Better understanding of basal ganglia physiology and circuitry and improvements in surgical techniques, neuroimaging, and electrophysiologic recording have allowed surgical procedures to be performed more accurately and with lower morbidity.

Surgery for movement disorders previously involved predominantly destructive lesioning of abnormally hyperactive deep brain nuclei; however, investigation of long-term DBS as a reversible alternative to lesioning procedures is led by the observation that high-frequency electrostimulation in the ventral lateral nucleus (VL) of the thalamus eliminates tremors in patients undergoing thalamotomy.

Continued enhancement of the knowledge of basal ganglia circuitry and PD pathophysiology has narrowed the focus of movement disorder surgery to 3 key gray-matter structures: the thalamus, the globus pallidus, and the subthalamic nucleus (STN). Currently, the STN is the most commonly targeted site for PD.

Subthalamic nucleus (STN) stimulation, globus pallidus interna (GPi) stimulation, and thalamic deep brain stimulation is included in DBS surgery. The UK National Collaborating Centre for Chronic Conditions notes the following indications for STN and GPi in patients with PD.

- The presence of motor complications refractory to medical therapy.
- The absence of significant comorbidities in a biologically fit individual.
- The absence of significant mental health problems (eg, depression, dementia).
- Response to levodopa.

A key to patient selection is that appropriate patients still experience a good response to levodopa, but that response cannot be adequately maintained through the day or is complicated by excessive dyskinesia.

In patients with predominantly severe and disabling tremor, thalamic DBS has been used. However, because it has been shown that other symptoms continue to progress, causing significant disability that is not controlled by thalamic DBS, this surgery is now rarely used in patients with PD.

The effectiveness of STN and GPi DBS for appropriate PD patients has been demonstrated by recent landmark studies [88]. Controlled trial of 255 patients enrolled in the Veterans Affairs (VA) Cooperative Studies Program (CSP) trial for patients with advanced PD, bilateral DBS (STN and GPi) was more effective than best medical therapy in improving on time without troublesome dyskinesia, motor function, and quality of life at 6 months; however, DBS was associated with an increased risk of serious adverse events In a randomized, [89]. In the same study, when the 2-year outcomes of 147 patients who received STN DBS and 152 patients who received GPi DBS were compared, motor function and adverse events were not significantly different between the 2 sites [90]. However, individuals who received GPi DBS had significantly less depression and those who received STN DBS had a greater reduction in dopaminergic medications [90].

Investigators from the EARLYSTIM Study Group reported that, before the appearance of severe disabling motor complications, relative to medical therapy alone, STN DBS in conjunction with medical therapy offers benefits earlier in the course of PD [91,92] Moreover, to medical therapy alone, subthalamic stimulation plus medical therapy was superior on several key measures of quality of life and motor function. However, compared to 44.1% of those in the medical-therapy group, 54.8% of the patients in the DBS group suffered serious adverse events [91,92] 17.7% of patients suffered serious adverse events related to surgical implantation or the neuro-stimulation device.

A study at the National Hospital for Neurology and Neurosurgery using an MRI-guided surgical technique without microelectrode recording by Foltynie, assessed 79 consecutive patients who underwent bilateral subthalamic nucleus DBS [93]. A mean improvement of 27.7 points (standard deviation, 13.8) was noted in the off-medication motor part of the Unified PD Rating Scale, at a median follow-up period of 12-14 months (UPDRS III), equivalent to a mean improvement of 52%. Significant improvements in dyskinesia duration, disability, and pain were noted. This suggests that image-guided STN DBS without microelectrode recording can lead to substantial improvements in motor disability and improvements in quality of life, with very low morbidity in well-selected patients with PD.

In patients with advanced PD without dementia who also received subthalamic nucleus stimulation (STN), a randomized trial by Moreau et al assessed the efficiency of the drug methylphenidate in improving gait disorders and freezing of gait. From 13 movement disorders departments in France, eighty-one patients were randomly assigned to methylphenidate or placebo for 90 days. Patients in the methylphenidate group used fewer steps at 90 days, compared with patients in the placebo group. These results suggest methylphenidate may improve gait hypokinesia and freezing although further study is needed to determine long-term risks [94].

There is evidence that long-term motor improvement from STN DBS is persistent overall. However, axial signs gradually decline over time and contribute to a waning of the initial benefit of this procedure [95].

7.5 Gene therapy approach

Gene therapy for the central nervous system is finding novel applications after the recent development of effective gene delivery systems. To deliver therapeutic transgenes to neurons in the basal ganglia viral vectors are used for most of the clinical trials. Initial trials used genes to relieve the major motor symptoms caused by nigrostriatal degeneration. As compare to existing symptomatic treatments these new genetic approaches still need to prove more effective thus there is a need for disease-modifying strategies. Combined with innovative gene delivery systems the investigation of the genetic factors implicated in Parkinson's disease is providing precious insights in disease pathology will hopefully offer novel opportunities for gene therapy interventions to slow down, or even halt disease progression.

Gene therapy approaches treating disease by genetically modifying populations of cells that are either directly functionally impaired or capable of relieving the underlying disease symptoms. These genetic modifications increase or reduce the expression of specific gene sets, or even restore the normal function of the product of these genes. These modifications can only be made on somatic cells and must spare the germline for ethical reasons in human therapeutic applications. A distinction is made between the direct genetic modification of cells inside the

body, and ex vivo gene therapy, which is based on the genetic modification of cells maintained in culture. Number of methods has been developed for gene delivery to the target cells, which consist of viral vectors, and nonviral systems. Nonviral methods used for gene transfer to the central nervous system (CNS), comprise chemical and physical methods, such as gene gun or electroporation.

7.6 Virus mediated gene therapy

The most commonly used approach in the CNS is in vivo gene transfer using viral vectors, with 20 trials listed in 2010 [96]. For inducing long-term transgene expression this approach takes advantage of the viruses' ability to deliver their genetic material to target cells, including nondividing cells. The ability of viral vectors to transduce nondividing cells is of crucial importance in the context of PD gene therapy as most of the cells in the CNS, including neurons, is postmitotic. Viral gene delivery systems lead to irreversible genetic modifications in the patient tissues, currently available vectors allows efficient and stable transgene expression in a broad range of cellular types across the brain. Several types of vectors have been developed on the basis of their packaging capacity, tropism, and immunogenicity. Most commonly used viral vector for gene delivery system are lentivectors, AAV (adeno-associated viruses)-Based Vectors etc.

AAV vectors represent ideal vectors to deliver genes in the CNS. AAV shows a very good safety profile, and provide efficient transduction and efficient durable expression of neurons.

For PD cell therapy gene therapy could also provide essential tools. Stem cells like induced pluripotent stem cells (iPSC) derived from the somatic cells of the patients differentiated into dopaminergic neurons [97]. In the striatum of PD patients these dopaminergic cells could then be implanted to compensate for the nigral cell loss occurring during PD. There is a distinct risk that they could carry mutations perpetuating the pathology once grafted in the patients because these cells are derived from PD patients. In a recent study this issue has been addressed reporting the generation of iPSC in which disease-causing point mutations have been corrected using zinc finger nucleases [98].

7.7 Ayurvedic treatment (Chikitsa)

For PD, Ayurvedic treatment is focussed on the treatment of vata (tremors) disturbance. The basis of the constitutional treatment is formed by Oleation and fomentation (Charaka Samhita). Oleation through massage (abhyanga) and enema (basti) are indicated as well as the ingestion of oils. Naturally, jatharagni must be strong enough to support such as a heavy routine. Gentle purification procedures should be administered first, if the patient exhibits significant ama and is strong enough. Ashwagandha (*Withania somnifera*) and bala (*Sida cordi-*

folia) medicated oils are commonly used to pacify vata and build ojas (energy). With a strong nourishing action on the nervous system, they are also known to be rejuvenative. The herb atmagupta (*Mucuna pruriens* or Kapikachhu) has received a lot of attention historically and again in recent years. A study in 1978, showed its effectiveness on 23 patients diagnosed with PD, published in the journal Neurology India. In this study only the powdered seed of the plant was used.

In 1990, Bala V. Manyam published that *Mucuna pruriens* contains levodopa, or L-DOPA, within its seeds, in the Journal Movement Disorders. This established the 1937 study by Damodaran and Ramaswamy published in the journal, Biochemistry [37,99]. L-DOPA is the precursor of dopamine, the neurotransmitter which is absent or decreased in PD. At the Southern Illinois University School of Medicine, which published research performed in the department of biology at the University of Groningen, the Netherlands, the findings of these studies were confirmed. In treating PD, a controlled trial using a derivative of *Mucuna pruriens* called HP 200 was found to be effective. Ayurveda teaches that a holistic treatment schedule offers the greatest chance of success with Parkinson's patients. In addition to using Mucuna pruriens (V-PK ++, sweet/bitter/cool/sweet), vata must be pacified at its site of origin in the colon, site of overflow in the rasa dhatu and at its site of relocation in the majja dhatu.

8. Surgical procedures

8.1 Deep brain stimulation

In deep brain stimulation (DBS), surgeons implant electrodes into a specific part of patient's brain. The electrodes are connected to a generator implanted in patient's chest near collarbone that sends electrical pulses to the brain and may reduce PD symptoms. Doctor may adjust the settings as necessary to treat patient's condition. Certain risks, including infections, stroke or brain hemorrhage is involved in Surgery. Some people experience problems with the DBS system or have complications due to stimulation, and the doctor may need to adjust or replace some parts of the system.

DBS is most often offered to people with advanced PD who have unstable medication (levodopa) responses. DBS can even out medication fluctuations, reduce or halt involuntary movements (dyskinesias), reduce tremor, reduce rigidity, and improve slowing of movement.

DBS is effective in controlling unpredictable and fluctuating responses to levodopa or for controlling dyskinesias that don't improve with medication adjustments.

However, it isn't helpful for problems that don't respond to levodopa therapy apart from tremor. Even if the tremor isn't very responsive to levodopa, it may be controlled by DBS.

Although DBS may provide sustained benefit for Parkinson's symptoms, it doesn't keep

PD from progressing.

9. References

1. Kim SJ, Sung JY, Um JW, Hattori N, Mizuno Y, Tanaka K, Paik SR, Kim J, Chung KC, Parkin Cleaves Intracellular -Synuclein Inclusions via the Activation of Calpain. 2003; Journal of Biological Chemistry. 278 (43): 41890–9.

2. Alzheimer's Association. Alzheimer's disease facts and figures. Alzheimers Dement, 2014; 10:e47–e92.

3. Van Den Eeden SK. Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. Am J Epidemiol, 2003; 157:1015–22.

4. De Lau LML, Breteler MMB, Epidemiology of Parkinson's disease. Lancet Neurol, 2006; 5:525–35.

5. Pringsheim T, Jette N, Frolkis A, Steeves TDL, The prevalence of Parkinson's disease: a systematic review and meta-analysis. Mov Disord, 2014; 29:1583–90.

6. Dorsey ER, Constantinescu R, Thompson JP, Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology, 2007; 68:384–86.

7. Noyce AJ, Bestwick JP, Silveira-Moriyama L, Meta-analysis of early nonmotor features and risk factors for Parkinson disease. Ann Neurol, 2012; 72:893–901.

8. Dickson DW. Parkinson's disease and parkinsonism: neuropathology. Cold Spring Harb Perspect Med, 2012; 2:a009258

9. Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M, Alpha-synuclein in Lewy bodies. Nature, 1997; 388:839–40.

10. Goedert M, Spillantini MG, Del Tredici K, Braak H, 100 years of Lewy pathology. Nat Rev Neurol, 2012; 9:13–24.

11. Beach TG, Adler CH, Sue LI, Multi-organ distribution of phosphorylated alpha-synuclein histopathology in subjects with Lewy body disorders. Acta Neuropathol, 2010; 119:689–702.

12. Braak H, Del Tredici K, Rüb U, de Vos RAI, Jansen Steur ENH, Braak E, Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging, 2003; 24:197–211.

13. Irwin DJ, White MT, Toledo JB, Neuropathologic substrates of Parkinson disease dementia. Ann Neurol, 2012; 72:587–98.

14. Halliday G, Hely M, Reid W, Morris J, The progression of pathology in longitudinally followed patients with Parkinson's disease. Acta Neuropathol, 2008; 115:409–15.

15. Kovacs GG, Wagner U, Dumont B, An antibody with high reactivity for disease-associated α-synuclein reveals extensive brain pathology. Acta Neuropathol, 2012; 124:37–50.

16. Schulz-Schaeffer WJ. The synaptic pathology of α-synuclein aggregation in dementia with Lewy bodies, Parkinson's disease and Parkinson's disease dementia. Acta Neuropathol, 2010; 120:131–43.

17. Cremades N, Cohen SIA, Deas E, Direct observation of the interconversion of normal and toxic forms of α-synuclein. Cell, 2012; 149:1048–59.

18. Kalia LV, Kalia SK, McLean PJ, Lozano AM, Lang AE, α-Synuclein oligomers and clinical implications for Parkinson disease. Ann Neurol, 2013; 73:155–69.

19. Tansey MG, Goldberg MS, Neuroinflammation in Parkinson's disease: its role in neuronal death and implications

for therapeutic intervention. Neurobiol Dis, 2010; 37:510–18.

20. Olson KE, Gendelman HE, Immunomodulation as a neuroprotective and therapeutic strategy for Parkinson's disease. Current Opinion in Pharmacology. 2009; 26, 87-95.

21. Phani S, Loike JD, Przedborski S, Neurodegeneration and infl ammation in Parkinson's disease. Parkinsonism Relat Disord, 2012; 18:S207–09.

22. Goetz CG. The history of Parkinson's disease: early clinical descriptions and neurological therapies. Cold Spring Harb Perspect Med, 2011; 1:a008862.

23. Gibb WR, Lees AJ, The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry, 1988; 51:745–52.

24. Marras C, Lang A, Parkinson's disease subtypes: lost in translation? J Neurol Neurosurg Psychiatry, 2013; 84:409–15.

25. Jankovic J, McDermott M, Carter J, Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. Neurology, 1990; 40:1529–34.

26. Khoo TK, Yarnall AJ, Duncan GW, The spectrum of nonmotor symptoms in early Parkinson disease. Neurology, 2013; 80:276–81.

27. Duncan GW, Khoo TK, Yarnall AJ, Health-related quality of life in early Parkinson's disease: the impact of nonmotor symptoms. Mov Disord, 2014; 29:195–202.

28. Postuma RB, Aarsland D, Barone P, Identifying prodromal Parkinson's disease: pre-motor disorders in Parkinson's disease. Mov Disord, 2012; 27:617–26.

29. Siderowf A, Lang AE, Premotor Parkinson's disease: concepts and definitions. Mov Disord, 2012; 27:608–16.

30. Hely MA, Morris JGL, Reid WGJ, Trafficante R, Sydney multicenter study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. Mov Disord, 2005; 20:190–99.

31. Hely MA, Reid WGJ, Adena MA, Halliday GM, Morris JGL, The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord, 2008; 23:837–44.

32. Sampson TR, Justine W, Thron DT, Wittung-Stafshede P, Knight R, Mazmanian SK, Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease. 2016; Cell 167, 1469–1480.

33. Parkinson J. An essay on the shaking palsy. Whittingham and Rowland for Sherwood, Needly and Jones, London, 1817.

34. Sylvius de la Boe F. Opera Medica. Danielem Elsevirium et Abrahamum Wolfgang, Amsterdam. 1680.

35. Sauvages de la Croix FB de. Nosologia methodica Amstelodami: Sumptibus Fratrum de Tournes. 1673.

36. Tyler K. A history of Parkinson's disease. In Handbook of Parkinson's disease (ed. Koller WC), 1992. pp. 1–34. Marcel Dekker, New York.

37. Manyam BV. Paralysis agitans and levodopa in "Ayurveda": ancient Indian medical treatise. Mov Disord, 1990; 5:47-8.

38. Zhang ZX, Dong ZH, Roma´n GC. Early descriptions of Parkinson's disease in ancient China. Arch Neurol. 2006; 63: 782–784.

39. Charcot JM. De la paralysie agitante. In Oeuvres Comple`tes (t 1) Lec¸ons sur les maladies du syste`me nerveux, 1872; pp.155–188.

40. Gowers WR. 1888. A manual of diseases of the nervous system. J and A Churchill, London.

41. Richer P, Meige H. 1895. Etude morphologique sur la maladie de Parkinson. Nouvelle Iconographie de la Salpeˆtrie`re 8:361–371.

42. Babinski J. Kine´sie parodoxale. Rev Neurol, 1921; 37:1266– 1270.

43. Greenfield JG, Bosanquet FD, The brain-stem lesions in Parkinsonism. J Neurol Neurosurg Psychiatry, 1953; 16:213– 226.

44. Hoehn MM, Yahr MD Parkinsonism: Onset, progression and mortality. Neurology, 1967; 17:427–442.

45. Adams RD, van Bogaert L, Vander Eecken H, Striatonigral degeneration. J Neuropathol Exp Neurol, 1964; 23:584–608.

46. Westphal ACO. U¨ ber eine dem Bilde der cerebrospinalen grauen Degeneration a¨hnliche Erkrankung des centralen Nervensystems ohne anatomischen Befund, nebst einigen Bemerkungen u¨ber paradoxe Contraction. Arch Psychiatr Nervenkr, 1883; 14: 87–95.

47. Bruyn GW, Bots GT, Staal A, Familial bilateral vascular calcification in the central nervous system. Psychiatr Neurol Neurochir, 1964; 67:342–376.

48. Muenter MD, Whisnant JP, Basal ganglia calcification, hypoparathyroidism, and extrapyramidal motor manifestations. Neurology, 1968; 18:1075–1083.

49. Richard D, Sweet MD, Fletcher H, Mcdowell, MD, Five Years' Treatment of Parkinson's disease with Levodopa: Therapeutic Results and Survival of 100 Patients. Ann Intern Med. 1975; 83(4):456-463.

50. DeLong MR. Primate models of movement disorders of basal ganglia origin. Trends Neurosci 1990; 13:281–5.

51. Alexander GE, Crutcher MD, Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci, 1990; 13:266–71.

52. Obeso JA, Rodriguez-Oroz MC, Rodriguez M, The basal ganglia and disorders of movement: pathophysiological mechanisms. News Physiol Sci, 2002; 17:51–5.

53. Ring HA, Serra-Mestres J, Neuropsychiatry of the basal ganglia. J Neurol Neurosurg Psychiatry, 2002; 72:12–21.

54. Niclis JC, Gantner CW, Alsanie WF, McDougall SJ, Bye CR, Elefanty AG, Stanley EG, Haynes JM, Pouton CW, Thompson LH, Parish CL, Efficiently Specified Ventral Midbrain Dopamine Neurons from Human Pluripotent Stem Cells Under Xeno-Free Conditions Restore Motor Deficits in Parkinsonian Rodents. 2017; Stem Cells Transl Med. 6(3):937-948.

55. Becker G, Mohamed Ali B, Michel A, Hustadt F, Garraux G, Luxen A, Lemaire C, Plenevaux A, Comparative assessment of 6-[18 F]fluoro-L-m-tyrosine and 6-[18 F]fluoro-L-dopa to evaluate dopaminergic presynaptic integrity in a Parkinson's disease rat model. 2017; J Neurochem. doi: 10.1111/jnc.14016.

56. Pezzi JC, de Bem CM, da Rocha TJ, Schumacher-Schuh AF, Chaves ML, Rieder CR, Hutz MH, Fiegenbaum M, Camozzato AL, Association between DNA methyltransferase gene polymorphism and Parkinson's disease. Neurosci Lett. 2017; 639:146-150.

57. Moors TE, Hoozemans JJ, Ingrassia A, Beccari T, Parnetti L, Chartier-Harlin MC, van de Berg WD, Therapeutic potential of autophagy-enhancing agents in Parkinson's disease. 2017; Mol Neurodegener. 12(1):11.

58. Langston JW, Ballard P, Tetrud JW, Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. Science, 1983; 219:979–80.

59. Burns RS, Chiueh CC, Markey SP, A primate model of parkinsonism: selective destruction of dopaminergic neurons

in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Proc Natl Acad Sci USA, 1983; 80:4546–50.

60. Mitchell IJ, Jackson A, Sambrook MA, The role of the subthalamic nucleus in experimental chorea. Evidence from 2-deoxyglucose metabolic mapping and horseradish peroxidase tracing studies. Brain, 1989; 112:1533–48.

61. Bergman H, Wichmann T, DeLong MR, Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science, 1990; 249:1436–8.

62. Aziz TZ, Peggs D, Sambrook MA, Lesion of the subthalamic nucleus for the alleviation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)- induced parkinsonism in the primate. Mov Disord, 1991; 6:288–92.

63. Laitinen LV, Bergenheim AT, Hariz MI, Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. J Neurosurg, 1992; 76:53–61.

64. Hariz MI. From functional neurosurgery to ''interventional'' neurology: survey of publications on thalamotomy, pallidotomy, and deep brain stimulation for Parkinson's disease from 1966 to 2001. Mov Disord, 2003; 18:845–52.

65. Mu¨nchau A, Bhatia KP, Pharmacological treatment of Parkinson's disease. Postgrad Med J, 2000; 76:602–10.

66. Langston JW, Quik M, Petzinger G, Investigating levodopa-induced dyskinesias in the parkinsonian primate. Ann Neurol, 2000; 47: S79–89.

67. Jenner P. The MPTP-treated primate as a model of motor complications in PD: primate model of motor complications. Neurology, 2003; 61: S4–11.

68. Olanow CW, Goetz CG, Kordower JH, A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. Ann Neurol, 2003; 54:403–14.

69. Freed CR, Greene PE, Breeze RE, Transplantation of embryonic dopamine neurons for severe Parkinson's disease. N Engl J Med, 2001; 344:710–19.

70. Hagell P, Piccini P, Bjorklund A, Dyskinesias following neural transplantation in Parkinson's disease. Nat Neurosci, 2002; 5:627–8.

71. Barker RA. Repairing the brain in Parkinson's disease: where next? Mov Disord, 2002; 17:233–41.

72. Bjorklund A, Dunnett SB, Brundin P, Neural transplantation for the treatment of Parkinson's disease. Lancet Neurol, 2003; 2:437–45.

73. Hurelbrink CB, Barker RA, The potential of GDNF as a treatment for Parkinson's disease. Exp Neurol 2004; 185:1–6.

74. Azzouz M, Martin-Rendon E, Barber RD, Multicistronic lentiviral vectormediated striatal gene transfer of aromatic L-amino acid decarboxylase, tyrosine hydroxylase, and GTP cyclohydrolase I induces sustained transgene expression, dopamine production, and functional improvement in a rat model of Parkinson's disease. J Neurosci, 2002; 22:10302–12.

75. Lang AE, Obeso JA, Challenges in Parkinson's disease: restoration of the nigrostriatal dopamine system is not enough. Lancet Neurol, 2004; 3:309–16.

76. Williams A, Waring R, The MPTP tale: pathway to prevention of Parkinson's disease? Br J Hosp Med 1993; 49:716–19.

77. Pound P, Ebrahim S, Sandercock P, Where is the evidence that animal research benefits humans? BMJ, 2004; 328:514–17.

78. Blakemore C, Peatfield T, Missing evidence that animal research benefits humans: Moratorium is unjustified. BMJ,

2004; 328:1017–18.

79. Lemon R, Dunnett SB, Surveying the literature from animal experiments. BMJ, 2005; 330:977–8.

80. Stocchi F, Rascol O, Kieburtz K, Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: the STRIDE-PD study. *Ann Neurol*, 2010; 68(1):18-27.

81. Hauser RA, McDermott MP, Messing S, Factors associated with the development of motor fluctuations and dyskinesias in Parkinson disease. *Arch Neurol*, 2006; 63(12):1756-60.

82. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE, A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. N Engl J Med, 2000; 342(20):1484-91.

83. Constantinescu R, Romer M, McDermott MP, Kamp C, Kieburtz K, Impact of pramipexole on the onset of levodopa-related dyskinesias. Mov Disord, 2007; 22(9):1317-9.

84. Thomas A, Bonanni L, Gambi F, Di Iorio A, Onofrj M, Pathological gambling in Parkinson disease is reduced by amantadine. *Ann Neurol*, 2010; 68(3):400-4.

85. Weintraub D, Sohr M, Potenza MN, Siderowf AD, Stacy M, Voon V, Amantadine use associated with impulse control disorders in Parkinson disease in cross-sectional study. *Ann Neurol*, 2010; 68(6):963-8.

86. Olanow CW, Kieburtz K, Odin P, Espay AJ, Standaert DG, Fernandez HH, Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. *Lancet Neurol*, 2014; 13(2):141-9.

87. Schapira AH, Barone P, Hauser RA, Mizuno Y, Rascol O, Busse M, Extended-release pramipexole in advanced Parkinson disease: a randomized controlled trial. *Neurology*, 2011; 77(8):767-74.

88. Shemisa K, Hass CJ, Foote KD, Okun MS, Wu SS, Jacobson CE, Unilateral deep brain stimulation surgery in Parkinson's disease improves ipsilateral symptoms regardless of laterality. *Parkinsonism Relat Disord*, 2011; 17(10):745-8.

89. Weaver FM, Follett K, Stern M, Hur K, Harris C, Marks WJ Jr, Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA*, 2009; 301(1):63-73.

90. Follett KA, Weaver FM, Stern M, Hur K, Harris CL, Luo P, Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med*, 2010; 362(22):2077-91.

91. Brooks M, Neurostimulation has benefits in early Parkinson's disease. *Medscape Medical News*. February 15, 2013.

92. Schuepbach WM, Rau J, et al, for the EARLYSTIM Study Group. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med*, 2013; 368(7):610-22.

93. Foltynie T, Zrinzo L, Martinez-Torres I, Tripoliti E, Petersen E, Holl E, MRI-guided STN DBS in Parkinson's disease without microelectrode recording: efficacy and safety. *J Neurol Neurosurg Psychiatry*, 2011; 82(4):358-63.

94. Moreau C, Delval A, Defebvre L, Dujardin K, Duhamel A, Petyt G, Methylphenidate for gait hypokinesia and freezing in patients with Parkinson's disease undergoing subthalamic stimulation: a multicentre, parallel, randomised, placebo-controlled trial. *Lancet Neurol*, 2012; 11(7):589-596.

95. Castrioto A, Lozano AM, Poon YY, Lang AE, Fallis M, Moro E, Ten-year outcome of subthalamic stimulation in Parkinson disease: a blinded evaluation. *Arch Neurol*, 2011; 68(12):1550-6.

96. Lim ST, Airavaara M, Harvey BK, Viral vectors for neurotrophic factor delivery: A gene therapy approach for neurodegenerative diseases of the CNS. 2010; Pharmacol Res, 61:14–26.

97. Soldner F, Hockemeyer D, Beard C, Gao Q, Bell GW, Cook EG, Hargus G, Blak A, Cooper O, Mitalipova M, Parkinson's disease patient-derived induced pluripotent stem cells free of viral reprogramming factors. 2009; Cell, 136:964–977.

98. Soldner F, Laganie`re J, Cheng AW, Hockemeyer D, Gao Q, Alagappan R, Khurana V, Golbe LI, Myers RH, Lindquist S, et al. Generation of isogenic pluripotent stem cells differing exclusively at two early onset Parkinson point mutations. 2011; Cell, 146:318–331.

99. Damodaran M, Ramaswamy R, Isolation of L-DOPA from the seeds of Mucuna Pruriens. Biochemistry, 1937; 31:2149-51.