

# Advancement in parkinsons treatment

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**Abstract**— Current advancements in the treatment of Parkinson’s disease (PD) are shifting from purely symptomatic management to a dual approach: refining the delivery of existing dopaminergic therapies and developing experimental disease-modifying and neurorestorative interventions. While levodopa remains the gold standard, its long-term use is complicated by motor fluctuations and dyskinesia, prompting the development of novel delivery systems like continuous subcutaneous infusions (e.g., Vyalev and Onapgo) and inhaled levodopa to provide steadier symptom control. Simultaneously, emerging therapies including stem cell transplantation (e.g., bemandeprocil), gene therapy (e.g., AB-1005), and immunotherapy targeting -synuclein are advancing through late-stage clinical trials with the goal of replacing lost neurons or halting disease progression

**Keywords**— Parkinsons disorder, Treatment, Advancement in treatment, Clinical Presentation.

## I. CHAPTER 1 INTRODUCTION

### 1.1 Parkinson Disorder {Pd}

In today’s era neurological disorders are major causes of disabilities in organisms. Parkinson is one of that whose prevalence is increasing more than that of other disorders. Parkinson disease is the most common type of parkinsonism, a term reflecting a group of neurological disorders with Parkinson disease–like movement problems such as rigidity, slowness, and tremor. Less common parkinsonism includes other neurodegenerative diseases (e.g., multiple system atrophy, progressive supranuclear palsy), drug-induced parkinsonism, and vascular parkinsonism. Parkinson's disease (paralysis agitans or PD) is a neurodegenerative disease of the substantia nigra, an area in the basal ganglia of the brain. An estimated 6.1 million individuals globally had a Parkinson disease diagnosis in 2016, 2.4 times higher than in 1990. (1)

The Parkinson’s Disease Foundation reports that approximately 1 million Americans currently have the disease. The incidence of PD in the U.S. is approximately 20 cases per 100,000 people per year (60,000 per year), with the mean age of onset close to 60 years. The prevalence of PD is reported to be approximately 1% in people 60 years of age and older and increases to 1% to 3% in the 80-plus age group. However, an important caveat associated with these numbers is that they do not reflect

undiagnosed cases. Parkinson disease is uncommon among individuals younger than 50 years and increases in prevalence with age, peaking between ages 85 and 89 years. (2) Although it is primarily a disease of the elderly, individuals have developed PD in their 30s and 40s. Gender differences pertaining to the incidence of PD are reflected in a 3:2 ratio of males to females, with a delayed onset in females attributed to the neuroprotective effects of estrogen on the nigrostriatal dopaminergic system. Parkinson disease may be more common among white people than those of Asian or African descent; however, the data are conflicting. In 2011, the estimated number of people living with Parkinson disease in Canada had reached 85 200. By 2031, the projected number of people with this disease will double. PD’s variable but pronounced progression has a significant impact on patients, families, and society. Advanced and end-stage disease may lead to serious complications, including pneumonia, which are often associated with death. (3-5).

Most cases of Parkinson disease are idiopathic, but there are known genetic and environmental contributions. Pesticide, herbicide, and heavy metal exposures are linked to an increased risk of Parkinson disease in some epidemiologic studies, whereas smoking and caffeine use are associated with decreased risks. Most people with Parkinson disease die from the same causes as age-matched individuals without Parkinson disease. However, if a person lives with Parkinson disease for years, they may die from Parkinson disease–related causes, such as aspiration pneumonia or complications from a fall.

This increasing prevalence was attributed to improved methods used to detect and diagnose Parkinson disease, greater awareness of the disease, aging populations, longer life expectancy, and possibly increased environmental exposures (e.g., pesticides, solvents, metals) associated with industrialization. Current treatment is focused on symptomatic management. Evidence suggests that PD patients may also benefit from a multidisciplinary approach to care that includes movement specialists, social workers, pharmacists, and other health care practitioners.

### 1.1.1 History

Parkinson’s disease (PD) was first described by Dr. James Parkinson in 1817 as a “shaking palsy.” It is a chronic, progressive neurodegenerative disease characterized by both motor and nonmotor features. The disease has a significant clinical impact on patients, families, and caregivers through its progressive degenerative effects on mobility and muscle control. The motor symptoms of PD are attributed to the loss of striatal dopaminergic neurons, although the presence of nonmotor symptoms supports neuronal loss in nondopaminergic areas as well. The term parkinsonism is a symptom complex used to describe the motor features of PD, which include resting tremor, bradykinesia, and muscular rigidity. (5)

### 1.1.2 Signs & Symptoms

<b>1. Motor</b>	<p><b>Bradykinesia</b> {Slowness and progressively smaller movements (hypokinesia) as an individual repeats a task (eg, tapping index finger and thumb, opening and closing fist) multiple times in a row.}</p> <p><b>Rigidity</b> {Involuntary, velocity-independent resistance to passive movement of a joint (eg, elbow, wrist) by an examiner, with or without a cogwheel phenomenon}</p> <p><b>Rest tremor</b> {A 4- to 6-Hz tremor in a fully resting limb, which temporarily disappears when the limb is held outstretched and then returns (reemergent tremor) and is not present during movement}</p> <p><b>Postural instability</b> {Balance impairment affecting a person’s ability to change or maintain postures such as walking or standing; typically a late Parkinson disease feature}</p>
<b>2. Non motor</b>	<p><b>Olfactory loss</b> {Decreased or absent sense of smell (hyposmia)}</p> <p><b>Sleep dysfunction</b> {Symptoms of rapid eye movement sleep behavior disorder, daytime sleepiness, sleep-maintenance insomnia}</p> <p><b>Autonomic dysfunction</b> {Constipation, delayed gastric emptying, urinary urgency and frequency, erectile dysfunction, orthostatic hypotension, blood pressure variability}</p> <p><b>Psychiatric disturbances</b> {Depression, anxiety, apathy, psychosis}</p> <p><b>Cognitive impairment</b> {Mild cognitive impairment or dementia, often initially affecting attention, executive, and visuospatial functions}</p> <p><b>Others</b> {Fatigue, hypophonia (softening of the voice), sialorrhea, trouble swallowing}</p>

Fig. 1 Signs & Symptoms of Parkinson (7,8)

### 1.2 Pathophysiology

PD is an extrapyramidal system neurodegenerative syndrome involving multiple motor and nonmotor neural circuits. Research in the late 1950s identified striatal dopamine depletion as the major cause of the motor symptoms of PD.

It is characterized by two major pathologic processes:

- (a) premature selective loss of dopamine neurons in the substantia nigra pars compacta (SNpc), which project to the striatum (the nigrostriatal pathway);
- (b) the accumulation of Lewy bodies (Pathologic hallmark), a neuronal inclusion composed of  $\alpha$ -synuclein, which become misfolded forms of ubiquitin proteins and accumulate in multiple systems of patients with Parkinson disease.

It is unclear which process occurs first. Based on pathologic studies, there is a stepwise degeneration of neurons over many years, with each affected site corresponding to specific symptomatology in Parkinson disease. When motor symptoms become evident, there is 30–70% cell loss evident in the substantia nigra on pathologic examination. Cognitive dysfunction, mood disorders and impulse control disorders are related to deficits of dopamine outside the basal ganglia or in serotonergic and noradrenergic systems. Further evidence suggests that PD may originate in the dorsal motor nucleus of the vagal and glossopharyngeal nerves and in the anterior olfactory nucleus, suggesting a disease pattern that begins in the brain stem and ascends to higher cortical levels. Autonomic dysfunction has been related to pathologies outside the brain, including the spinal cord and peripheral autonomic nervous system.

The most widely cited model to explain neuropathological progression of Parkinson disease is the Braak hypothesis. This model suggests that Parkinson disease starts (stages 1 and 2) in the medulla and the olfactory bulb. This early pathology is associated with symptoms occurring prior to the movement disorder onset, such as rapid eye movement, sleep behaviour disorder (in which individuals lose normal rapid eye movement sleep paralysis and physically act out their dreams while sleeping) and decreased smell. In stages 3 and 4, pathology progresses to the substantia nigra pars compacta and other midbrain and basal forebrain structures. Pathology in these areas is associated with classic Parkinson disease motor symptoms. Parkinson

disease is typically diagnosed at this stage. In advanced Parkinson disease, the pathology progresses to the cerebral cortices with onset of cognitive impairment and hallucinations. (20-25)

In summary, PD is a complex neurodegenerative disease involving an array of molecular pathways, all of which may be implicated in the neuropathophysiology of the disease. The mainstay of therapy aims to replace dopamine with dopaminergic medications and modulate the dysfunctional circuit. As Parkinson disease protein aggregations are associated with death of dopamine-producing cells. That's why treatments supplementing dopamine are the mainstay of Parkinson disease treatment. However, other neurotransmitter systems are also dysfunctional in Parkinson disease, including serotonin, acetylcholine and norepinephrine systems. This explains why some Parkinson disease symptoms are refractory to dopamine-based medications. Some novel therapeutic approaches target these alternative neurotransmitter systems.

**1.2.1 Risk factors associated with PD**

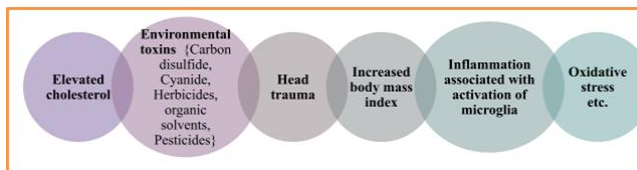


Fig.2 Risk Factors Associated with Parkinson's Disease (10)

**1.2.2 Gene Mutations Associated with Parkinson's Disease**

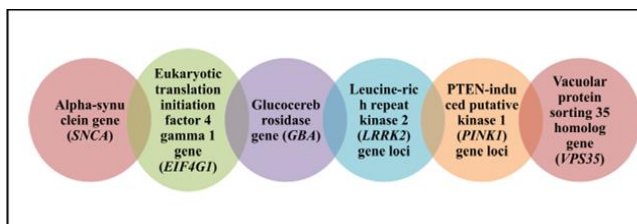


Fig. 3 Gene Mutations Associated with Parkinson's Disease (12)

**1.2.3 Clinical Presentation**

Parkinson disease causes motor and nonmotor symptoms. Motor symptoms consist of movement and physical tasks: tremor, stiffness, slowness, and imbalance. Nonmotor (nonmovement) symptoms affect many organ systems, such as gastrointestinal and genitourinary systems, and are heterogeneous. Patients may not proactively volunteer nonmotor symptoms because they are embarrassed, appointment time is focused on motor symptoms, or they are unaware that the symptoms could be Parkinson disease related. Individuals diagnosed with Parkinson disease typically have gradual development of nonmotor symptoms for years before movement symptoms begin, but often they will not mention these symptoms unless specifically queried. These prodromal nonmotor features include rapid eye movement sleep behaviour disorder, loss of smell, constipation, urinary dysfunction, orthostatic hypotension, excessive daytime sleepiness, and depression. (9)

These symptoms are not Parkinson disease specific, but when they co-occur, the risk of a subsequent Parkinson disease diagnosis is greater. Rapid eye movement sleep behaviour disorder, particularly if identified on polysomnography, is strongly associated with increased risk of a subsequent diagnosis of Parkinson disease. More than 90% of individuals with idiopathic rapid eye movement sleep behaviour disorder eventually develop a synuclein-related neurodegenerative disease, usually Parkinson disease or a related condition (dementia with Lewy bodies, multiple system atrophy). An estimated 30% to 50% of individuals with Parkinson disease have rapid eye movement sleep behaviour disorder. Prodromal symptoms are associated with early Parkinson disease brainstem pathology. Once neuropathological progression results in loss of approximately half of cells in the caudal substantia nigra, motor signs and symptoms of Parkinson disease appear, and individuals present with personal or family concerns regarding gradual onset of resting tremors, slowness, and/or generalized (not joint-specific) stiffness. Approximately 20% of individuals with Parkinson disease do not present with resting tremors. (28)

**1.3 Diagnosis**

The differential diagnosis of PD should include a comprehensive history and physical examination. Difficult or questionable cases should be referred to a movement-disorder specialist for further evaluation. There are no definitive tests to confirm the diagnosis of PD; therefore, a clinical diagnosis requires the clinician to review the

patient’s history, to assess symptoms, over time based on the response to dopamine agents and the development of motor fluctuations and to rule out alternative diagnoses, such as multiple-system atrophy, DLB disease, and essential tremor. A classic symptom is resting tremor, usually affecting one upper limb, although 20% of patients do not have it; 30% may first present with tremor in a lower extremity, and there may also be a lip, jaw or even tongue tremor at rest. Head and voice tremors are uncommon, so one should consider essential tremor in the differential diagnosis in such cases. Of all the major features, bradykinesia has the strongest correlation with the extent of dopamine deficiency. Diagnosis has been formalized by the criteria of the UK Parkinson’s Disease Society Brain Bank, with diagnostic accuracy of up to 90%. Others are the presence of levodopa-induced dyskinesias {involuntary dance-like choreoathetoid movements that occur with dopaminergic therapy. Dyskinesias usually occur years after Parkinson disease medications are initiated and have limited benefit for diagnosis at symptom onset.}, or the presence of either olfactory loss or cardiac sympathetic denervation on iodine-123-meta-iodobenzylguanidine myocardial scintigraphy (an imaging test that assesses cardiac norepinephrine uptake, which depends on intact postganglionic sympathetic neuron function [decreased in Parkinson disease]). (26-30)

The cardinal motor features of PD—described as the “classical triad”—include a 4-Hz to 6-Hz resting tremor, “cogwheel” rigidity, and bradykinesia. These cardinal features are often reported as the first clinical findings of the disease. A fourth feature, postural instability, occurs in approximately 50% of PD patients within five years of diagnosis. Although PD is considered to be a disease of the elderly, some genetic variants are present in younger patients. Clinically, younger individuals (under 60 years of age) may present with less rigidity and bradykinesia, and this may result in a delayed or missed diagnosis.

In some settings, Parkinson disease cannot be confirmed if medications may be responsible for the patient’s signs and symptoms or if additional findings suggest an alternative diagnosis. Dopamine transporter single-photon emission computed tomography (DaT SPECT) identifies the presynaptic dopamine neuronal dysfunction present in Parkinson disease and other neurodegenerative parkinsonisms by demonstrating reduced uptake of a radioactive tracer that binds to dopamine transporters in the basal ganglia. DaT SPECT is highly accurate (98%-100% sensitivity and specificity) in detecting nigrostriatal cell loss in individuals with parkinsonism.

In 2011, the US Food and Drug Administration (FDA) approved DaT SPECT imaging for distinguishing Parkinson disease from essential tremor, but these scans are not routinely needed. DaT scans are generally useful only when the presence of parkinsonism is uncertain on examination. If a patient has unequivocal parkinsonism, the scans are typically positive and add little to the diagnostic assessment. They cannot differentiate between Parkinson disease and other parkinsonisms (e.g., multiple system atrophy, progressive supranuclear palsy) that also involve dopamine transporter dysfunction. (11-15)

Magnetic resonance imaging (MRI) is not typically helpful for diagnosing Parkinson disease. Specific MRI findings (ego, the magnetic resonance parkinsonism index, which is abnormal in progressive supranuclear palsy) can help differentiate Parkinson disease from other parkinsonisms; advanced techniques have future diagnostic and prognostic potential.<sup>24,25</sup> MRI findings of extensive cerebrovascular disease or basal ganglia lacunes can suggest a potential vascular contribution. Largely used outside the United States, iodine-123-meta-iodobenzylguanidine myocardial scintigraphy aids in evaluating for sympathetic nerve dysfunction, which commonly occurs as part of parkinsonisms.

Advancements in neuroimaging studies, including transcranial Doppler ultrasonography,<sup>51</sup> positron emission tomography (PET), single-photon emission computed tomography (SPECT), morphometric MRI studies, tractography, functional MRI and perfusion imaging are being used to differentiate idiopathic Parkinson disease from other parkinsonian disorders.

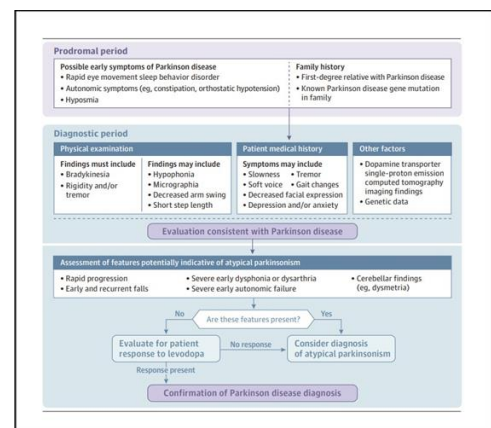


Fig. 4 Diagnosis (29)

Table 1 Early and late motor and nonmotor features in patients with Parkinson disease (50)

Early motor features	Early nonmotor features (may precede the diagnosis)	Late features (usually develop 5–10 yr. after disease onset)	Late nonmotor features
Difficulty turning in bed, Stiffness, numbness or pain in limb	Constipation (30%)	Motor fluctuations	Dysphagia (50% at 15 yr.)
Frozen shoulder, Micrographia, Difficulty with fine finger movements (bradykinesia)	REM sleep behavior disorder (50%, often preceding the diagnosis by median of 14 yrs.)	Dyskinesia (complication of dopaminergic treatment, more so with levodopa); typically, choreiform, involving the neck, head, limbs and trunk	Neuropsychiatric symptoms (50% at 15 yrs.), including hallucinations, sleep disturbance and dementia
Soft voice, decreased arm swing, dragging a leg	Olfaction impairment (most consistent nonmotor feature predicting Parkinson disease); up to 97% of patients.	Gait freezing	Seborrheic dermatitis (usually involving the forehead, with flaky oily skin)
Tremor of hand, jaw, foot, Decreased facial expression	Depression occurs with a prevalence of 35% in Parkinson disease, and 10%–15% will have depression at the time of diagnosis.	Falls	Autonomic disturbances (70%–80%), including sweating, orthostasis, sialorrhea and urinary dysfunction

#### 1.4 Treatment

The primary goal in the management of PD is to treat the symptomatic motor and nonmotor features of the disorder, with the objective of improving the patient’s overall quality of life. Appropriate management requires an initial evaluation and diagnosis by a multidisciplinary team consisting of neurologists, primary care practitioners, nurses, physical therapists, social workers, and pharmacists. It is also important that the patient and his or her family have input into management decisions. Effective management should include a combination of nonpharmacological and pharmacological strategies to maximize clinical outcomes.

Moreover, dopaminergic medications are the mainstay of symptomatic therapy for motor symptoms in Parkinson disease. Discovered in the 1960s, levodopa was the first

symptomatic treatment for Parkinson disease, followed by the availability of dopamine agonists and monoamine oxidase B inhibitors. Until recently, the decision regarding which treatment to initiate has been debated. There is no one medication that is recommended for treatment initiation currently, but factors such as symptom severity, embarrassment, ability to perform activities, cost and patient preference should be taken into account. If symptoms are very mild, the patient may choose not to begin therapy. Because patients with early-onset disease are more likely to develop levodopa-induced abnormal movements (dyskinesia), dopamine agonists are often introduced as initial treatment; however, this early advantage of dopamine agonists over levodopa diminishes over time (about 10 yr.). There is also some controversial evidence for neuroprotection with the monoamine oxidase B inhibitor rasagiline at the 1 mg daily dose; however, its cost is not covered in most provinces and may require

application to the exceptional access program, as is done in Ontario. (42-47)

Because of the increased risk of neuropsychiatric adverse effects from dopamine agonists in late-onset Parkinson disease, levodopa is often started first. Levodopa achieves somewhat better control of motor symptoms of Parkinson disease than dopamine agonists and monoamine oxidase B inhibitors, but dyskinesias and motor fluctuations develop after long-term use or high-dose treatment. The patient will likely need multiple medication adjustments over time with the addition of adjunctive treatments. Most patients taking dopamine agonists will also need levodopa after two to five years. Because Parkinson-plus syndromes (e.g., multiple system atrophy and progressive supranuclear palsy), respond in the very early stages to levodopa, this medication should be tried for at least several months with doses up to 1000 mg/d before concluding non-responsiveness. The diagnosis should also be re-evaluated after a trial of levodopa. Responsiveness to levodopa occurs in about 80% of patients with idiopathic Parkinson disease. Although bradykinesia and rigidity respond well to levodopa, this consistent response is not seen for tremor.

Anticholinergics, such as trihexyphenidyl, may be used in patients with early-onset Parkinson disease and severe tremor, but not as a first choice owing to limited efficacy and propensity for neuropsychiatric adverse effects. Recent data show that injections of botulinum toxin may effectively treat tremor from Parkinson disease. Behavioral addictions and impulse control disorders occur in 5% of patients with Parkinson disease and up to 20% of those taking dopamine agonists. Risk factors for impulse control disorders include younger age (perhaps related to prescribing behavior of dopamine agonists in this group), novelty-seeking personality, family history of addiction, use of dopamine agonists and prior history of impulse control disorders.

Dopamine dysregulation syndrome is a form of addictive behavior that occurs in up to 4% of patients and is characterized by compulsive overuse of dopaminergic medications, which are typically short-acting (e.g., levodopa and apomorphine), impairing physical, social and occupational functioning. Punding involves repetitive, often purposeless, stereotyped behaviours, such as sorting or disassembling, and occurs in up to 15% of patients with Parkinson disease. Impulse control disorders can occur any time after starting dopamine agonists; dopamine dysregulation syndrome and punding can occur with use of short-acting dopaminergic agents, including levodopa.

About 40% of patients with Parkinson disease use one or more forms of alternative therapies to complement their standard treatments. Exercise therapy may be considered as a means of improving motor function in patients with Parkinson disease, but there is no good evidence that it is neuroprotective. There is good evidence for physiotherapy, but the effect often dissipates when the intervention stops. Physiotherapy should address specific motor features such as falls, freezing and deconditioning. For patients with early disease, it is reasonable to encourage exercise (e.g., gym settings, regular walks or even dance therapy). Speech therapy may be considered to improve speech volume, with evidence in favor of the Lee Silverman Voice Treatment. Occupational therapy should be employed for practical home issues and activities of daily living, and may be helpful with driving assessments.

Antiparkinsonian medications should not be withdrawn abruptly to avoid acute akinesia or neuroleptic malignant syndrome. Dopamine agonists should not be rapidly discontinued because of the risk of dopamine agonist withdrawal syndrome (occurs in 15% of patients taking dopamine agonists; the risk is higher among those with impulse control disorders). (51-52)

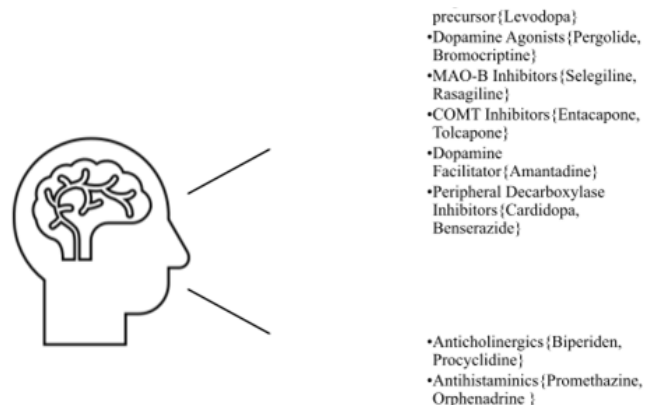


Fig.5 Anti-Parkinsonian Drugs (38)

### 1.5 Advancement In Treatment

L-dopa is still the gold standard, and its combination with dopamine agonist, monoamine oxidase type B inhibitor,

catechol-O-methyltransferase inhibitor and/or non-dopaminergic medication has been used to treat L-dopa related motor and non-motor complications for many years. However, in the advanced stage, despite adjustments to these medications, it is impossible to manage these complications, and finally surgical intervention is required in some patients. The use of stereotactic neurosurgery declined with the introduction of the drug L-dopa as an effective oral medication; but stereotactic neurosurgery was revived when it was shown to be effective in treating motor complications including wearing-off and dyskinesia. Later, deep brain stimulation (DBS) was introduced, and became the gold standard of treatment for advanced PD motor features.

Today, various advanced treatments such as DBS, radiofrequency, MR-guided focused ultrasound (MRgFUS), gamma knife, levodopa-carbidopa intestinal gel (LCIG), and apomorphine are available, although the availability of treatments varies depending on country and region. Clinical practice guidelines for early treatment of PD have been published in various countries and are often recommended by experts. Standard pharmacological and non-pharmacological treatments are required during treatment, and the need for personalized medicine becomes more obvious when aiming to achieve an appropriate symptomatic and disease-modifying treatment with the right dose, right time, and minimum side effects in a specific patient. On the other hand, guidelines for the treatment of advanced PD have not been established, and in particular, the indication criteria and exclusion criteria for device-aided therapy have not been clarified.

The initial surgical management of PD was limited to lesioning procedures; over time, however, particularly in the last 25 years, deep brain stimulation has become the predominant therapy. DBS and LCIG are the most established treatments for advanced stage PD in recent years, apomorphine subcutaneous infusion and MRgFUS have also become available, and efforts to incorporate them into personalized medicine will become

important in the future. The term “advanced treatments” refers to DBS, LCIG, apomorphine injection, MRgFUS, and other non-medication approaches. (27)

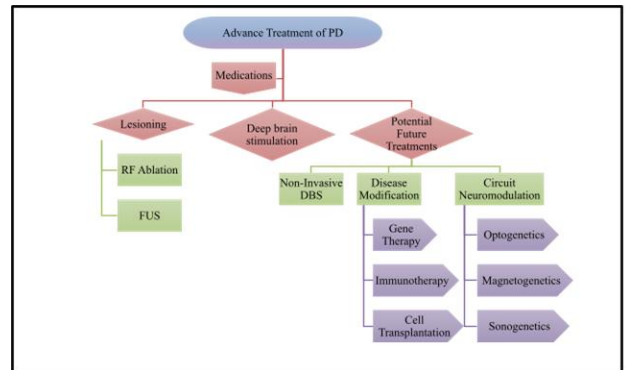


Fig. 6 Advance Treatments (32)

### 1.5.2 General Treatment

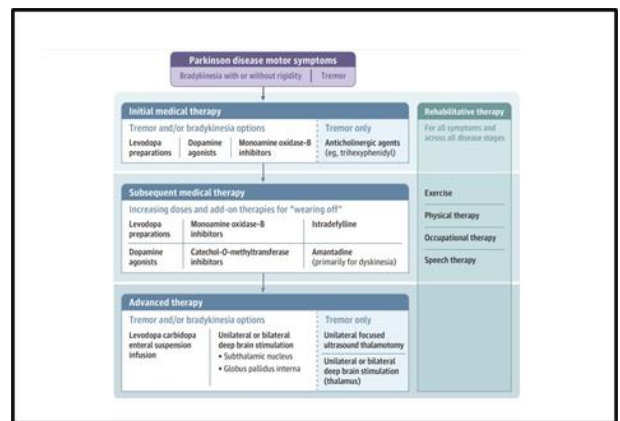


Fig.7 Treatment (41)

### 1.6 Magnetogenetics

There have been a number of recent advances in the field of neuromodulation for PD, including exploring new anatomical targets, improving technology, and exploring novel therapies. Since the early pallidotomies, the basal ganglia have been targeted to treat the motor symptoms of PD. Currently, the internal segment of the pallidum (GPi) and the subthalamic nucleus (STN) are the predominant surgical targets. Surgical targeting of all the desired nuclei has improved with better imaging techniques, including high field strength magnetic resonance, tractography and functional imaging, and more detailed understanding of the abnormal and surrounding electrophysiology. These advances have helped to optimize surgical accuracy and reduce adverse effects.

Electrical deep brain stimulation (DBS) is a well-established method for treating disordered movement in Parkinson's disease. However, implanting electrodes in a person's brain is an invasive and imprecise way to stimulate nerve cells. Researchers report in ACS' Nano Letters a new application for the technique, called magnetogenetics, that uses very small magnets to wirelessly trigger specific, gene-edited nerve cells in the brain.

The treatment effectively relieved motor symptoms in mice without damaging surrounding brain tissue. Magnetogenetics offer the potential to use magnetic nanostructures to wirelessly trigger specific, gene-edited nerve cells in the brain from outside the body. To test this, the researchers injected these nanoparticles into a specific area of the brain called the subthalamic nucleus (STN) in PD mice. They found that this technique significantly improved movement and balance in mice with PD compared to untreated mice without damaging surrounding brain tissue. Importantly, these effects lasted over time. The authors report that this method offers a promising, non-invasive way to deliver precise stimulation to the brain cells involved in PD symptoms, potentially providing a safer and more effective treatment approach. (20-31)

□ Magnetogenetics means the use of magnetic fields along with magnetic actuators can be used to modulate biological functions in a non-invasive way, paving the way for the development of exciting tools useful in basic research and clinical applications.

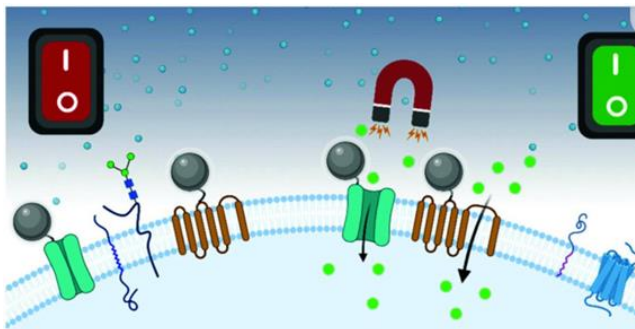


Fig.8 Magnetogenetics (20)

Our cells utilize a set of receptors capable of perceiving physical cues from their environment, which are involved in physiological processes such as touch or nociception and in pathological processes like cardiomyopathies or

cancer progression.<sup>1</sup> During the last years, much effort has been devoted to the development of tools for remote manipulation of these cellular functions, using non-invasive stimuli such as light, electricity, ultrasound or magnetic fields. These technologies can contribute to shedding light on our understanding of biological processes, paving the way for the development of exciting tools useful in basic research and clinical applications.

Optogenetics for instance has provided great advances during the last decades for neuromodulation.<sup>2</sup> This technique uses light to modulate cells that have been previously engineered to respond to those wavelengths, and is extremely useful because of its fast response and the availability of a large number of light-responsive receptors. However, when light has to reach deep structures, a fibre optic implant is routinely needed, as light in the ultraviolet and visible range does not penetrate well into the tissue. In order to overcome such problems, an emerging tool to control biological functions is based on the use of magnetic fields along with magnetic actuators, approach coined as magnetogenetics. The main advantage of this technique is that magnetic fields can penetrate deep tissues, which is especially relevant for in vivo applications. In addition, another advantage of this technique over optogenetics is the possibility to precisely modulate the external field, allowing a wide range of stresses and forces (fN to nN) to be applied without damaging the sample.

This approach has been extensively used to study mechanotransduction processes, that is, how cells respond to mechanical stimuli and convert them into biochemical signalling. In nature, mechanical stimulation of cells comprises phenomena such as compression, tension or fluid flow, each triggering different downstream cellular responses. In this context, many studies over the past decades have used magnetic microparticles and techniques such as magnetic tweezers or traction force microscopy to highlight how mechanical cues can impact biological processes. However, the size of magnetic microparticles results in multivalent binding, causing clustering of receptors and activation of intracellular signalling even in the absence of a magnetic field, preventing the required spatial control at the molecular level. Therefore, the use of smaller magnetic actuators such as ferritin or magnetic nanoparticles (MNPs), with sizes comparable to conventional proteins, permits a specific targeting of cell receptors. Such magnetic actuators, in combination with magnetic fields, are emerging as new instruments to precisely manipulate mechanical forces, providing an

exclusive approach to the study of mechanotransduction. Although to a lesser extent, magnetic actuators have also been used for magnetothermal stimulation, activating intracellular pathways connected to temperature-sensitive proteins. Overall, this technology offers exciting opportunities for the manipulation of different functions in vitro and in vivo in a subtle way. Pioneering works during the last decade have used it to open ion channels, to regulate cell fate or even to manipulate individual receptors with exquisite control. (15-20)

The general idea behind magnetogenetics is that a magnetic actuator exposed to a magnetic field will induce a mechanical load or will generate heat, activating intracellular pathways. Therefore, there are three main components for the remote activation of cellular functions based on magnetic materials:

- (i) the magnetic field (that exerts a specific force or delivers energy to the actuator),
- (ii) the magnetic actuator (e.g., MNPs (single core or clusters) or ferritin) and
- (iii) the target being activated at the cellular level.

In particular, the actual mechanism involved in the magnetic activation of a biological receptors will depend on many parameters such as:

- (i) the type of magnetic fields being applied, either a static or a rotating direct current (DC) field, a DC gradient (static, pulsed or with some kind of movement) or an alternating current (AC) field,
- (ii) the magnetic properties of the magnetic actuator, and
- (iii) the intrinsic physical properties (thermal, mechanical, etc.) of the targeted cell receptors.

In general, both DC and AC fields have been employed for the manipulation of magnetic actuators. The main difference between them is that, for a given point in space kept at the same distance from the source generating the field, the DC field maintains its direction and magnitude over time, while an AC field periodically reverses its direction and changes its magnitude with time.

Using the nanoscale magnetic force actuators (m-Torquer), which deliver torque force under rotating magnetic fields to activate pre-encoded Piezo1 ion channels on target neurons, our system enables wireless and STN-specific DBS without implants, addressing key unmet challenges in the DBS field. In both late- and early-stage PD mice, MMG-DBS significantly improved locomotor activity and

motor balance by 2-fold compared to untreated PD mice. Moreover, MMG-DBS enabled sustained therapeutic effects. This approach provides a non-invasive and implant-free DBS with cellular targeting capability for the effective treatment of Parkinsonian symptoms. (45)

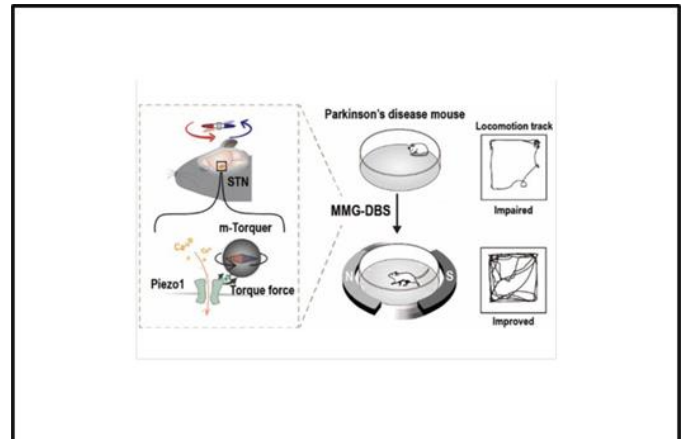


Fig.9 Magnetogenetics in mice (30)

- Magnetogenetics utilizes a similar principal to optogenetics, but relies on the activation of neurons via magnetic fields that pass through the tissue to activate genetically expressed magnetoreceptors or nanoparticles. The challenge with magnetogenetics is that there is less temporal precision, as the activation/ deactivation kinetics are slower than physiological neural activity. The receptors may also be susceptible to endogenous stimuli like temperature and pH changes, potentially limiting the applicability.

The noninvasive activation of neuronal activity was executed through an iron-sulfur assembly protein, iron-sulfur cluster assembly protein 1 (Isca1) [18– 20]. We speculate that this iron-containing magnetoreceptor- tor might form as an iron-sulfur cluster that could bind to cellular plasma membrane through either cytoskeletons or filaments [18,21,22]. We found that this magnetoreceptor could evoke membrane depolarization and action potentials, generate calcium influx, and trigger neuronal activity in both HEK-293 and cultured primary hippocamp

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the landscape of currently available neuro perturbation and neuromodulation toolboxes including optogenetics and deep-brain stimulation. This novel technology makes the exclusively non-invasive dissection of complex brain circuitry as well as the modulation of deep-brain regions possible, opening a new door to non-invasive, remote, and magnetic control of neuronal activities in the intact mammalian brains and biological processes in other organisms.

### 1.6.2 Advantages over other techniques

- In traditional DBS, a battery pack externally sends electrical signals through wires, activating nerve cells in a region of the brain called the subthalamic nucleus (STN). STN activation can relieve motor symptoms of Parkinson’s disease, including tremors, slowness, rigidity and involuntary movements. However, because the potential side effects, including brain hemorrhage and tissue damage, can be severe, DBS is usually reserved for people who have late-stage Parkinson’s disease or when symptoms are no longer manageable with medication.

- Optogenetics enables the manipulation of neuronal activity using microbial membrane opsins that are sensitive to light (such as channelrhodopsin or halorhodopsin). While DBS affects multiple nuclei simultaneously, optogenetics can potentially excite or inhibit specific cell-types within a focal region of nuclei, which would enable more precise neuromodulation. This technique is temporally and spatially very precise, but requires invasive surgery and is limited by the opacity of the brain and is reliant on a light source.

- Adverse events are typically related to lead placement during surgery for deep brain stimulation, and the most worrisome include infection, requiring device removal and antibiotics (1.2%–15.2%), and intracranial hemorrhage (5%), causing permanent deficit or death in 1.1% of patients. Diathermy, electrocautery and MRI should be avoided in patients with deep brain stimulation. (46-50)

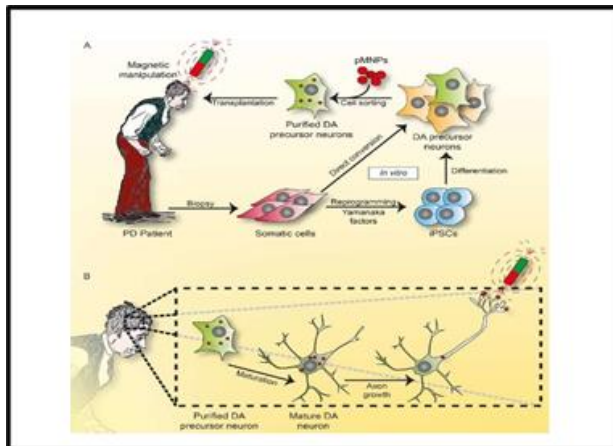


Fig. 10 Mechanism of Magnetogenetics (42)

## II. CHAPTER 2

### LITERATURE SURVEY

1. Antonini et al. (2018) suggested the presence of off-symptoms for more than 2 h a day, troublesome dyskinesia for more than 1 h a day, and levodopa administration of more than 5 times a day may be indicators for advanced PD.
2. For a step toward a less invasive treatment, Minsuk Kwak and Jinwoo Cheon (2018) worked with their colleagues to develop a wireless method to effectively reduce motor dysfunction in people with Parkinson's disease because the potential side effects, including brain hemorrhage and tissue damage, can be severe, DBS is usually reserved for people who have late-stage Parkinson's disease or when symptoms are no longer manageable with medication.
3. Knöpfel T (2012) Genetically encoded optical indicators for the analysis of neuronal circuits.
4. A recent study by Grossman et al. (2017) demonstrated that non-invasive stimulation might be possible by utilizing offsetting non-physiologic high frequency stimulation (i.e., 2.00 kHz and 2.01 kHz) to create focal subcortical low frequency stimulation at a specific desired location.
5. Fox SH, Katzenschlager R, Lim SY, et al (2018) Movement Disorder Society Evidence-Based Medicine Committee. International Parkinson and movement disorder society evidence-based medicine review give update on treatments for the motor symptoms of Parkinson's disease.
6. Luquin MR, Kulisevsky J et. al (2017) give consensus on the definition of advanced Parkinson's disease.

7. Suwijn SR, van Boheemen CJ et. al (2015) studied the diagnostic accuracy of dopamine transporter SPECT imaging to detect nigrostriatal cell loss in patients with Parkinson's disease or clinically uncertain parkinsonism.
8. Gray R, Ives N, Rick C, et al (2014) PD Med Collaborative Group states the long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED).
9. Knöpfel T (2012) worked on genetically encoded optical indicators for the analysis of neuronal circuits.
10. Stefani A, Lozano AM, Peppe A, Stanzione P, Galati S et. al (2007) Bilateral deep brain stimulation of the pedunculo-pontine and subthalamic nuclei in severe Parkinson's disease.
11. Cotzias (1960) initiated the use of high-dose therapy, and the modern regimen for L-dopa therapy was established. L-dopa is still the gold standard, and its combination with dopamine agonist, monoamine oxidase type B inhibitor, catechol-O-methyltransferase inhibitor and/or non-dopaminergic medication has been used to treat L-dopa related motor and non-motor complications for many years.
12. Narabayashi et al. (1952) performed the world's first pallidotomy for PD patients and described its positive effect.

### III. CHAPTER 3 DISCUSSION

This report focuses on the advanced treatment of PD including cell therapy and gene therapy. Furthermore, we discuss aspects of personalized medicine that are currently available for the advanced treatment of PD. In this report, the term "advanced treatments" refers to DBS, LCIG, apomorphine injection, MRgFUS, and other non-medication approaches. Parkinson's disease (PD) affects over 8.5 million people globally, and prevalence has doubled in the past 25 years. The disease causes a number of issues including problems with movement, sleep, and mental health. There is currently no cure, but therapies and medicines can reduce symptoms and help to manage pain. One such therapy is electrical deep brain stimulation, but implanting electrodes to stimulate the nerve cells is invasive and can be imprecise, running the risk of hardware failure and hemorrhage. So, to overcome the issues arising during the use of DBS and optogenetics a new such technology called Magnetogenetics have been developed.

The introduction of the magneto-mechanical-genetic (MMG)-driven wireless deep brain stimulation (DBS) using magnetic nanostructures for therapeutic benefits in

the mouse model of Parkinson's disease (PD) was done to analyse it. Using the nanoscale magnetic force actuators (m-Torquer), which deliver torque force under rotating magnetic fields to activate pre-encoded Piezo1 ion channels on target neurons, the system enables wireless and STN-specific DBS without implants, addressing key unmet challenges in the DBS field. In both late- and early-stage PD mice, MMG-DBS significantly improved locomotor activity and motor balance by 2-fold compared to untreated PD mice. Moreover, MMG-DBS enabled sustained therapeutic effects. This approach provides a non-invasive and implant-free DBS with cellular targeting capability for the effective treatment of Parkinsonian symptoms.

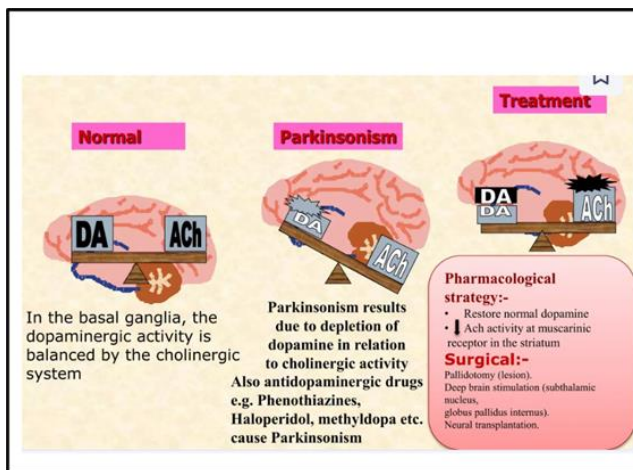


Fig.11 Parkinson

#### IV. CHAPTER 4 CONCLUSION

Despite the various current therapies' effectiveness, there is a significant need for developing treatments to modify the disease process itself. To date, gene therapy, immunotherapy, and cell transplantation trials have had both promising and disappointing results. Newer techniques being developed (optogenetics, magnetogenetics, and sonogenetics) are exciting possibilities for the future.

Over the other technologies magnetogenetics is non-invasive, remote, penetrative, uniform, and safe. Compared to the optic fiber used in optogenetics and the electric wire assembled in deep-brain stimulation, there is no need for chronic surgical implantation of any invasive devices since the external magnetic fields can penetrate

deeply into the intact mammalian brain or other biological systems.

The non-invasive activation of neurons was achieved by neuronal expression of an exogenous magnetoreceptor, an iron-sulfur cluster assembly protein 1 (Isca1). In HEK-293 cells and cultured hippocampal neurons expressing this magnetoreceptor, application of an external magnetic field resulted in membrane depolarization and calcium influx in a reproducible and reversible manner, as indicated by the ultrasensitive fluorescent calcium indicator GCaMP6s.

Moreover, the magnetogenetic control of neuronal activity might be dependent on the direction of the magnetic field and exhibits on-response and off-response patterns for the external magnetic field applied. The activation of this magnetoreceptor can depolarize neurons and elicit trains of action potentials, which can be triggered repetitively with a remote magnetic field in whole-cell patch-clamp recording.

Overall, here, we have discussed various advanced treatments for advanced PD. In the future, there may be additional advanced treatment options, including cell therapy and gene therapy. In addition, the development of optogenetics, magnetogenetics, and sonogenetics is expected. Therefore, it is important to consider the individual symptoms, patient background, and cost of these options when deciding on advanced treatment.

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