



# REVIVE ON PARKINSON'S DISEASE

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**Abstract:** The Parkinson's disease is one of most mysterious disease on which vary less amount of the data available Parkinson's disease is fatal. Parkinson's disease is not a direct killer, like stroke or heart attack. That said, much depends on the quality of your care, both from your medical team and yourself. As the disease progresses, you may become more vulnerable to falls, which can be dangerous. is a progressive, neurodegenerative disorder of aging that affects both motor and cognitive function. The etiology of PD is mostly unknown, but it likely involves both genetic and environmental factors. In contrast, the network-level pathology of PD is reasonably well understood. In this review we see about

## I. INTRODUCTION

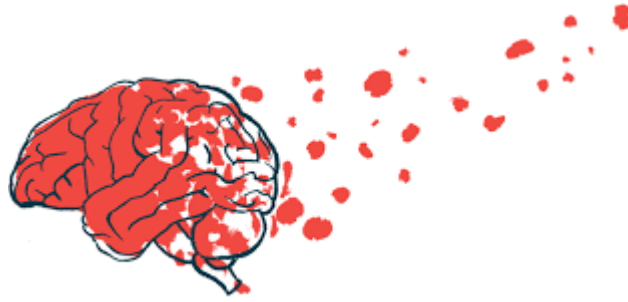
Parkinson's disease (PD) was first described by Dr. James Parkinson in 1817 as a "shaking palsy." It is a chronic, progressive neurodegenerative disease characterized by both motor and nonmotor features. The disease has a significant clinical impact on patients, families, and caregivers through its progressive 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. PD is the most common cause of parkinsonism, although a number of secondary causes also exist, including diseases that mimic PD and drug-induced causes.

Research suggests that the pathophysiological changes associated with PD may start before the onset of motor features and may include a number of nonmotor presentations, such as sleep disorders, depression, and cognitive changes. Evidence for this preclinical phase has driven the enthusiasm for research that focuses on protective or preventive therapies.

PD is one of the most common neurodegenerative disorders. The Parkinson's Disease Foundation reports that approximately 1 million Americans currently have the disease.<sup>5</sup> 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.

Although it is primarily a disease of the elderly, individuals have developed PD in their 30s and 40s.<sup>7</sup> 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. 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.<sup>1</sup> 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



## II. HISTORY

Parkinson's disease was first medically described as a neurological syndrome by James Parkinson in 1817, though fragments of Parkinsonism can be found in earlier descriptions (Parkinson 1817). As examples, Sylvius de la Boë wrote of rest tremor, and Sauvages described festination (Sylvius de la Boë 1680; Sauvages 1768; Tyler 1992). Much earlier, traditional Indian texts from approximately 1000 BC and ancient Chinese sources also provide descriptions that suggest Parkinson's disease (Manyam 1990; Zhang et al. 2006)

Jean-Martin Charcot, in his teaching at the Salpêtrière over 50 years later, was more thorough in his descriptions and distinguished bradykinesia as a separate cardinal feature of the illness (Charcot 1872) Charcot and his students described the clinical spectrum of this disease, noting two prototypes, the tremorous and the rigid/akinetic form. They described in full detail the arthritic changes, dysautonomia, and pain that can accompany Parkinson's disease. Charcot was also the first to suggest the use of the term "Parkinson's disease" rejecting the earlier designation of paralysis agitans or shaking palsy, because he recognized that Parkinson's disease patients are not markedly weak and do not necessarily have tremor (Charcot 1872)

William Gowers, working in London, contributed an important study of Parkinson's disease demographics in his "Manual of Diseases of the Nervous System," describing his personal experience with 80 patients in the 1880s. He correctly identified the slight male predominance of the disorder and studied the joint deformities typical of the disease. Known for his descriptive prose, Gowers offered one of the most memorable similes regarding Parkinsonian tremor (Gowers 1888)

Further clinical descriptions and studies of the pathologic changes related to Parkinson's disease were predominantly reported by the French neurologic school. Richer and Meige (1895) Babinski commented on the strange motor fluctuations intrinsic to the disease itself (Babinski 1921). Brissaud first proposed damage to the substantia nigra as the anatomical seat of Parkinson's disease, and Trétiakoff and Foix and Nicolesco pursued further pathologic studies of the midbrain in relationship to the disease during the 1920s (Trétiakoff 1921; Brissaud 1925; Foix and Nicolesco 1925). The most complete pathologic analysis of Parkinson's disease and the clear delineation of the brain stem lesions was performed in 1953 by Greenfield and Bosanquet (Greenfield and Bosanquet 1953). The time-honored staging 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 (Hoehn and Yahr 1967).

## III. PATHOPHYSIOLOGY

Biochemical studies show a decrease of dopamine (DA) in the caudate nucleus and putamen; PD is therefore considered to be a disease of the neuronal system, which largely involves the nigrostriatal dopaminergic system [2]. This disease is identified on the premise of two considerable pathological processes: early selective loss of dopamine neurons, and the buildup of Lewy bodies (LBs) made up of  $\alpha$ -synuclein that become misfolded and accumulate in a number of body systems of Parkinson's patients [1]. The central nervous system is composed of groups of various nerve cells which form complex interactions that allow for skillful movement. The substantia nigra located in the midbrain is of essential importance to PD, as nigral neurons give rise to an extensive axonal network which innervates the basal ganglia. Lee et al. *Neuroimmunol Neuroinflammation* 2021;8:222-44 I <http://dx.doi.org/10.20517/2347-8659.2020.58> Page 224 Liberation of dopamine, a neurotransmitter, by neurons of the substantia nigra allows for communication with neurons of the basal ganglia. Fine tuning of an organism's movements is possible due to this biochemical interaction. Substantia nigra neurons degenerate progressively, leading to lowered levels of dopamine available for neurotransmission in the corpus striatum. This makes Parkinson's a neurological disorder in which movement is affected. Resting tremor, rigidity, declining balance and motor coordination, and bradykinesia, which is characterized by a creeping slowness of voluntary movement, are all movement-related symptoms of PD. Dopamine has indirect roles in the striatum, which decreases cortical excitation of striatal neurons [18]. Boosts in the physiological state of corticostriatal glutamatergic transmission may possibly be an effect of Parkinsonism impairment of dopaminergic neurotransmission. Furthermore, this may

consequently emphasize the imbalance between subsets of striatal neuronal systems that regulate the basal ganglia's functional output. LBs are fibrillar aggregates composed majorly of  $\alpha$ -synuclein. LBs and Lewy neurites are pathologically important to Parkinson's as they serve to be a prominent indication of the disease, being actively associated with Parkinson's pathogenesis[4]. The formation of LBs has been considered an explanation to the neuronal degeneration that occurs in PD patients since neuronal loss has been found in predilection sites for LBs. Of the 70+ molecules that have been identified in LBs,  $\alpha$ -synuclein is the most prominent. Immunohistochemistry of this constituent has uncovered that diffuse cytoplasmic staining cultivates into pale bodies, which are anti-ubiquitin antibodies, by compaction. The peripheral portion of pale bodies give rise to LBs. This abnormality has been identified in 10% of pigmented neurons in the substantia nigra and over 50% in the locus coeruleus in PD. Six genetic PD-associated mutations of  $\alpha$ -synuclein have been discovered. Three mutations related to PD have demonstrated acceleration of  $\alpha$ -synuclein aggregation, while an additional three show delay of aggregation kinetics. It is therefore troublesome to provide a unifying mechanism describing how familial PD-associated mutations affect the structure of  $\alpha$ -synuclein, and how their accumulation and function link with PD, as there have been several suggestions pointing in this direction. For instance, membrane binding studies propose that a minute number of these PD mutants strongly bind to synthetic membrane vesicles, while others show a weakened ability to bind to the membrane. PD mutations have not been shown to drastically alter the toxicity of  $\alpha$ -synuclein oligomers or fibrils, although more recent studies have indicated that the most potent toxic species responsible for PD are oligomers that are formed early on in the disease process. A30P is the only mutant that has been found to form faster oligomers and slowed the conversion from oligomers to fibrils. It is plausible that every mutation associated with PD alters  $\alpha$ -synuclein biology in various ways, which is possibly responsible for the pathogenesis of this disease. PD pathology affects more than just the dopaminergic nigrostriatal system. Non-motor symptoms can be better explained when examining the effects of multi-system neurodegeneration. Decades of research point to altered cholinergic neurotransmissions. LBs have been found in the neurons of the nucleus basalis of Meynert, the source of cholinergic innervation of the cerebral cortex. The basal forebrain complex, which provides the principal cholinergic input of the entire cortical mantle, degenerates in PD and can lead to symptoms such as dementia, depression, or apathy. Anosmia and hyposmia are common side effects of PD. While the pathophysiology is not fully understood, it could be related to  $\alpha$ -synuclein deposits in the olfactory bulb, medulla oblongata, anterior olfactory nucleus, and limbic rhinencephalon. Progressive, non-linear loss also occurs in serotonergic terminals, although slower than the progressive loss seen in dopaminergic terminals. It can lead to both motor and non-motor symptoms such as depression, tremors, weight loss, and visual hallucinations. Reduced levels of serotonin and its metabolite are found in the caudate nucleus, hippocampus, brainstem, and frontal cortex. Additionally, adrenergic neurons are impacted. One study has shown an increase in  $\alpha 1$  and  $\beta 1$  receptors, especially in demented PD patients, and Page 225 Lee et al. Neuroimmunol Neuroinflammation 2021;8:222-44 | <http://dx.doi.org/10.20517/2347-8659.2020.58> a decrease in  $\alpha 2$  receptors within the pre-frontal cortex. Disruptions in adrenergic pathways may lead to or worsen dementia and depression. **GBA-associated PD** Common risk factors for PD are mutations in the glucocerebrosidase (GBA) gene, which is a gene that encodes for the lysosomal enzyme. During a clinical study on patients with Gaucher's disease (GD), a rare lysosomal storage disorder, this risk factor was identified. It has been discovered that mutations in the GBA gene are more prominent than in any other implicated genes, including dardarin (LRKK2),  $\alpha$ -synuclein (SNCA), and parkin (PARKIN2), in the majority of the PD population. GD is a recessive disorder in which there is a deficiency in the GBA enzyme. It typically involves

the mononuclear phagocyte system in which the lysosomes within macrophage lineage cells become excessively stored with lipids. This disease is induced by bi-allelic variants in the GBA gene, which encodes acid beta-glucosidase (glucocerebrosidase). Manifestations such as hepatosplenomegaly, anemia, thrombocytopenia, and bony involvement are common with this disorder. As of yet, 300 distinct mutations have been pinpointed on this gene. These mutations include point mutations, frameshift mutations, splice-site alterations, and recombinant alleles that embody segments of the pseudogene sequence. Gaucher patients who develop parkinsonian features, dementia, or both, are amid the more atypical and uncommon Gaucher phenotypes. A group of 17 GD and Parkinsonism patients were described in 2003. The parkinsonian manifestations were aligned with those of sporadic PD. Many of these patients were in their 40s when they experienced the disease onset, and most responded positively to levodopa (L-DOPA). The GBA gene in these patients was sequenced and it was discovered that there were 12 different genotypes;

the most prominent type being 1 N370S allele, which was found in 14 of the 17 patients, including five N370S homozygotes. Four patients had an autopsy performed on them, which revealed LB inclusions, predominantly in the cerebral cortex and the hippocampus. Research has shown that the onset of motor impairments among GBA mutation carriers occurs 1.7- 6.0 years sooner than in those without mutations. Screening showed that



GBA mutations were twice as common in PD patients with an early onset (< 50 years) than those with a late onset. 951 patients were screened for N370S and L444P that had an onset of PD before 51 years of age and it was discovered that 6.7% were carriers for the GBA mutation, which is equivalent to the prevalence of patients with homozygous or heterozygous PARK2 mutations. It was also found that GBA mutation carriers developed clinical symptoms earlier than non-mutation carriers when comparing with patients who developed PD before 50 years of age. Analyses from a study screening for GBA mutations found that GBA carriers were primarily male, had greater occurrences of cognitive dysfunction or dementia, and experienced hallucinations more frequently (not associated with drug treatment) when compared to patients without GBA mutations. A second study recorded that GBA mutation carriers with PD more frequently suffer dementia than non-carriers. UPDRS, mini-mental state examination, and Hoehn and Yahr staging scales did not detect any noteworthy differences in the magnitude of PD manifestations or the rate of disease progression between GBA carriers and non-carriers. However, several other studies have documented greater rates of cognitive decline, bradykinesia, olfactory dysfunction, and less rigidity correlated with GBA mutations. A German PD study found that GBA mutation carriers have higher frequencies of dementia, neuropsychological disturbances, and autonomic dysfunction, when they compared 20 GBA mutation patients with 20 patients without the mutation. The exact mechanisms that contribute to GBA-associated Parkinsonism are not fully known. Further studies are necessary to identify these mechanisms and to discover related risk factors that work in adjunction with Lee et al. GBA and favor the progression of Parkinsonism. Aging has a role in the onset and development of PD. Factors that change during the aging process such as an increase in  $\alpha$ -synuclein cellular concentrations, and declining numbers of lysosomes and poorer lysosomal function may play a part. Much is known about the GBA protein, especially when compared to other genes associated with PD. Considerable therapeutic strategies for the treatment of Gaucher's disease may lead to stabilization of GBA or improvement of enzymatic activity which could influence the development of parkinsonian neurodegeneration. A deeper understanding of this enigmatic protein and its role in the progression of Parkinsonism could improve

genetic counseling for those who are GBA mutation carriers and enhance therapeutic approaches for GBA-associated Parkinsonism, possibly altering the treatment of all PD patient

#### IV. SYMPTOMS

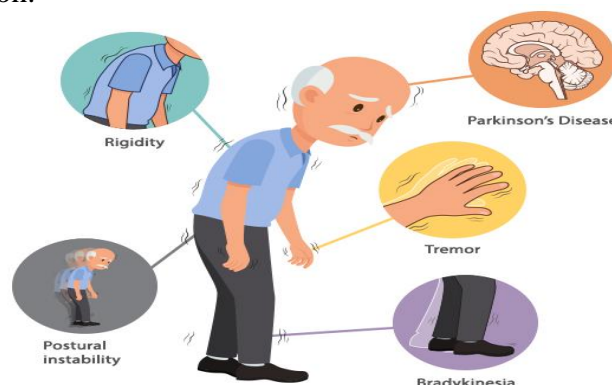
Parkinson's disease signs and symptoms can be different for everyone. Early signs may be mild and go unnoticed. Symptoms often begin on one side of the body and usually remain worse on that side, even after symptoms begin to affect the limbs on both sides.

Parkinson's signs and symptoms may include:

**1. Tremor** A tremor, or rhythmic shaking, usually begins in a limb, often your hand or fingers. You may rub your thumb and forefinger back and forth. This is known as a pill-rolling tremor. Your hand may tremble when it's at rest. The shaking may decrease when you are performing tasks.

**2. Slowed movement (bradykinesia)** Over time, Parkinson's disease may slow your movement, making simple tasks difficult and time-consuming. Your steps may become shorter when you walk. It may be difficult to get out of a chair. You may drag or shuffle your feet as you try to walk.

**3. Rigid muscles** Muscle stiffness may occur in any part of your body. The stiff muscles can be painful and limit your range of motion.



**4. Impaired posture and balance** -Your posture may become stooped. Or you may fall or have balance problems as a result of Parkinson's disease.

**5. Loss of automatic movements** - You may have a decreased ability to perform unconscious movements, including blinking, smiling or swinging your arms when you walk.

**6. Speech changes** You may speak softly, quickly, slur or hesitate before talking. Your speech may be more of a monotone rather than have the usual speech patterns.

**Writing changes** It may become hard to write, and your writing may appear small.

## V. CAUSES

In Parkinson's disease, certain nerve cells (neurons) in the brain gradually break down or die. Many of the symptoms are due to a loss of neurons that produce a chemical messenger in your brain called dopamine. When dopamine levels decrease, it causes atypical brain activity, leading to impaired movement and other symptoms of Parkinson's disease.

The cause of Parkinson's disease is unknown, but several factors appear to play a role, including:

**1. Genes** Researchers have identified specific genetic changes that can cause Parkinson's disease. But these are uncommon except in rare cases with many family members affected by Parkinson's disease.

However, certain gene variations appear to increase the risk of Parkinson's disease but with a relatively small risk of Parkinson's disease for each of these genetic markers.

**2. Environmental triggers** Exposure to certain toxins or environmental factors may increase the risk of later Parkinson's disease, but the risk is small.

Researchers have also noted that many changes occur in the brains of people with Parkinson's disease, although it's not clear why these changes occur. These changes include:

**3. The presence of Lewy bodies** Clumps of specific substances within brain cells are microscopic markers of Parkinson's disease. These are called Lewy bodies, and researchers believe these Lewy bodies hold an important clue to the cause of Parkinson's disease.

**4. Alpha-synuclein found within Lewy bodies** Although many substances are found within Lewy bodies, scientists believe an important one is the natural and widespread protein called alpha-synuclein (a-synuclein). It's found in all Lewy bodies in a clumped form that cells can't break down. This is currently an important focus among Parkinson's disease researchers.

## VI. Risk factors

Risk factors for Parkinson's disease include:

### 1. Age

Young adults rarely experience Parkinson's disease. It ordinarily begins in middle or late life, and the risk increases with age. People usually develop the disease around age 60 or older. If a young person does have Parkinson's disease, genetic counseling might be helpful in making family planning decisions. Work, social situations and medication side effects are also different from those of an older person with Parkinson's disease and require special considerations.

**2. Heredity.** Having a close relative with Parkinson's disease increases the chances that you'll develop the disease. However, your risks are still small unless you have many relatives in your family with Parkinson's disease.

**3. Sex.** Men are more likely to develop Parkinson's disease than women.

**4. Exposure to toxin**Ongoing exposure to herbicides and pesticides may slightly increase your risk of Parkinson's disease.

## VII. COMPLICATIONS

### Complications

Parkinson's disease is often accompanied by these additional problems, which may be treatable:

**1. Thinking difficulties** You may experience cognitive problems (dementia) and thinking difficulties. These usually occur in the later stages of Parkinson's disease. Such cognitive problems aren't usually helped by medications.

**2. Depression and emotional changes.** You may experience depression, sometimes in the very early stages. Receiving treatment for depression can make it easier to handle the other challenges of Parkinson's disease.

You may also experience other emotional changes, such as fear, anxiety or loss of motivation. Health care providers may give you medication to treat these symptoms.

**3. Swallowing problems.** You may develop difficulties with swallowing as your condition progresses. Saliva may accumulate in your mouth due to slowed swallowing, leading to drooling.

**4. Chewing and eating problems.** Late-stage Parkinson's disease affects the muscles in the mouth, making chewing difficult. This can lead to choking and poor nutrition.

**5. Sleep problems and sleep disorders.** People with Parkinson's disease often have sleep problems, including waking up frequently throughout the night, waking up early or falling asleep during the day.

People may also experience rapid eye movement sleep behavior disorder, which involves acting out your dreams. Medications may improve your sleep.

**6. Bladder problems.** Parkinson's disease may cause bladder problems, including being unable to control urine or having difficulty in urinating.

**7. Constipation.** Many people with Parkinson's disease develop constipation, mainly due to a slower digestive tract.

### You may also experience:

**1. Blood pressure changes.** You may feel dizzy or lightheaded when you stand due to a sudden drop in blood pressure (orthostatic hypotension).

**2. Smell dysfunction.** You may experience problems with your sense of smell. You may have difficulty identifying certain odors or the difference between odors.

**3. Fatigue.** Many people with Parkinson's disease lose energy and experience fatigue, especially later in the day. The cause isn't always known.

**4. Pain.** Some people with Parkinson's disease experience pain, either in specific areas of their bodies or throughout their bodies

**Sexual dysfunction.** Some people with Parkinson's disease notice a decrease in sexual desire or performance.

## VIII. TREATMENT

### Levodopa

#### 1) Problems with current levodopa treatment

Levodopa is the most reliable anti-PD drug for improvement of motor symptoms. However, the half-life of levodopa

in blood is short (about 90 min), which causes fluctuations in blood levels that result in changes in clinical symptoms in

the advanced stage, manifesting as the wearing-off phenomenon. Thus, the development of levodopa therapy with a longer half-life using a different route of administration or formulation is being examined.

Neurotoxicity of levodopa was also suggested in the 1990 s, which decreased the use of the drug for some time. However, it is now clear that neurotoxicity does not occur at the dose used in clinical practice, and the use of levodopa has since been reestablished. This return to use of levodopa is also partially due to the influence of advances in device and formulation technology that allow for continuous dopaminergic stimulation (CDS) with levodopa, as shown by the following representative formulations.

## 2) Levodopa/carbidopa intestinal gel

To overcome the short half-life of levodopa and improvemotor symptoms during daytime activity, levodopa/carbidopa intestinal gel (LCIG) was developed. The drug is continuously infused into the upper jejunum through gastrostomy during daytime activities. LCIG was approved in Japan in 2016. In a study in East Asian patients with 3 h off-timeper day, use of LCIG shortened the off-time by 4-5 h and extended the on-time without harmful dyskinesia

## 3) Sustained release preparation of levodopa

A sustained release capsule preparation (IPX066) packed with levodopa/carbidopa beads with a variety of fast to slow rates of dissolution in the gastrointestinal tract was developed to maintain the blood levodopa level longer than that using immediate release tablets. In a phase III study, the offtime was significantly shortened by IPX066 compared to immediate release tablets (4). Use of IPX066 has already been approved in western countries, but not in Japan.

## 4) Levodopa inhalant

A levodopa inhalant (CVT-301) has been approved in the US, but not in Japan, as a rescue medication during offtime. Levodopa is inhaled and rapidly absorbed from the lung. In a phase III study of inhalation of an 84-mg capsule, containing 42 mg of levodopa, motor symptoms during offtime tended to be improved after 10 min and were significantly improved after 30 min, compared with those before inhalation

## 5) Other levodopa formulations under development

Levodopa formulations currently under development include an Accordion Pill® capsule utilizing a drug delivery system with a biodegradable polymeric film. The capsule is loaded with a folded multilayer film including levodopa/carbidopa. The ingested capsule dissolves in the stomach, and the folded film opens into a sheet shape and stays in the stomach for a maximum of 12 h. Gradual release of levodopa/carbidopa from the film maintains a stable blood level, and the film is dissolved in the intestine after completion of drug release A continuous subcutaneous levodopa injection (ND0612), of which efficacy to reduce fluctuations in plasma concentrations was shown in a phase 2 study , for PD patients with off-time is also under development. Phase 3 studies of both formulations are underway as of July 2021

## Monoamine oxidase-B inhibitors

### 1) Novel MAO-B inhibitors

MAO-B inhibitors increase the amount and duration of action of dopamine through inhibition of dopamine metabolism by MAO-B in the brain. In Japan, selegiline was approved in 1998 and has now been used for more than 20 years, while rasagiline was approved in 2018 and safinamide in 2019 as new MAO-B inhibitors. Single-agent administration of rasagiline at a dose of 1 mg/day improves motor symptoms in early-stage PD patients (8), and addition of 0.5 or 1 mg/day rasagiline significantly shortens the off-time and improves motor symptoms in advanced stage PD patients with motor complications under oral levodopa treatment (9). Safinamide extends the on-time and decreases the off-time in PD patients with a wearing-off phenomenon not accompanied by problematic dyskinesia and also improves motor symptoms during on-time (10). Selegiline, rasagiline and safinamide have different characteristics (Table 1), so selecting the most appropriate MAO-B inhibitor is now feasible. For example, safinamide has non-dopaminergic activity, including inhibitory effects on sodium channels and glutamate release, indicating a probable inhibitory effect on dyskinesia (11). However, the accumulation of further knowledge concerning appropriate use of MAO-B inhibitors is required.



## 2) Monotherapy with a MAO-B inhibitor for de novo PD

2) Monotherapy with a MAO-B inhibitor for de novo PD Selegiline was initially developed as an antidepressant in the 1960s. Its utility for motor symptoms of PD was first reported in the mid-1970s, and selegiline has become used mainly as an adjuvant of levodopa. In Japan, selegiline was approved in 1998 for concomitant use with levodopa. Administration of selegiline without levodopa activates the patient's endogenous dopamine, and overseas studies conducted before the approval of selegiline in Japan suggested that improvement of motor symptoms was acquired with monotherapy in patients with early PD. In Japan, administration of selegiline without concomitant levodopa was approved for health insurance coverage in 2011, enabling monotherapy. MAO-B inhibitors were initially described as an option for first-line treatment in the 2018 edition of the Japanese guidelines for treatment of PD. MAO-B inhibitors have beneficial effects in addition to direct improvement of motor symptoms. Thus, initiation of early treatment with selegiline delays the time at which levodopa becomes necessary, compared with placebo (14), and concomitant use of selegiline within six months after treatment initiation with levodopa improves long-term motor symptoms and keeps the required dose of levodopa at a low level (15). Reduced aggravation of activities of daily living (ADL) and gait by using selegiline or rasagiline from the early stage has also been reported (16). These findings suggest a neuroprotective effect of MAO-B inhibitors, but this has not been shown clinically. In the PD-MED study (17), the clinical course was investigated based on the drug used for early treatment. Patients treated without levodopa had a lower rate of dyskinesia during a maximum seven-year course than those who received levodopa, and there were also fewer motor complications in non-levodopa cases treated with MAO-B inhibitors compared to dopamine agonists (17). MAO-B inhibitor monotherapy is useful, but its effects vary widely among cases. For example, we administered selegiline alone to 28 unmedicated patients with PD and observed a range of improvement in motor symptoms that varied from high to low among cases (18). Improvement of motor symptoms by MAO-B inhibitor monotherapy as firstline treatment may be poor and lead to the requirement for concomitant levodopa or a dopamine agonist in some cases, but use of a MAO-B inhibitor from the early stage may be significant for the long-term course. A combined formulation of rasagiline and pramipexole, which has an effect complementary to the MAO-B inhibitor, is currently being developed for first-line treatment of PD (19). Further discussion of the positioning of MAO-B inhibitors as first-line treatment is needed

### COMT inhibitors

Entacapone is a COMT inhibitor that promotes levodopa entry into the brain by inhibiting metabolism of levodopa by COMT in the periphery. Entacapone has been used for several years in Japan, and opicapone was approved as a second COMT inhibitor in 2020. In patients with PD with motor complications under treatment with oral levodopa, opicapone significantly shortened the off-time and extended the on-time without accompanying harmful dyskinesia at both doses of 25 and 50 mg/day compared with placebo (20). The long duration of action of opicapone permits once-a-day administration that supports levodopa activity at all time points. In contrast, entacapone has a relatively short duration of action that requires the drug to be taken simultaneously with levodopa at each time point. Appropriate use based on the status of each patient and characteristics of the drugs is required

### Dopamine agonists

Many dopamine agonists came into practical use in the 1980s to 1990s. Since these drugs have longer half-lives than levodopa and a low incidence of motor complications after early treatment, dopamine agonists are recommended to deal with the wearing-off phenomenon in early treatment and the advanced stage. Ergot-derived dopamine agonists were first used, but the main dopamine agonists have changed to non-ergot-derived drugs, as a risk of fibrosis, such as valvular disease of the heart, was pointed out with the earlier drugs. Sustained release preparations of two nonergot-derived drugs, pramipexole and ropinirole, were produced with the aim of achieving CDS, and a patch capable of maintaining a stable blood level by once-a-day replacement has also been developed. In Japan, a rotigotine patch was approved in 2013 and a ropinirole patch was approved in 2019, increasing the options for dopamine agonists. The affinity for receptor subtypes varies among these agonists, and different clinical effects may be expected. Furthermore, an overnight switch between dopamine agonists is possible, whereas 2-week withdrawal is necessary when switching MAO-B inhibitors. This is useful for selecting the most appropriate drug for each patient, and the safety of switching has also been shown for the recently approved ropinirole patch (21). Intern Med Advance Publication DOI: 10.2169/internalmedicine.8940-21 4 Other advances in dopamine agonists include approval by the FDA in 2020 of a sublingual film formulation of apomorphine that can be easily handled. Continuous subcutaneous injection of apomorphine has already been approved in western countries. Whereas, only subcutaneous injection is approved in Japan as a rescue medication during off-time. In addition, most dopamine agonists



developed for PD treatment mainly stimulate the dopamine D2 receptor, but an agonist with affinity for the D1/D5 receptor, tavapadon, is now under development with a phase III study underway as of July 2021.

### **Adenosine A2A receptor inhibitor**

Istradefylline received the first approval worldwide in Japan in 2013 as an inhibitor of the adenosine A2A receptor in the indirect pathway in the relatively hyperfunctional state among patients with PD. The indication is for improvement of the wearing-off phenomenon in PD under treatment with a regimen including levodopa, but an off-time shortening effect has also been observed, and this use was approved by the US FDA in 2019.

### **Amantadine sustained release Amantadine,**

which was introduced as an agent for type A influenza in the 1970s, inhibits dyskinesia by inhibition of the NMDA receptor. This drug was also approved by the FDA in 2017 in a sustained release formulation (amantadine 274 mg capsule), after a demonstration of the efficacy of this formulation in the EASE LID study (23). Sustained release of amantadine also improves motor symptoms during off-time in patients with PD with motor complications under treatment with levodopa, and this indication was added by the FDA in 2021.

### **Therapeutic drugs for psychosis PD**

may be accompanied by hallucinations and delusions, and aggravation of motor symptoms by drugs interfering with the dopaminergic system is a concern. Pimavanserin, an inverse agonist of the 5-HT<sub>2A</sub> receptor, was approved in the US in 2016 for the treatment of hallucinations and delusions related to neurologic manifestations in patients with PD.

### **Disease-modifying therapy PD**

It is a heterogeneous disease for which the pathophysiology is increasingly becoming understood. This includes dysfunction in mitochondria or lysosomes, formation of toxic aggregates of  $\alpha$ -synuclein, neuroinflammation, oxidative stress, and other issues. These events are all potential targets of disease-modifying therapy that affects the underlying fundamental pathophysiology of the disease. Numerous studies have attempted to identify medications to inhibit progression of PD, and new compounds are under development. Drugs already used to treat other conditions and related disorders in clinical practice are also being repurposed as agents to treat PD in a process referred to as 'drug repositioning'. Such repositioning of already approved drugs can save costs and time compared to the development of new drugs. In the second section of the review, we introduce candidate disease-modifying drugs currently in phase 2 or more advanced clinical trials. A summary of these drugs is shown in

#### **1. $\alpha$ -synuclein targeting therapy**

##### **1) Immunization for $\alpha$ -synuclein $\alpha$ -Synuclein**

is a 140-amino acid protein that is encoded by the SNCA gene. The physiological role of  $\alpha$ -synuclein is unclear, but its aggregation is toxic for neurons. The  $\alpha$ -synuclein oligomer causes mitochondrial dysfunction, endoplasmic reticulum stress, proteostasis dysregulation, synaptic impairment, cell apoptosis and neuroinflammation. Cell-to-cell propagation of  $\alpha$ -synuclein through prion-like spread is considered to be a pathophysiology of PD, and this propagation may occur during secretion of  $\alpha$ -synuclein by exosome exocytosis and endocytosis. According to Braak's theory, the pathology of  $\alpha$ -synuclein aggregation is proposed to begin in the medulla and spread gradually to the brain. Therefore, removal of extracellular  $\alpha$ -synuclein may prevent progression of the pathology and/or clinical symptoms of PD. Immunization with anti- $\alpha$ -synuclein oligomer monoclonal antibodies is currently being explored. For passive immunization, BIIB054 (cinpanemab), a monoclonal antibody that binds to the oligomeric and fibrillary forms of  $\alpha$ -synuclein, showed good tolerability and safety in a phase 1 trial, but the development of BIIB054 was halted in 2021 because of a lack of efficacy in the primary outcome of improvement of motor symptoms in the phase 2 (SPARK) study. PRX002 (prasinezumab) is also a monoclonal antibody directed against aggregated  $\alpha$ -synuclein. The safety and tolerability of PRX002 have been shown in a phase 1 study (29) and PRX002 is currently in phase 2 trials for PD (PASADENA study and PADOVA study). As an active vaccine for  $\alpha$ -synuclein, PD01A, which mimics the C-terminal region of  $\alpha$ -synuclein, has shown safety and tolerability in PD patients (30), and the AFFiRiS Corporation stated in 2020 that a phase 2 trial of PD01A for PD was in preparation.

##### **2) Inhibitor of misfolding of $\alpha$ -synuclein**

NPT200-11 inhibits misfolding of  $\alpha$ -synuclein and subsequently inhibits its accumulation. NPT200-11 (UCB0599) and related compounds were developed through structure-based drug-discovery that utilized dynamic molecular modeling to identify and target specific regions of the  $\alpha$ -synuclein protein critical for the formation of misfolded oligomers. Experiments using transgenic mice overexpressing human wild-type  $\alpha$ -synuclein showed that NPT200-11 reduced  $\alpha$ -synuclein pathology in the cortex, reduced associated neuroinflammation (astrogliosis), normalized striatal levels of the dopamine transporter (DAT) and improved

the motor function. Currently, a phase 2 study of the effects of NPT-200 on the motor and cognitive function and

## 2. Enhancers of $\beta$ -glucocerebrosidase

### 1) $\beta$ -glucocerebrosidase in PD $\beta$ -glucocerebrosidase (GBA)

is a lysosomal enzyme that cleaves glucocerebroside into ceramide and glucose by hydrolysis. Genetic variants of GBA are associated with Gaucher disease and PD. Decreased GBA activity results in the accumulation of glucocerebroside in neurons, which mediates decreased lysosomal activity, formation of toxic  $\alpha$ -synuclein oligomers and consequent higher risks of developing PD, more severe disease and faster progression of the disease. Drugs that affect the GBA function are under development.

#### 2) Ambroxol

is an expectorant that has been shown to improve GBA activity in cells carrying GBA mutations and lysosomal activity in cells from patients with GBA mutation-linked PD. In the AiM-PD study, a non-randomized and non-controlled study, treatment with ambroxol improved the motor function of PD patients with and without GBI-1 mutations (A phase 2 study of the effects of ambroxol on the cognitive and motor function and cerebrospinal fluid and MRI findings in PD is currently underway).

#### 3) PR001A

is injected intrathecally as a gene-replacement therapy using adeno-associated virus 9 (AAV9) to deliver a functional copy of the GBA1 gene to the brain. A phase 1-2a open label trial of PR001A for patients with GBA-associated PD is currently being performed.

#### 4) LTI-291

is an allosteric modulator of GBA that enhances its activity. The results of a phase 1 trial have been published and showed that LTI-291 is well tolerated. According to an announcement on October 1, 2020, on the company's homepage (<https://www.bial.com/com/>, accessed on September 19, 2021), a phase 2 trial should be ready to start in 2021.

#### 5) Venglustat (GZ/SAR402671)

Venglustat is a glucocerebroside synthase inhibitor designed to reduce production of glucosylceramide. This "substrate reduction therapy" inhibits an upstream enzyme to reduce pathogenic substrate accumulation and is expected to have therapeutic efficacy for PD with GBA mutations. However, a phase 2 trial of the efficacy of venglustat in PD patients with GBA mutations (MOVES-PD study) did not meet the primary or secondary endpoints. Thus, further follow-up was terminated in 2021.

## 3. Medication with neuroprotective effects

### 1) Glucagon-like peptide 1 receptor agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists are used to treat type II diabetes mellitus. GLP-1 receptor stimulation has also been shown to protect dopaminergic neurons from neurodegeneration in PD model mice. The proposed mechanism involves enhanced mitochondrial biogenesis, suppression of microglial activation and inflammation, enhancement of autophagy and clearance of aggregated proteins. A phase 2 study of exenatide, a GLP-1 receptor agonist, showed efficacy for motor symptoms and a reduced rate of decline in nigrostriatal dopaminergic neurons using DAT imaging. A phase 3 trial to examine the disease-modifying effect of exenatide in PD is ongoing. Phase 2 trials of other GLP-1 receptor agonists, including semaglutide, liraglutide, lixisenatide, LNY01 and a sustained release form of exenatide (PT320), are also ongoing in PD patients.

### 2) c-Abl inhibitor

The protein Abelson (c-Abl) is a non-receptor tyrosine kinase that is activated by oxidative and cellular stress. c-Abl plays a role in the pathogenesis of PD, including in the aggregation of  $\alpha$ -synuclein and formation of Lewy bodies, autophagic impairment, mitochondrial dysfunction, and activation of microglia. Therefore, inhibition of c-Abl may influence the pathogenesis of PD. Some c-Abl inhibitors are already approved for treatment of chronic myelogenous leukemia, and recent studies in PD model mice suggest that c-Abl inhibitors may have neuroprotective effects. Clinical studies have shown that nilotinib increased the CSF level of homovanillic acid, a dopamine metabolite reduced that of  $\alpha$ -synuclein oligomers, and improved the motor and cognitive function, suggesting a disease-modifying effect. However, another trial of nilotinib showed no improvement in motor symptoms of PD patients. Two other c-Abl inhibitors-K-0706, which is also under the development for chronic myeloid leukemia, and radotinib-are also in phase 2 clinical trials.

### 3) Ceftriaxone

Ceftriaxone is a widely used antibiotic that has exhibited neuroprotective functions in an animal model of PD with dementia (PDD). Based on these findings, a phase II study to investigate the efficacy and safety of ceftriaxone in patients with mild to moderate PDD is ongoing in Taiwan.

### 4) Sigma-1 receptor agonist

Sigma-1 receptor is a chaperone protein localized in the mitochondria-associated endoplasmic reticulum membrane. Activation of sigma-1 receptor has neuroprotective effects, such as modulation of toxic intracellular cascades involving calcium ions and anti-inflammatory effects as well as the elevation of neurotrophic growth factors. Agonists of sigma-1 receptor induce autophagy and increase proteostasis capacity and are candidate therapeutic agents for neurodegenerative diseases especially PDD. A phase 2 study of blarcamesine (ANAVEX 2-73), a sigma-1 receptor agonist, is ongoing in PDD patients.

#### 4. Anti-oxidative stress drugs

##### 1) Iron chelators

In PD patients, iron accumulates in neurons of the substantia nigra and the accumulated intracellular iron has a neurotoxic effect due to increased reactive oxygen. Intern Med Advance Publication DOI: 10.2169/internalmedicine.8940-21 7 stress. Therefore, iron chelators may be effective for preventing neuronal damage in PD. A phase 2 trial in 22 patients with mild PD showed that deferiprone, an iron chelator, was able to improve motor symptoms and decrease iron concentrations in the dentate and caudate nuclei. In the FAIRPARK trial, patients who started deferiprone immediately showed a significantly better motor performance at 6 or 12 months than those who started 6 months later. A phase 2 study of the efficacy of deferiprone (FAIRPARK-II study) is currently underway in patients with PD.

##### 2) Analogs of coenzyme

Q10 Idebenone is an analog of the well-known antioxidant coenzyme Q10 (CoQ10) and has been shown to mitigate motor impairment and to increase the neuron survival in PD model animals (56). Clinical trials of idebenone for protection against the development of PD in patients with REM sleep behavior disorder (SEASEiPPD study) and therapeutic effects on motor and non-motor symptoms in patients with early PD (ITEP study) are ongoing.

3) **Myeloperoxidase inhibitors** Oxidative stress is one of the implicated pathogenesises of PD. Myeloperoxidase (MPO) is a reactive oxygen generating enzyme, and MPO-immunoreactive cells are increased in brain regions affected by neurodegeneration in PD. Oxidative stress is associated with neuroinflammation and neural damage in PD, and inhibition of MPO may reduce oxidative stress, neuroinflammation and neuronal damage in PD patients. A phase 2 study of AZD3241 (verdiperstat), a MPO inhibitor, in PD patients showed a reduction in distribution of activated microglia using <sup>11</sup>C-PBR28 positron emission tomography. Other clinical trials for PD were planned, but whether or not the further development of AZD 3241 for PD is underway is unclear.

#### 5. Anti-inflammatory agents and immunosuppressants

##### 1) Non-steroidal anti-inflammatory drugs (NSAIDs) and immunosuppressants

Dysregulated inflammatory and immune systems, in which activated astrocytes, microglia and peripheral immune cells as well as inflammatory cytokines are present, are also implicated in the etiology of PD. Regular use of NSAIDs at baseline has been associated with a reduced risk of PD, and among NSAIDs, ibuprofen has been shown to have a particularly marked effect. A population-based case-control study of United States Medicare beneficiaries showed that the use of immunosuppressants, such as azathioprine, and corticosteroids was also associated with a reduced risk of emergence of PD. Therefore, anti-inflammatory drugs and immunosuppressants may have disease-modifying effects in PD. Among immunosuppressants, azathioprine, which reduces the proliferation of B and T cells via the inhibition of nucleic acid synthesis, is widely used in various immune-related disorders in clinical practice. A phase 2 randomized placebo-controlled, double-blind trial of the effects of azathioprine on progression of motor and non-motor symptoms in early PD patients (AZA-PD study) is in preparation. 2) **Statins** Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and are commonly used in clinical practice to treat dyslipidemia. These drugs have also been suggested to have anti-oxidative and anti-inflammatory effects to reduce intraneuronal  $\alpha$ -synuclein aggregation. A population study showed that the continuation of lipophilic statin therapy was associated with a decreased incidence of PD compared to patients with discontinuation of statins. A recent trial showed that lovastatin treatment in patients with early-stage PD was associated with a trend of reduced exacerbation of motor symptoms. These findings suggest that statins are candidates for neuroprotective treatment for PD. A phase 2 trial examining the effect of simvastatin on PD with a wearing-off phenomenon is currently ongoing, and the effects of lovastatin on motor symptoms in early PD patients are being examined in a phase 2 trial. 6. **Recovery of the mitochondrial function** Mitochondrial dysfunction is a pathogenesis of PD and believed to



be a promising target for disease-modifying therapy. Mortiboys et al. showed that ursodeoxycholic acid, which has been used for the treatment of liver disease for over 30 years, improved the mitochondrial production of ATP in an in vitro study using parkin-mutant fibroblasts and LRRK2G2049S mutant fibroblasts. Ursodeoxycholic acid has also been shown to rescue the function of mitochondria in LRRK2G2019S carriers in vivo. Therefore, ursodeoxycholic acid may ameliorate the pathophysiology of PD by improving mitochondrial dysfunction. A phase 2 trial to ascertain the effect of ursodeoxycholic acid on mitochondrial activity, progression of motor symptoms and other effects in patients with PD is ongoing. Conclusion In this review, we focused on recent developments of symptomatic and disease-modifying therapy for patients with PD. The search for medications for PD has continued with treatment utilizing already existing drugs, as well as the development of new drugs. Levodopa is still the gold standard for PD, but the high prevalence of motor fluctuation with levodopa is a concern. Treatment options for motor fluctuation as symptomatic therapy are being developed with novel agents and advances in device and formulation technology. Disease-modifying therapy is not yet available in clinical practice, but progress in this area is likely as the pathophysiology of PD is further understood, and this approach may become practical in the near future.

## VIII. FUTURE ASPECTS

### 1. Gene therapy

Gene therapy is one of treatment options where human gene therapy is implemented in somatic cells. Generally with gene modifications by either overexpressing or inhibiting particular target genes can restore the normal function of these genes. Currently, there are two types of vectors are used in gene therapy, such as viral mediated vectors, and nonviral systems. In viral vectors, it can transport the genetic material to target cells. Non-viral vector delivers the genes to the CNS by physical and chemical methods like a gene gun or electroporation. Various kinds of vectors have been constructed with differing by their packaging capacity, tropism, and immunogenicity. Adeno-associated virus (AAV) and lentivirus derived vectors are under CNS gene therapy clinical trials.

### Stem cell therapy

Dopamine modulates transmission of signals in the highly specialized areas of the brain, like the basal ganglia, concerned with the body and limb movements, which leads to tremors, rigidity, freezing and slurring of speech.

Recent advances in stem cell research involves administration of genetically modified stem cells which are able to produce dopamine and also can convert dopamine producing cells to treat PD patients. Furthermore, in stem cell research, the mesenchymal cells are infused into the part of the brain, where these cells are multiplied into healthy cells in substantia nigra, resuming normal production of dopamine that helps in retrieving much of the normal functions.

### 2. Biotechnology drugs

Initially atremorine showed the potent neuroprotective activity at the hippocampal level during deprivation of oxygen and glucose deprivation in human neuroblastoma SH-SY5Y cells. A recent concern has been initiated by E-Podofavalin-15999 (Atremorine®), a novel compound, obtained through a non-denaturing biotechnological non-GMO manipulation of Vicia faba L. moieties. When tested in experimental animals, this compound exerted a significant protection against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced dopaminergic neurodegeneration while also inhibiting MPTP-induced microglia activation and neurotoxicity in substantia nigra. The above effect showed notable changes in motor functions of mice. In a most recent clinical trial, a single dose of atremorine administered to patients exhibited the tolerable increased level of DA to be up to  $4556.61 \pm 678.95$  pg/mL ( $p < 0.001$ ) after an hour wards, irrespective of the gender. Interestingly, all naïve patients showed a dopamine level increase from 0.29 to  $2041.24 \pm 249.12$  pg/mL ( $p < 0.001$ ) but also 98% of those under chronic treatment showed an increase of  $2139.2 \pm 804.72$  to  $9168.11 \pm 1657.27$  pg/mL ( $p < 0.001$ ). Plasma DA response to Atremorine was in part associated with the APOE genotype where APOE-carriers showed a stronger response than APOE-3 > APOE-4 carriers.

### 3. Ultrasound treatment

Nowadays, neurodegenerative diseases exist as an increasing challenge for people related to ageing. The pharmacological interventions are routinely followed for neurological diseases, unlike for cancers where they carry out non-pharmaceutical procedures. The use of ultrasound treatment for this Parkinson disease proved to be useful for instigating focused lesions, regulating neuronal function, eliminating protein aggregates, etc.

#### 4. Active immunization therapy

Vaccination is being scrutinized to be the prospective or possible treatment for Parkinson disease. This vaccination found to be a better option for these neurological diseases because of the unusual administration, less production costs for the huge amount of people, etc. In preclinical animal models of previous decade, there was progress in the active immunization against alpha-synuclein

#### 5. Rehabilitation

Other than pharmacological and surgery treatments, rehabilitation act as an adjuvant for less complications and maximize functional ability in Parkinson disease. When compared to physiotherapy, virtual reality technology leads to much improvement. It is a new rehabilitation tool where it revives the movement by computer based in a virtual reality environment. A recent meta-analysis report identified that rehabilitation could instigate short-lasting, but significant benefits for gait and balance. But rehabilitation program should be organized as goal-based, where number of variables has to be identified and program should be made according to the individual's characteristics .

### IX. CONCLUSION

This review highlights that there is a paucity of information about PD worldwide. There are very few research groups working on neurodegenerative type of disorders. Diagnosis is of paramount importance for clinical manifestation and treatment strategies for PD. Medication and routine exercise, is primary to treatment strategies for this neurodegenerative disease. The social and psychological issues in PD affected patients should also be considered and might vary in individual patients. Therapies, such as deep brain stimulation and surgical lesioning ought to be explored. Further research should be encouraged for the better understanding of the disease involving its characteristics and etiology. Future scientific research involving Parkinson's disease might enlighten our knowledge of disease onset and progression and can deliver some added aspects/components to help find more effective therapies to improve quality of life of patients with PD.

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