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Advancements in Understanding and Treating Parkinson's Disease: A Comprehensive Review

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Abstract
Parkinson's disease (PD) is a neurological illness that causes movement disorders such as bradykinesia, rest tremors, and stiffness. Additionally, there is postural instability. Current treatments for Parkinson's disease primarily aim to restore dopaminergic tone in the striatum. Non-dopamine-dependent characteristics of Parkinson's disease, such as freezing of gait, cognitive impairment, and other non-motor symptoms, have a significant influence on quality of life and cannot be altered by these treatments. Advancements in understanding the pathophysiology of Parkinson's disease are leading to new therapy options. Some treatments for Parkinson's disease try to control symptoms without causing side effects, while others aim to halt pathology and reduce neuronal loss. Treatments for Parkinson's disease aim to control symptoms while minimising negative side effects. Current treatments aim to slow pathology, reduce neuronal loss, and delay disease progression. In this latter regard, there has been much interest in drug repurposing (the use of established drugs for a new indication), with many drugs being reported to affect PD-relevant intracellular processes. This approach offers an expedited route to the clinic, given that pharmacokinetic and safety data are potentially already available. Gene therapies and cell-based treatments, as well as neurosurgical strategies like deep brain stimulation, are entering clinical trials to improve symptomatic and regenerative treatments for Parkinson's disease. The treatment landscape is expected to evolve significantly in the coming years. This article presents an overview of emerging therapeutic techniques in clinical trials.

Keywords
Deep brain stimulation; drug repurposing; immunotherapies; gene therapies; neural grafting; Parkinson’s disease

Introduction:

Parkinson's disease (PD) is a debilitating neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons in the substantia nigra region of the brain. Over the past decades, significant progress has been made in unraveling the complexities of PD pathophysiology and developing novel therapeutic strategies. This review aims to provide a comprehensive overview of recent advancements in our understanding of PD etiology, pathogenesis, diagnostic modalities, and therapeutic interventions.[1]

The condition is marked by movement disorders such as bradykinesia, rest tremor, rigidity, postural instability, subtle motor features, and non-motor features. The loss of dopaminergic neurons in the substantia nigra pars compacta, which project axons to the striatum, is responsible for several core motor aspects. Current treatments for Parkinson's disease mostly focus on restoring dopaminergic tone in the striatum.[2]

Etiology and Pathogenesis:

The etiology of PD remains multifactorial, involving a complex interplay of genetic susceptibility, environmental factors, and oxidative stress mechanisms. Recent studies have elucidated the role of alpha-synuclein aggregation, mitochondrial dysfunction, neuroinflammation, and impaired protein degradation pathways in disease pathogenesis. Furthermore, emerging evidence suggests the involvement of gut-brain axis dysfunction and the role of gut microbiota in PD development, opening new avenues for exploration.[2]

Diagnostic Modalities:

Accurate and early diagnosis of PD is crucial for timely intervention and disease management. Advances in neuro-imaging techniques, including positron emission tomography (PET), single-photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI), have facilitated the detection of characteristic dopaminergic neuronal loss and pathological changes in the brain. Biomarker discovery efforts, focusing on cerebrospinal fluid (CSF) and peripheral blood markers, hold promise for improving diagnostic accuracy and monitoring disease progression.[3]

Therapeutic Interventions:

Current treatment options for PD primarily aim to alleviate motor symptoms and improve patients' quality of life. Levodopa remains the gold standard for symptomatic relief, although long-term use is often associated with motor complications. Dopamine agonists, monoamine oxidase inhibitors, and deep brain stimulation (DBS) surgery are among the other therapeutic modalities employed in PD management. Recent therapeutic advancements include targeted drug delivery systems, gene therapy approaches, and neuroprotective agents aimed at modifying disease progression and preserving neuronal integrity.[4]

SYMPTOMATIC THERAPY

In the 1960s, dopamine insufficiency in the striatum was identified in Parkinson's disease patients. Levodopa, a medication, has been created to improve symptoms and prognosis. This medicine remains the most effective treatment for Parkinson's disease. In the mid-1970s, it was discovered that long-term use of levodopa can lead to motor problems, including wearing-off. Drug development for Parkinson's disease has mostly aimed to reduce these consequences. To address the limitations of levodopa, medicines with different mechanisms of action have been developed. Dopamine agonists stimulate neuronal dopamine receptors, MAO-B inhibitors block dopamine metabolism in the brain, and COMT inhibitors prevent levodopa degradation in the peripheral.[5] This review covers medicines used for symptomatic treatment of Parkinson's disease.

1. Levodopa

I.Problems with current levodopa treatment

Levodopa is the most effective anti-PD medication for alleviating motor symptoms. Nonetheless, the half-life of levodopa.The brief duration of blood infusion generates oscillations in blood levels, leading to clinical complaints and the "wearing-off" phenomena in the advanced stage.

The development of levodopa therapy with a longer half-life by a different mode of administration or formulation is being investigated. In the 1990s, there were concerns about the neurotoxicity of levodopa, which led to a decline in

its use. Levodopa's use in clinical practice has been reinstated due to the lack of neurotoxicity at the current dose. Levodopa's resurgence can be attributed to advancements in device and formulation technologies, which enable continuous dopaminergic stimulation (CDS), as demonstrated by the following formulations.[6]

I.Levodopa/carbidopa intestinal gel

To address the short half-life of levodopa and enhance motor symptoms during daytime activities, levodopa/carbidopa intestinal gel (LCIG) was created. During the day, the medication is constantly pumped into the upper jejunum via a gastrostomy. LCIG was approved in Japan in 2016. A study of East Asian patients with 3 hours of off-time per day found that using LCIG reduced off-time by 4-5 hours and increased on-time without deleterious dyskinesia by 5-6 hours. [6]

II.Sustained release preparation of levodopa

IPX066 is a sustained release capsule that contains levodopa/carbidopa beads with varying rates of dissolution in the gastrointestinal tract. Its purpose is to maintain blood levodopa levels for longer periods than immediate release tablets do. [6]

III.Levodopa inhalant

However, it is not used in Japan as a rescue drug during off-time. Levodopa is quickly absorbed by the lungs after inhalation. A phase III research found that inhaling an 84-mg capsule with 42 mg of levodopa improved motor symptoms during offtime within 10 minutes and significantly after 30 minutes, compared to before inhalation. [6]

IV.Other levodopa formulations under development

Levodopa formulations in development include an Accordion Pill capsule with a biodegradable polymeric covering. The capsule contains a folded multilayer film with levodopa/carbidopa. The capsule dissolves in the stomach, causing the folded film to form a sheet and remain there for up to 12 hours. The film gradually releases levodopa/carbidopa, resulting in stable blood levels. The film dissolves in the intestine following medication release.[7]

2. MONOAMINE OXIDASE-B INHIBITORS

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. Rasagiline at a dose of 1 mg/day improves motor symptoms in early-stage Parkinson's disease patients, while adding 0.5 or 1 mg/day reduces off-time and improves motor symptoms in advanced-stage PD patients with motor complications under oral levodopa treatment. Safinamide improves motor symptoms during on-time and reduces off-time in Parkinson's disease patients who do not have significant dyskinesia.

Safinamide may decrease dyskinesia via inhibiting sodium channels and glutamate release, in addition to its dopaminergic activity. However, there is a need for more information on appropriate.[8]

Monotherapy with a MAO-B inhibitor for *de novo* PD

Although MAO-B inhibitors can be beneficial, their effectiveness varies depending on the individual instance. For example, we used selegiline. The study involved 28 unmedicated patients with Parkinson's disease and found varying levels of improvement in motor symptoms. First-line MAO-B inhibitor monotherapy may not improve motor symptoms and may require concomitant levodopa or dopamine agonists in some individuals. However, early usage of an MAO-B inhibitor may have a major long-term impact. A formulation of rasagiline and pramipexole, which

complements the MAO-B inhibitor, is being developed as a first-line treatment for Parkinson's disease. Further discussion is needed on whether MAO-B inhibitors should be used as the first-line treatment. [8]

3. COMT inhibitors

Entacapone, a COMT inhibitor, enhances levodopa entrance into the brain by blocking its metabolism by COMT in the peripheral. Entacapone has been used in Japan for several years, while opicapone was licenced as a second COMT inhibitor in 2020. Opicapone at doses of 25 and 50 mg/day effectively reduced off-time and increased on-time in individuals with Parkinson's disease with motor problems treated with oral levodopa, without causing deleterious dyskinesia. [8]

4. Dopamine agonists

In 2020, the FDA approved a sublingual film formulation of apomorphine, making it easier to administer. Western countries have already approved continuous subcutaneous injection of apomorphine. In Japan, only subcutaneous injections are permitted as rescue treatment during off-time. Most dopamine agonists used to treat Parkinson's disease target the D2 receptor. However, tavapadon, an agonist with affinity for the D1/D5 receptor, is now in development, with a phase III study scheduled for July 2021. [9]

5. Adenosine A2A receptor inhibitors

In 2013, Japan became the first to approve istradefylline as an inhibitor of the adenosine A2A receptor in the indirect pathway for patients with Parkinson's disease who are hyperfunctional. The US FDA approved the use of levodopa to enhance the wearing-off phenomena in Parkinson's disease. However, off-time shortening has also been seen and approved for this purpose in 2019. [9]

6. Amantadine sustained release

Amantadine, first used to treat type A influenza in the 1970s, reduces dyskinesia by blocking the NMDA receptor. In 2017, the FDA approved a sustained release version of amantadine (274 mg capsule) based on efficacy demonstrated in the EASE LID study. Amantadine's sustained release improves motor symptoms during off-time in patients with Parkinson's disease with motor difficulties treated with levodopa. The FDA expanded this indication in 2021.[10]

7. Therapeutic drugs for psychosis

Drugs that interfere with the dopaminergic system may worsen symptoms of Parkinson's disease, including hallucinations and delusions. Pimavanserin, an inverse agonist of the 5-HT2A receptor, was licenced in the US in 2016 to treat hallucinations and delusions in individuals with Parkinson's disease. [10]

II. DISEASE-MODIFYING THERAPY

The mechanism of Parkinson's disease is being better understood, despite its diverse nature. Symptoms may include mitochondrial or lysosomal malfunction, toxic α-synuclein aggregation development, neuroinflammation, oxidative stress, and other difficulties. Disease-modifying therapies can target these events and impact the disease's pathogenesis. Several research have been conducted to identify drugs that can slow the progression of Parkinson's disease. New compounds are now being developed. [11]

- ***α-synuclein targeting therapy***

Immunization for α-synuclein

The SNCA gene encodes α-synuclein, a 140-amino acid protein. The physiological role of α-synuclein is uncertain, but its aggregation can be harmful to neurons . The α-synuclein oligomer leads to mitochondrial malfunction, endoplasmic reticulum stress, proteostasis dysregulation, synaptic impairment, cell death, and neuroinflammation. The aetiology of Parkinson's disease involves the spread of α-synuclein from cell to cell by prion-like dissemination.

This can happen via α-synuclein secretion via exosomes or endocytosis. Braak's idea suggests that α-synuclein aggregation begins in the medulla and subsequently spreads to the brain. Removing extracellular α-synuclein may reduce the progression of Parkinson's disease and its symptoms. [11]

Inhibitor of misfolding of α-synuclein

NPT200-11 prevents α-synuclein misfolding and accumulation. NPT200-11 (UCB0599) and related compounds were discovered using structure-based drug-discovery. Dynamic molecular modelling was used to identify and target specific areas of the alphasynuclein protein that cause misfolded oligomers. Experiments with transgenic mice overexpressing human wild-type α-synuclein revealed that NPT200-11 reduced α-synuclein pathology in the cortex, reduced neuroinflammation (astrogliosis), normalised striatal dopamine transporter (DAT), and enhanced motor performance. [12]

- ***Enhancers of β-glucocerebrosidase***

β-glucocerebrosidase in PD

The lysosomal enzyme β-glucocerebrosidase (GBA) hydrolyzes glucocerebroside to produce ceramide and glucose. GBA genetic variations are linked to Gaucher disease and Parkinson's disease (PD). diminished GBA activity causes glucocerebroside buildup in neurons, leading to diminished lysosomal activity, toxic α-synuclein oligomers, and increased risk of developing and progressing Parkinson's disease. Drugs that impact GBA function are in development. [13]

Ambroxol

Ambroxol, an expectorant, has been found to increase GBA activity in cells containing GBA mutations and lysosomal activity in cells from patients with GBA mutation-linked Parkinson's disease. The AiM-PD trial found that ambroxol medication enhanced motor function in PD patients with and without GBI-1 mutations. The study was not randomised or controlled. A phase 2 research of ambroxol's impact on cognitive and motor function, cerebrospinal fluid, and MRI results in Parkinson's disease is presently underway. [13]

PR001A

PR001A is a gene-replacement therapy that injects a functional copy of the GBA1 gene into the brain via AAV9. A phase 1-2a open label trial of PR001A for patients with GBA-associated Parkinson's disease is currently underway. [14]

LTI-291

LTI-291 is an allosteric modulator of GBA, increasing its activity. A phase 1 experiment shown that LTI-291 is well tolerated. announced that a phase 2 study would begin in 2021. [14]

Venglustat (GZ/SAR402671)

Venglustat inhibits glucocerebroside synthase, which reduces the formation of glucosylceramide. This "substrate reduction therapy" inhibits an upstream enzyme, reducing pathogenic substrate buildup. It is likely to be effective for PD with GBA mutations. The MOVES-PD study, a phase 2 trial of venglustat in Parkinson's disease patients with GBA mutations, failed to reach primary or secondary goals. Therefore, further follow-up was ended in 2021. [14]

- ***Medication with neuroprotective effects***

Glucagon-like peptide 1 receptor agonists

GLP-1 receptor agonists are used to treat type 2 diabetes mellitus. GLP-1 receptor activation can protect dopaminergic neurons from neurodegeneration in PD model mice.

This treatment promotes biogenesis, suppresses microglial activation and inflammation, boosts autophagy, and eliminates protein aggregates. Exenatide, a GLP-1 receptor agonist, was found to effectively treat motor symptoms and slow the decrease of nigrostriatal dopaminergic neurons in a phase 2 research employing DAT imaging. Exenatide is currently being studied in a phase 3 trial for its disease-modifying effect in Parkinson's disease. Other GLP-1 receptor agonists, such as semaglutide, liraglutide, lixisenatide, LNY01, and PT320, are currently undergoing phase 2 trials in Parkinson's disease patients. [14]

c-Abl inhibitor

C-Abl is a non-receptor tyrosine kinase that responds to oxidative and cellular stress. c-Abl contributes to the pathophysiology of Parkinson's disease by aggregating α-synuclein, forming Lewy bodies, impairing autophagy, causing mitochondrial dysfunction, and activating microglia. Inhibiting c-Abl may affect the pathophysiology of Parkinson's disease. Some c-Abl inhibitors are authorised for treating chronic myelogenous leukaemia, and recent investigations in PD model animals suggest they may also have neuroprotective effects. Clinical trials indicate that nilotinib has a disease-modifying impact by increasing the CSF level of homovanillic acid, a dopamine metabolite, decreasing α-synuclein oligomers, and improving motor and cognitive function. [15]

Ceftriaxone

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Sigma-1 receptor agonist

The Sigma-1 receptor is a chaperone protein found in the mitochondria-associated endoplasmic reticulum membrane. Activating the sigma-1 receptor has neuroprotective effects by modulating harmful calcium ion cascades, reducing inflammation, and increasing neurotrophic growth factors. Sigma-1 receptor agonists promote autophagy and proteostasis, making them potential therapeutic agents for neurological illnesses such as Parkinson's disease. Blarcamesine (ANAVEX 2-73), a sigma-1 receptor agonist, is now being studied in a phase 2 clinical trial for PDD. [15]

ANTI-OXIDATIVE STRESS DRUGS

Iron chelators

Iron accumulation in substantia nigra neurons in Parkinson's patients might cause neurotoxicity due to increased reactive oxygen stress. Iron chelators may protect neurons from damage in Parkinson's disease. A phase 2 trial of 22 individuals with moderate Parkinson's disease found that deferiprone, an iron chelator, improved motor symptoms and decreased iron concentrations in the dentate and caudate nuclei. The FAIRPARK experiment found that individuals who started deferiprone promptly had significantly improved motor ability at 6 or 12 months compared to those who started later. A phase 2 trial (FAIRPARK-II) is now underway to evaluate the efficacy of deferiprone in Parkinson's disease patients. [16]

Analogs of coenzyme Q10

Idebenone, an analogue of CoQ10, has been demonstrated to improve motor function and neuron survival in Parkinson's disease model mice. Idebenone is currently being studied for its potential to prevent Parkinson's disease in patients with REM sleep behaviour disorder (SEASEiPPD study) and to treat motor and non-motor symptoms in patients with early PD (ITEP study). Clinical trials are underway. [16]

Myeloperoxidase inhibitors

Oxidative stress is a potential cause of Parkinson's disease. MPO, a reactive oxygen-generating enzyme, is found in areas of the brain damaged by neurodegeneration in Parkinson's disease.

Inhibiting MPO may lessen oxidative stress, neuroinflammation, and neuronal damage in Parkinson's disease (PD) patients. In a phase 2 research in Parkinson's disease patients, AZD3241 (verdiperstat), an MPO inhibitor, was found to reduce the distribution of activated microglia using 11C-PBR28 positron emission tomography. There are plans for additional clinical studies for Parkinson's disease, however it is uncertain if AZD 3241 is currently being developed. [16]

- ***Anti-inflammatory agents and immunosuppressants***

Non-steroidal anti-inflammatory drugs (NSAIDs) and immune-suppressants

Parkinson's disease is associated with dysregulated immunological and inflammatory systems, including activated astrocytes, microglia, and peripheral immune cells, as well as inflammatory cytokines. Regular usage of NSAIDs at baseline has been linked to lower incidence of Parkinson's disease, with ibuprofen having a particularly significant effect. A case-control study of US Medicare members found that taking immunosuppressants such azathioprine and corticosteroids lowers the likelihood of developing Parkinson's disease.

Anti-inflammatory and immunosuppressive medications may help treat Parkinson's disease.
Azathioprine, an immunosuppressant that inhibits nucleic acid production, is commonly used in clinical settings to treat immune-related illnesses. A phase 2 randomised placebo-controlled, double-blind trial of azathioprine's impact on progression of motor and non-motor symptoms in early Parkinson's disease patients (AZA-PD study) is in development. [16]

Statins

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and are extensively used in clinical practice to treat dyslipidemia. These medications may have anti-oxidative and anti-inflammatory properties, as well as inhibit intraneuronal α-synuclein aggregation. In a population research, individuals who continued using lipophilic statins had a lower risk of developing Parkinson's disease compared to those who stopped. A recent trial found that treating patients with early-stage Parkinson's disease with lovastatin prevented worsening of motor symptoms. [17]
Statins may be a promising neuroprotective treatment for Parkinson's disease, according to recent research. Simvastatin is currently being studied in a phase 2 trial for Parkinson's disease with wearing-off, while lovastatin is being studied for motor symptoms in early PD patients. [17]

- ***Recovery of the mitochondrial function***

Mitochondrial dysfunction is a pathophysiology of Parkinson's disease and a promising target for disease-modifying therapies. In an in vitro investigation using parkin-mutant and LRRK2G2049S mutant fibroblasts, Mortiboys et al.

discovered that ursodeoxycholic acid, a therapy for liver illness for almost 30 years, enhanced mitochondrial ATP synthesis. Ursodeoxycholic acid has been found to restore mitochondrial function in LRRS2G2019S carriers in vivo. Ursodeoxycholic acid may improve mitochondrial dysfunction, potentially reducing the pathogenesis of Parkinson's disease. A phase 2 experiment is now underway to evaluate the impact of ursodeoxycholic acid on mitochondrial function, motor symptoms progression, and other consequences in Parkinson's disease patients. [18]

Conclusion:

In conclusion, ongoing research efforts continue to deepen our understanding of PD pathophysiology and refine therapeutic strategies for better disease management. Collaborative interdisciplinary approaches integrating genetics, neuroimaging, biomarker discovery, and clinical trials are essential for advancing personalized medicine and ultimately finding a cure for Parkinson's Disease. In recent years, many experimental treatments for Parkinson's disease have made their way to the clinic. Despite promising pre-clinical outcomes, many potential medicines failed in clinical trials, highlighting the importance of rigorous trial design. Advancements in understanding the pathogenic mechanisms and anatomical foundation of Parkinson's disease have led to the development of new therapeutic options. The future of Parkinson's disease care is expected to change considerably.

This study examines current breakthroughs in symptomatic and disease-modifying therapies for Parkinson's disease patients. The hunt for treatments for Parkinson's disease continues, with existing drugs and new ones being developed. Although levodopa is the preferred treatment for Parkinson's disease, it is associated with a high risk of motor fluctuations. Novel drugs and advancements in device and formulation technology are being used to offer treatment alternatives for motor fluctuations as symptomatic therapy. Although disease-modifying therapy is not yet available in clinical practice, better understanding of the pathophysiology of Parkinson's disease may lead to its practical application in the near future.

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