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# Studies on the improvement of treatments for Parkinson's disease

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**Abstract.** Parkinson's disease is a common nervous system degenerative disease in the middle-aged and elderly. Its core characteristics include motor symptoms (bradykinesia, resting tremor, muscle rigidity, postural balance disorder) and non-motor symptoms (cognitive impairment, autonomic dysfunction, etc.), which seriously affect the quality of life and health of patients. At present, the main treatment methods of Parkinson's disease include drug therapy, surgical treatment, cell therapy, and gene therapy. This paper summarizes the research results of the last five years of research into the treatment of Parkinson's disease, including ABBV-951, optimized DBS technology, induced pluripotent stem cells, and FAM171A2, with thje aim of providing a comprehensive and effective strategy for its treatment. Through the analysis of the mechanisms and advantages of different treatment methods, it is believed that the stable administration of ABBV-951 and the precise treatment of Deep Brain Stimulation are more advantageous, and may become the main treatment methods in the future. In addition, the treatment of Parkinson's disease is constantly improving and developing towards non-invasive, precise and personalized. Utilising findings from the literature, this paper discusses the improvements in pharmacological and surgical therapies compared to traditional therapies, as well as describing the therapeutic mechanisms of two new therapies, cellular therapy and gene therapy.

**Keywords:** Parkinson's disease, treatment method, advantages, experimental validation

## 1. Introduction

Parkinson's disease, also known as tremor palsy, is a complex chronic neurodegenerative disease. It is mainly characterized by the progressive loss of dopamine neurons in the substantia nigra compacta (SNc) and the accumulation of these insoluble proteins, Lewy bodies and Lewy neurites in the cytoplasm. The traditional treatment method is oral levodopa, which acts as a precursor to dopamine that can pass the blood brain barrier and be converted to dopamine in the brain, for use in supplementing striatal dopamine deficits and improving motor symptoms. In addition, traditional Deep Brain Stimulation (DBS) surgery is performed by implanting electrodes to stimulate the subthalamic nucleus (STN) or the medial part of the globus pallidus (GPi) to regulate abnormal nerve electrical activity and improve motor symptoms. However, there are many disadvantages to using traditional treatment methods. For example, the commonly used oral levodopa may lead to a diminished drug reactions, and if the dose is increased, it can lead to psychiatric symptoms such as motor fluctuations and urinary difficulties [1]. Traditional DBS surgery carries a high risks of infection, bleeding, and nerve damage, which further compromises human health. Therefore, this paper introduces some new treatments for Parkinson's disease and the improvement of traditional treatment by means of literature review. It aims to understand the latest research results in the treatment of Parkinson's disease and provide strategies for subsequent treatment quality. New treatments may drive industrial change, such as gene editing, stem cell therapy, etc. to promote the development of precision medicine, and the birth of biotechnology enterprises, neural regulation technology (such as the upgraded version of DBS) to promote the upgrading of medical equipment. It can also improve the quality of life of patients, reduce the cost of long-term treatment, and enhance social acceptance.

## 2. Treatment methods

### 2.1. ABBV-951

ABBV-951 is a novel prodrug of levodopa and carbidopa developed by AbbVie, which aims to address the limitations of traditional oral levodopa therapy [1]. Due to the short half-life of drugs, traditional treatment requires patients to take medication frequently, resulting in frequent "off" periods and "on" periods of symptom fluctuations throughout the day, which brings great

inconvenience to patients' daily life [1]. However, ABBV-951 has extremely high aqueous solubility and can be continuously administered for 24 hours through a portable subcutaneous infusion device to maintain stable drug concentrations. This continuous infusion better simulate dopamine secretion in the human physiological state, enabling smoother symptom control and reducing fluctuations [2]. Notably, the infusion device is compact and portable, allowing patients to easily manage treatment at home or outside, which improves the convenience of treatment, and significantly improves their quality of life. This is an important breakthrough for patients suffering from long-term fluctuations in Parkinson's disease symptoms.

In a pivotal phase 3 clinical trial (M15-736 study), ABBV-951 significantly prolonged the "ON" time (defined as time without dyskinesia and with functional mobility) compared with oral immediate-release levodopa/carbidopa (LD/CD) [3]. At week 12 of treatment, the "ON" time increased by 2.72 hours in the ABBV-951 group, while the oral LD/CD group increased by only 0.97 hours ($p = 0.0083$). The mean adverse "Off" time in the ABBV-951 group improved from baseline. And after 12 weeks of treatment, "Off" time decreased by 2.75 hours in the ABBV-951 group and by 0.96 hours in the oral drug group ($p=0.0054$). In addition, the majority of adverse events in the ABBV-951 group were mild to moderate, with no treatment-related deaths [3]. These experimental results show that ABBV-951 has significant advantages of pver conventional oral levodopa/carbidopa in term of improved "Good On" time and reducing "Off" time, and that continuous subcutaneous infusion reduces the fluctuation of drug concentration. As a result, this treatment can provide consistent and stable dopaminergic stimulation, reduce drug fluctuations and motor fluctuations, and significantly improve patient symptoms.

## 2.2. DBS optimized

In recent years, the continuously optimization of DBS technology has driven the continuous improvement of.brain pacemaker functions. Compared with the traditional brain pacemaker, intelligent perceptible brain pacemaker, like the PerceptTM PC, can not only perform electrical stimulation, but also sense EEG signals to achieve precise treatment. Intelligent perceptible brain pacemaker can monitor the brain activity of patients in real time, and automatically adjust the electrical stimulation parameters according to the monitoring data to achieve more accurate treatment effect. In term of hardware design, the Intelligent perceptible brain pacemaker has also made many improvements, such as battery life, MRI compatibility, comfort, etc [4].. A ADAPT-PD trial involving 68 patients implanted subthalamic nucleus or medial globus pallidus DBS leads connected to a Medtronic PerceptTM PC neurostimulator. During enrollment, clinicians identified LFP (8-30Hz,$\geq$1.2μVp) control signals in 84.8 % of patients during medication (65% bilateral signals) and in 92% of patients off medication (78% bilateral signals) [4]. This result indicates that the Percept™ PC neurostimulator can effectively sense brain activity in most patients, providing reliable data support for real-time adjustment of aDBS technology. Secondly, the traditional open-loop DBS system is mature in technology and relatively simple to operate, but the disadvantage are obvious. It cannot monitor and respond to changes in the patient's brain activity in real time, and requires frequent manual adjustments by the doctor. In contrast, closed-loop stimulation technology can detect EEG signals in real time and automatically adjust the stimulation parameters, which not only improve the therapeutic effect, but also reduce side effects [5]. For example, the BrainSense launched by Medtronic™ adaptive deep brain stimulation system uses real-time feedback and automatic adjustment to better adapt to disease fluctuations, enhancing treatment efficacy and the quality of life of patients [6]. In December 2020, Medtronic initiated a 45 patients trial to evaluate the feasibility of single-threshold or dual-threshold aDBS. Compared with open-loop DBS, single-threshold aDBS extended the "ON" time by 0.6±3.6 hours, and double-threshold aDBS increased it by 1.4±3.0 hours in a statistically significant manner (97.5% confidence interval 0.2-2.5,$p<0.0125$). In addition, compared with continuous DBS, the total energy consumption of aDBS was reduced (single-threshold median 13%, double-threshold aDBS median 11%). 97.8% of patients chose to continue using aDBS in follow-up [7]. These results indicate the feasibility of closed-loop stimulation. Furthermore, surgical robots and stereotactic frame technology can achieve precise electrode implantation, reducing operation time and complications, while multi-target joint stimulation remains an area for further exploration to optimize therapeutic effects.

## 2.3. Induced Pluripotent Stem Cells

Induced Pluripotent Stem Cells (iPSCs) are cells that are reprogrammed and differentiate from mature somatic cells into embryonic stem cells through specific genetic recombination techniques [8]. iPSCs exhibit pluripotent differentiation potential similar to embryonic stem cells, capable of differentiating into all cell types in the body. The advent of iPSCs technology enables scientists to derive pluripotent stem cells from a patient's own somatic cells, thus circumventing immune rejection and ethical concerns. By inducing the differentiation of iPSCs into dopaminergic neurons and transplanting these cells into the brain of patients, the damaged dopaminergic neurons can be replaced and the supply of dopamine can be restored to improve the symptoms of Parkinson's disease [9]. Compared with traditional drug and surgical treatment, iPSCs offer advantages in direct neuronal repair, safety and long-term efficacy. In non-human primate experiment, a Parkinson's disease monkey model was established by injecting MTPT into the unilateral internal carotid artery, and monkeys presenting with a series of typical motor symptoms were treated. The treatment results showed that clinical-grade hPESC differentiated into neuroepithelial cells and

regional-specific neural stem cells, which further differentiated into dopaminergic neurons, survived, and migrated in the monkey brain without forming tumors. Overall, the experiment improved the symptoms of the monkeys [10]. In addition, in a phase 1 clinical trial evaluating neural stem cell tumorigenicity and biodistribution, no risk of teratoma or tumorigenesis was identified in any of the animals injected with ISC-hpNSC. In addition, injection of ISC-hpNSC cells was not associated with any proliferative risk or other serious adverse events at any dose or time interval. Biodistribution analysis by immunohistochemistry and qPCR revealed no ISC-hpNSC presence in peripheral organs, further supporting their safety and feasibility [11]. The core advantage of iPSC is the potential for cell replacement and autologous transplantation, which reduces the risk of immune rejection and offers a revolutionary new strategy for the treatment of Parkinson's disease.

### 2.4. New types of gene therapy

Gene therapy aims to introduce functional genes into a patient's cells to repair or compensate abnormalities caused by defective genes. With the advancement of gene editing technology, the potential of gene therapy in the field of neurodegenerative diseases is increasing. For example, FAM171A2 is a neuronal cell membrane protein that plays an important role in the transmission of pathological α-synuclein. Its discovery provides new therapeutic direction for Parkinson's disease. FAM171A2 acts as a molecular gateway that selectively grabs pathological α-synuclein and bring it inside the neuron, leading to misfolding of α-synuclein and ultimately triggering neuronal death and pathological spread. Therefore, inhibiting FAM171A2 function can effectively block pathological α-synuclein spread, potentially delaying Parkinson’s progression.. Based on cellular and animal models of Parkinson's disease, Yu et al. validated the efficacy of FAM171A2 targeted therapy. It was found that FAM171A2 overexpression enhanced the endocytosis of α-Syn fibers, worsening the pathological spread and neurotoxicity. Conversely, reducing FAM171A2 expression attenuated the endocytosis of α-Syn fibers, protected dopaminergic neurons, and improved the exercise capacity of mice. These results reveal the important role of FAM171A2 in Parkinson's disease and provide critical insignts for developing novel therapeutic agents [12]. However, current research on FAM171A2 remains in the preclinical stage, with no clinical trials initiated yet.

## 3. Conclusion

This article focuses on novel treatment of Parkinson's disease by exploring improvements in pharmacological and surgical treatments compared to traditional pharmacological and surgical treatment. It also introduces two new therapeutic methods of cell and gene therapy, and their therapeutic mechanism. Generally speaking, the treatment of Parkinson's disease is constantly developing towards non-invasive, precise and personalized. For example, ABBV-951 stablilise non-invasive drug delivery and personalized subcutaneous injection techniques. The new DBS technology allows for more accurate and reduces invasive procedures. Stem cells and FAM171A2 also provide a new personalized treatment strategy, which is an important development direction of regenerative medicine and precision medicine.

In the future, the treatment of Parkinson's disease is likely to evolve in a multidisciplinary path. By combining technology and knowledge from fields such as neuroscience, genetics, molecular biology and artificial intelligence, it is expected that the shortcomings of traditional treatments can be remedied, and more precise and effective therapies can be developed. For example, new neuromodulation therapies may lead to breakthroughs, targeted gene therapy is also expected to be a new direction, while the improvement and optimization of drugs and surgery will continue to advance. Even more promisingly, AI may play an important role in drug screening, disease prediction and treatment planning.

However, this article only ddresses some of the new treatment in recent years, and the most recently developed drugs and treatments are not mentioned in this paper. Moreover, the clinical data of the relevant treatments cited in this article are rather limited, and only targeted experimental study and data are provided. As well as this paper only based on the review content of the analysis, lack of relevant empirical experimental data support. In addition, there is no mention of the disadvantages of the new treatment method, such as the tumor risk of induced pluripotent stem cells, immune rejection, and the protein structure of the FAM171A2 is not fully resolved. In the future, improved research will be conducted on the shortcomings of treatment methods, such as research on reducing the risk of tumorigenesis and immune rejection of stem cells through gene editing technology, and improving stem cell therapy.

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