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Experimental Treatments for Parkinson Disease

Jintian Du

1. Abstract

Parkinson's disease is a chronic and progressive neurodegenerative disorder that primarily affects motor function. Although modern treatments can relieve and help patients manage symptoms, there is still an urgent need for innovative new therapies that can slow down the disease's severity progression. This review examines numerous innovative and promising experimental treatments for Parkinson's disease that are either in development or clinical trial. It will review the potential L-Dopa therapy – namely using a dopamine replacement agent during the treatment of the Parkinson's disease to manage the symptoms of patients. Additionally, the review also covers developing neuromodulation techniques, including deep brain stimulation, which attempts to modulate brain activity as a way of alleviating Parkinson's symptoms. The review evaluates the current status in treatment for each experimental approach, summarizing their suggested mechanisms of treatment, preclinical discoveries, and clinical trials. It also discusses the main challenges and obstacles in relation to these therapies. In conclusion, while significant barriers and limitations remain, the review highlights the progress made in the development of newer potential treatments that may improve conditions for patients living with Parkinson's disease.

Keywords: parkinson's disease, L-Dopa therapy, Deep brain stimulation

2. Introduction

Parkinson's disease is a neurodegenerative disorder that primarily affects human movement and the function of motor units. It is nowadays the second most common neurodegenerative disease after Alzheimer's and had been affecting the lives of over 6 million people globally by 2020. (Dorsey, 2018) The main markers of the disease, plummeting dopamine production and the development of cardinal motor symptoms, is triggered by the incremental loss of dopaminergic neurons in the substantia nigra in the brain.

The most representative symptoms of Parkinson's disease include resting tremor – typically an unconscious tremble beginning in one hand or arm and eventually spreading to other limbs; bradykinesia - a general slowness in initiating and executing movements of the patient; rigidity - which can make voluntary movements difficult and restrict range of motion; and postural instability. (Jankovic, 2008) – this symptom might increase the risk of falls and will lead to impaired balance and coordination.

In addition to the symptoms mentioned above, patients with Parkinson's are also likely to develop non-motor symptoms that can significantly impact quality of life - for instance, cognitive impairment, depression, insomnia, autonomic and sensory dysfunction. (Schapira, 2017) As the disorder is heterogeneous and progressive, the conditions vary greatly among different clinical trials and patients.

While the actual cause of Parkinson's disease remain a mystery to scientists, it is believed that the disorder is linked with complex genetic and environmental factors that may lead to selective degeneration of dopaminergic neurons. (Poewe et al, 2017)

Given the severity and significance of Parkinson's disease globally, there is an urgent need to enhance interventions and treatments that can slow, halt, or potentially reverse the neurodegenerative nature of the disorder. The following sections will explore several innovative experimental treatments that are currently in different stages of research and clinical investigation.

1.1 L-Dopa Therapy

L-Dopa stands for Levodopa, which is the precursor for dopamine (which, due to the nerve cell impairment or death, decreases production), therefore, this particular substance can be used as a dopamine replacement agent during the treatment of the Parkinson's disease. It is most effective when controlling bradykinetic disorders and symptoms in patients. Data have shown that levodopa can not only slow down the progression of Parkinson's disease but can also leave patients with lasting post-treatment benefits. The most typical administration is oral L-Dopa Therapy, which requires immediate-release tablets, disintegrating tablets, controlled-release tablets, or extended-release tablets. The treatment should start with small doses, recommended to be 300-1200mg, separated

into 3-12 doses. As recommended, the titration schedule should be to take a 100mg increment for every 3-4 days. In this case, patients should take the therapy orally to decrease gastrointestinal upset. Furthermore, to enhance patients' absorption, levodopa should be ingested 1 before or 2 hours after meals that include proteins.

1.2 Deep Brain Stimulation

Deep Brain Stimulation for the moto thalamus and the ventral intermedius nucleus was initially used in 1986 to cure medically refractory tremors in Parkinson's disease patients. As it has expanded in usage, deep brain stimulation of various basal ganglia nuclei has been enhanced into a highly effective and efficient treatment for numerous disorders. In treatment of Parkinson's disease, deep brain stimulation of internal globus pallidus and the subthalamic nucleus were considered to be effective targets. The advantage of chronic deep brain stimulation for Parkinson's disease is that it leads to only negligible tissue damage and is thus highly reversible. As bilateral deep brain stimulation can be implemented with minimal side effects, it has become possible to adjust stimulation parameters after postoperative reviews and consideration of specific symptoms. In different randomized controlled trials deep brain stimulation showed better functional outcomes with significantly less side effects that might sabotage the human body. (Schuurman et al. 2000). In this case, deep brain stimulation almost completely superseded lesioned surgery in some countries.

3. Thesis

The thesis of this scientific review is that both types of treatments have their advantages in accordance with each patient's symptoms, and that the utilization of each treatment modality must be considered under specific conditions of the patient – for example, the stage of the disease, the financial affordability, the potential side effects, the preferences of the patient, etc.

4. Evaluation

Two most promising and primary disorder treatments for Parkinson's disease are oral levodopa (L-dopa) therapy and deep brain stimulation (DBS). L-dopa has been the most commonly utilized pharmaceutical approach since its development and introduction in the late 1960s, while DBS has emerged as an effective surgical option over the past two decades. This review provides a comparative evaluation of these two treatments, weighing their mechanisms, efficacy, limitations, and advantages.

4.1 L-Dopa Therapy

L-dopa, being a metabolic precursor to the hormone dopamine, has become the most commonly used and effective pharmacological intervention for managing Parkinson's disease. When taken orally, L-dopa is converted to dopamine in the brain, helping to replenish plummeting dopamine levels and revive motor function. (Olanow, 2013)
Studies have shown the treatment having considerable symptomatic benefits. In early-stage Parkinson's, L-dopa can significantly enhance motor function by reducing tremor, body rigidity, and bradykinesia. (Fahn, 2000) However, as the disease progresses, the effectiveness of L-dopa diminishes, and reversely, patients may develop motor complications such as dyskinesias (involuntary movements) and response fluctuations (Ahlskog, 2001). Moreover, when the patient is associated with long term usage of the treatment, the neuropsychiatric side effects like impulse control disorders and dopamine dysregulation syndrome (Weintraub, 2010) might emerge.
The use of L-Dopa treatment for Parkinson's disease has proven to be overall effective according to the data collected (see Fig.1). In the table, 63 patients out 80 showed more than 50% of objective range of functional improvement after 2 months of treatment, indicating that the improvement is significant for about 80% of the clients in total. This suggests that, in general, L-Dopa therapy will significantly enhance symptomatic recovery from Parkinson's disease.

TABLE VI.—Results of L-DOPA in Parkinson's Disease
Total Number: 80 Patients

Objective range of functional improvement (after two months of treatment)		*No. of patients*	*%*
80—100%	(Very good)	9	11.2
50— 79%	(Good)	54	67.5
20— 49%	(Moderate)	9	11.2
0— 20%	(Poor)	8	10.0

Fig. 1 (Created by Science & Research)

However, although having a considerable effect on improving clinical conditions of patients of the Parkinson's disease, L-Dopa therapy also has strong side effects. In Fig. 2, it is explicitly shown that 43.7% of all patients that took this specific treatment experienced nausea and/or vomiting, and 50% of the patients endured abnormal involuntary movements.

TABLE VII.—Side Effects with L-DOPA
(80 patients treated for more than two months)

Symptoms	*No. of cases*	*%*
A. CLINICAL		
Nausea and/or vomiting	35	43.7
Hypotension:		
symptomatic 9		
asymptomatic 16	25	31.2
Hypertension	1	1.2
Anorexia with loss of weight	1	1.2
Polyuria	4	5.0
Somnolence	4	5.0
Palpitations or arrhythmias	6	7.5
Confusion, hallucinations or vivid dreams	13	16.2
Depressive episodes	9	11.2
Abnormal involuntary movements	40	50.0

Fig. 2 (Created by Science & Research)

4.2 Deep Brain Stimulation

Involving the implantation of electrodes into target regions of the brain (most commonly the subthalamic nucleus or globus pallidus interna), deep brain stimulation enhances patients' conditions by delivering continuous electrical stimulation to modulate neural activity. (Benabid, 2009)

DBS has become an effective treatment option, particularly for patients with advanced Parkinson's disease who experience motor complications or a diminishing response to L-dopa therapy. Randomized controlled trials have indicated the superiority of DBS over continued medical therapy in improving motor function and reducing disability caused by the Parkinson's Disease. (Weaver, 2009) (Deuschl, 2006)

Research has shown that tremors caused by Parkinson's disease was successfully eliminated in the majority of the patients, as 72.5% of the patients found long-term improvement in frequency and severity of tremors. However, other motor dysfunctions caused by Parkinson's disease, such as freezing, speech and swallowing difficulties remained stable and unaffected by the treatment. (Frederick et al. 2018)

However, research has shown that deep brain stimulation may potentially worsen patients' expression of intelligible speech. According to one study, patients' percentage of words that are understandable declined from 91.9% to 80.8% at 1 year of treatment, decreased to 70.2% after 5 years, and further decreased to 63.5% at 8 years. (Information Services Division, 2018)

4.3 Overview

Both L-dopa and DBS have demonstrated the ability to considerably improve patients' motor functions and quality of life after suffering the disorder. However, the symptomatic advantages of DBS may be more durable, specifically in advanced disease stages when L-Dopa therapy has diminished effects. DBS has been shown to provide greater improvements in motor scores, in reducing prescription requirements, and in decreasing incidence of dyskinesias compared to that of L-Dopa. (Weaver, 2009) (Deuschl, 2006)

L-dopa is generally well-tolerated, yet long-term usage can lead to the debilitation of motor complications, as well as causing multiple neuropsychiatric side effects. DBS, on the other hand, while serves as an invasive procedure, has a relatively favorable safety guarantee when performed by professionals. However, one of the most common adverse effects of DBS is hardware-related complications, such as infection or lead migration. (Okun et al, 2010)

Nevertheless, L-dopa therapy is generally more accessible and affordable than DBS to the public, as the latter requires specialized surgical expertise and infrastructure to initiate, and that the cost of DBS surgery and hardware can be substantial. (Spottke et al, 2002) Furthermore, L-dopa therapy is the common first choice for managing Parkinson's disorder and is well suited for a wide range of

patients, from early to advanced disease stages. DBS has more limited usage, and is typically prescribed for patients with advanced Parkinson's who have motor complications or a diminishing response to medication such as L-dopa.

5. Conclusion

In conclusion, L-Dopa therapy and deep brain stimulation are 2 distinct approaches that have the potential to alleviate the symptoms of Parkinson's disease patients and which both may bring new insights to long-term treatment of this particular disorder. L-dopa remains the first choice for pharmacological treatment, providing considerable relief to patients that are in the early stage of the disease. DBS, comparatively, has emerged as a highly effective surgical intervention for patients suffering advanced Parkinson's, offering more sustained improvements.

The research supports this study's thesis, as the evaluation shows that the choice between the two treatments should be based on individualized criteria, taking into account the patient's disease stage, symptom type, treatment history, and personal preferences. The ultimate goal for all treatments is to provide a comprehensive and personalized system that maximizes recovery, relief, functional independence, and quality of life for individuals living with this neurodegenerative disorder.

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