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THE RELEVANCE OF IMPROVING SCIENTIFIC RESEARCH ON THE TREATMENT AND PREVENTION OF PARKINSON'S DISEASE

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Abstract. Parkinson's disease (PD) is a neurological disorder that worsens over time and causes both motor and non-motor symptoms that significantly lower quality of life. PD has been treated with pharmaceuticals, mostly levodopa. However, their long-term efficacy is sometimes limited by adverse effects such dyskinesias and motor irregularities. The entire landscape of neurosurgical therapies has changed in the last several decades due to advances and developments. This narrative review examines clinical research on gene therapy, neurosurgery, and other contemporary PD treatments. Three additional papers were extracted from other databases, and 47 studies were found in the PubMed search. The most well-established neurosurgical method, deep brain stimulation (DBS), has compelling evidence that it can alleviate motor symptoms. Although focused ultrasound (FUS) offers a noninvasive alternative, most research on it still lacks long-term evidence. Although they are still in the early stages of clinical development, gene therapy approaches such as AAV2-hAADC and ProSavin have demonstrated early-phase safety and efficacy. In the future, robotic surgery and more advanced imaging methods may be crucial to PD-related surgery. Newer neurosurgical and gene therapy techniques are expanding the choices for treating Parkinson's disease. Although the current results are encouraging, more extensive, controlled trials are needed to demonstrate long-term safety and effectiveness. This review is very significant, according to research in the literature, because it addresses numerous rehabilitation therapy for Parkinson's disease patients in a single document for the first time. This review article's objective is to compare the efficacy of two different therapy interventions for Parkinson's disease patients.

Keywords. Parkinson's disease, thalamotomy, pallidotomy, deep brain stimulation, targeted ultrasonic stimulation, levodopa.

Introduction. Parkinson's disease (PD) is the second most common type of neurodegenerative illness and a severe dysfunction of the human nervous system. Lewy bodies and Lewy neuritis are aberrant intra-neuronal aggregates of α-synuclein that are pathologically associated with Parkinson's disease. Dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc) gradually decrease as a result of this long-term, progressive neurodegenerative disease. The process involves the conversion of L-tyrosine into tyrosine-derived dopamine, which is then stored in synaptic vesicles and released from the axon terminals, which originate from a nigrostriatal DA neuron. Parkinson's patients see a very gradual deterioration in this process. Approximately 7 million persons globally are impacted. Currently, 1% of Americans over 60 and an estimated 4% of the oldest Americans have a Parkinson's disease diagnosis. By 2030, this phenomenon is predicted to double. Age is now the sole known risk factor for Parkinson's disease (PD); early diagnosis typically occurs at age 60, however young onset PD

can also occur and diagnosis can occur later in life. Other risk factors that have been extensively studied include gene polymorphism, tobacco usage, alcohol and caffeine use, pesticides, history of head trauma, hypertension, and diabetes mellitus [1-5]. However, it is still unclear how these factors affect the likelihood of developing Parkinson's disease (PD). Male sex has been identified by epidemiological research as a significant risk factor for Parkinson's disease (PD) across all age groups and nationalities. Male to female ratios for incidence rates vary from 1.37 to 3.7, and a comprehensive meta-analysis research indicates that twice as many men as women had Parkinson's disease (PD) over any given time period. The neurodegenerative disease known as Parkinson's disease (PD) usually manifests in later life as bradykinesia, or a general slowing of movements, combined with other symptoms including stiffness or resting tremor. Constipation, sleep problems, loss of smell, excessive salivation, mood abnormalities, and excessive periodic limb movements during sleep are other symptoms. PD is the second most prevalent neurodegenerative illness and the one with the greatest growing rate in terms of related prevalence, disability, and mortality globally, according to the 2015 Global Burden of illness estimates [6-11]. Levodopa and other medication therapies have been the main treatment for Parkinson's disease (PD) symptoms, but they have not been able to maintain the desired long-term results. Levodopa induces fluctuations, dyskinesias, and refractory tremors in Parkinson's disease. In order to treat movement disorders, neurosurgeons initially employed ablative techniques in the 1930s. This was due to a growing understanding of basal ganglia and subcortical anatomy as well as evidence connecting pathology in the basal ganglia to abnormalities in movement. Later, to treat Parkinson's disease (PD), dystonia, and other movement disorders, lesioning of the globus pallidus (pallidotomy) and the thalamus (thalamotomy) was frequently performed in the 1950s and 60s. Pallidotomy and thalamotomy were largely superseded in the early 1990s by deep brain stimulation (DBS), which was approved by the FDA to treat Parkinson's disease. Furthermore, after DBS is implanted, it can assist alter abnormal neural circuits and shows greater clinical outcomes compared to medical-only treatment. The purpose of this narrative review is to examine the most recent developments in neurosurgical treatments for Parkinson's disease (PD) and evaluate their impact on patient outcomes, safety, and clinical efficacy [12-18]. It covers developments in neuromodulation techniques, deep brain stimulation technology, and more recent surgical treatments that may open up new avenues for research and treatment of Parkinson's disease. Gene therapy, cell replacement treatment, light therapy, deep brain stimulation, and repetitive transcranial magnetic stimulation are some of the recently established non-pharmacological therapeutic approaches that have been proposed to help alleviate parkinsonian symptoms. This review's primary goal is to close the gaps in the literature by offering current, useful information on the most recent studies that have been published in recent years and that can provide the most comforting plausibility for promoting Parkinson's disease treatment. Physical therapy, occupational therapy, specialty therapies for specific purposes, and newly created therapies are the four primary groups of rehabilitative therapies that are covered in this review. In order to conduct literature research, current information on general or particular rehabilitation therapy used on Parkinson's disease patients was gathered from various reviews, reports, and original studies [19-26].

The main purpose of the presented manuscript is to provide a brief analysis of the relevance of improving scientific research on the treatment and prevention of Parkinson's disease based on the results of authoritative scientific works.

The development of neurosurgical methods. ***The first methods of surgery.*** Early in the 20th century, rather than treating Parkinson's disease (PD) alone, surgery for movement disorders primarily addressed hyperkinetic illnesses in their entirety. In the 1930s, Bucy and Case excised the cerebral cortex to treat Parkinsonian tremors. But because this type of ablative

surgery resulted in hemiparesis, it was subsequently discontinued. In 1953, Cooper accidentally sliced the anterior choroidal artery while performing surgery on a Parkinsonian patient; to stop the bleeding, the artery had to be ligated. The procedure's unexpected and startling reduction of contralateral side tremor and rigidity led to its increased use in PD patients, despite the procedure's about 10% death rate. During the same period, the studies of Spiegel et al. on the advantages of pallidotomy started to surface with the introduction of modern stereotactic surgery [3-11]. Thalamotomy was finally found to be able to lessen Parkinsonian tremor. Parkinson's disease was also treated with electrical coagulation techniques involving the globus pallidus, thalamus, and ansa lenticularis in addition to early stereotaxic operations. Early surgical therapies were hampered by the lack of medical neurologists' involvement, which raised concerns about erroneous reporting, a lack of long-term follow-up, and the potential for morbidity minimization. When levodopa was found to dramatically lessen the symptoms of Parkinson's disease (PD), there was a temporary pause in the surgical treatment of PD in the 1960s. This finally resulted in a drop in PD surgical treatments. Lastly, activating the deep brain areas was an entirely different method of treating the tremors. Although deep brain stimulation has previously been performed, Benabid and colleagues' research that activated the ventral intermediate nucleus of the thalamus signaled the start of the modern era of persistent deep brain stimulation (DBS). In PD patients, this stimulation dramatically decreased tremors [14-21].

Current Methods. The technique known as "deep brain stimulation" involves surgically inserting stimulation leads into particular motor parts of the cortico-basal ganglia-thalamo-cortical circuit, such as the ventral intermediate nucleus (ViM), globus pallidus internus (GPi), and subthalamic nucleus (STN). Internal pulse generators (IPGs), which are usually implanted in the subclavicular area, are connected to leads and electrodes in DBS in order to alter the signals from the leads. High-frequency electrical oscillations of deep brain stimulation (DBS) targeted at the Subthalamic nuclei or GPi regions suppress the pathogenic activity, relieving or reducing the debilitating clinical symptoms of Parkinson's disease (PD), such as tremors, rigidity, and bradykinesia. The use of DBS in the treatment of Parkinson's disease has three main indications. Patients with tremors that are resistant to treatment are the main target audience. Patients who have problems with long-term levodopa therapy, such as levodopa-induced dyskinesias and the wearing-off phenomena, are covered by the second important indication for DBS. It is also a remarkable substitute for individuals who could be intolerant to dopaminergic drugs like levodopa [2-9]. Deep brain stimulation primarily targets our brain's globus pallidus internus and subthalamic nucleus. The standard for assessing the severity and progression of Parkinson's disease is the Unified Parkinson's Disease Rating Scale (UPDRS). The UPDRS is used by several researchers to assess and distinguish between the effects of STN and GPi DBS. According to these studies, STN DBS and GPi DBS have comparable outcomes and are useful in reducing tremor, improving gait, and mitigating negative effects like mood swings and apathy. There are documented dangers associated with DBS; a meta-analysis of 11 studies including 1368 patients revealed that 21% of PD patients following DBS experienced postoperative delirium (POD). The primary predictors of POD were higher non-motor symptom load, worse cognitive function, and older age. Gender, motor symptoms, and comorbidities, on the other hand, did not clearly correlate. These results imply that cognitive and non-motor evaluations could be useful in identifying patients who are at risk for issues prior to DBS surgery [15-22].

Neurosurgical innovations. ***Advanced Imaging Methods.*** For the early diagnosis and treatment of neurodegenerative illnesses like Parkinson's disease, advanced neuroimaging is crucial. Improvements in MRI, PET, and other imaging methods have improved our ability to detect subtle changes in the brain, allowing for early treatments. AI integration shows promise for enhancing early detection techniques. To maximize the potential of neuroimaging

advancements, these challenges must be resolved. Parkinson's disease (PD) is a neurological condition that makes early identification difficult, highlighting the need to slow the illness's progression and improve treatment effectiveness. Molecular resonance imaging (MRI) has been identified as an efficient imaging biomarker for early differential diagnosis and treatment efficacy evaluation in vivo. For molecular imaging, proton magnetic resonance spectroscopy (MRS) has good test-retest repeatability, is noninvasive and economical, and does not require contrast agents [8-18]. It can be extended to standard public health institutions and is not limited to specialized centers. *In vivo* insights into Parkinson's disease pathology have been made possible by recent developments in magnetic resonance spectroscopy, such as improved magnetic fields and reliable methods for absolute metabolite quantification. In Parkinson's disease (PD), reduced NAA levels in cortical-basal ganglia networks are indicative of neuronal loss and impaired mitochondrial metabolism. Movement-related neuronal excitatory and inhibitory processes may be compromised by changes in glutamate and GABA levels seen in Parkinson's disease patients. When it comes to PD differential diagnosis and treatment, proton magnetic resonance spectroscopy has proven to be quite helpful [19-25].

Discussion. 199 of the 350 articles that were initially found were chosen for a thorough analysis on different treatments. Physiotherapy has been demonstrated in studies to produce short-term advantages for Parkinson's disease. It's still unknown, though, which therapeutic interventions work best. Instead of offering a "recipe" for treatment, this article offers a framework for guidance. Numerous rehabilitative therapy approaches have been tested to treat Parkinson's disease (PD), according to this review. To support the best choice of therapy intervention and the outcomes measured, more focused trials with better treatment methodologies are required. The literature search indicates that this narrative review is unique in that it discusses numerous rehabilitative therapy for Parkinson's disease patients in a single piece for the first time. Increasing (or maximizing) mobility quality, functional independence, and overall fitness while preventing (or reducing) secondary problems and maximizing safety are the goals of physiotherapy, which encompasses a variety of approaches [3-11]. Therefore, self-management assistance and engagement in movement-related activities are included in physical therapy (PT). Exercise (such as yoga and pilates therapy), practice, and compensatory strategy training (such as cueing, treadmill, dancing, material arts, hydrotherapy, and strategies for complex motor sequences) are the most crucial treatment methods employed by physiotherapists. A discussion of several significant physical therapies from the literature is provided below. For postural instability in Parkinson's disease, there is currently no proven treatment. Although it hasn't been proven yet, HPT may be beneficial for PD sufferers. Research on how HPT affects patients' balance is few. Andrade and colleagues evaluated the impact of aquatic workouts on seven Parkinson's disease patients using a therapy plan that included stretching, static and dynamic balancing exercises, and adaptation to the aquatic environment [13-20]. The outcomes demonstrated that the 12-session course of treatment encouraged an improvement in balance. Vivas and colleagues examined how HPT and traditional PT activities affected PD patients' postural stability and mobility. The range of physiotherapy interventions being evaluated for the treatment of Parkinson's disease is highlighted in this study. By concentrating on enhancing balance, posture, gait, upper limb function, physical capacity, and cognition as well as reducing falls, various rehabilitation therapies for Parkinson's disease (PD) have the potential to maximize functional ability and minimize secondary complications. This will maximize people's independence, safety, and well-being, ultimately improving quality of life. Research has demonstrated the short-term benefits of physiotherapy for Parkinson's disease (PD), however it is yet unknown which physiotherapy strategy works best [21-26].

Conclusions. In summary, advances in noninvasive technologies, gene therapy, and neurosurgical techniques are revolutionizing the way Parkinson's disease is treated. The way we treat Parkinson's disease is beginning to alter thanks to new neurosurgical and gene-based therapies. With strong data supporting its use, deep brain stimulation is still the most reliable method. Although there is currently little and short-term study on focused ultrasound, it presents a promising, less invasive approach. Although gene therapy is still in its infancy and needs further investigation, it may provide a long-term answer. These more recent methods, when combined with contemporary imaging and robot-assisted surgery, show how Parkinson's disease might be approached very differently. As these alternative approaches develop, choosing the right patients and increasing access to these treatments will be just as important as advancing the science. A customized approach to PD treatment will be made possible by upcoming studies and trials.

Although gene therapy has not yet shown to be a cure for Parkinson's disease (PD), there is growing evidence that it may be a significant treatment option in the future. Before stem cell therapy becomes the next main option for treating Parkinson's disease, it must continue to advance and be tested on humans and living animals. The most promising new stem cell technology is induced pluripotent stem cells (iPSCs), not only for therapeutic purposes but also for drug testing and disease modeling. NIr therapy is acceptable to employ in combination with other treatments due to its neuroprotective potential and lack of side effects. For instance, as a first-line treatment, patients may receive NIr therapy with a lower dosage of medications; the neuroprotective impact of NIr may prolong the effectiveness of the medication therapy.

Additionally, PD patients who are chosen for DBS may also have simultaneous surgical implantation of an NIr optical fiber, which may provide neuroprotection for the remaining DA cells. If DBS is used as soon as motor irregularities develop, quality of life may be improved. DBS must be taken into account for those with severe Parkinson's disease whose symptoms are not sufficiently managed by the most effective conventional treatments. According to the studies, rTMS helps PD patients with their motor symptoms. Key modulators of rTMS effects include combinations of rTMS location and frequency as well as the quantity of rTMS pulses. Despite the aforementioned benefits of several types of therapies, further research is still required to ascertain which of these therapies best reduces motor and non-motor symptoms, as well as the required dosage and intensity of these therapies and long-term retention effects.

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