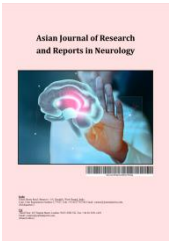

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GLP-1 Agonist in the Treatment of Parkinson, New Innovations: A Literature Review

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative condition marked by the gradual deterioration of dopaminergic neurons, leading to severe motor and non-motor symptoms. Conventional treatments primarily focus on symptom management rather than addressing the underlying disease progression. However, recent scientific investigations have illuminated the potential of GLP-1 agonists in offering neuroprotection and enhancing motor function among individuals with PD. Originally designed to tackle type 2 diabetes, GLP-1 (glucagon-like peptide-1) agonists have attracted considerable interest due to their multifaceted impacts extending beyond glycemic regulation. In the realm of PD, preclinical trials have unveiled the neuroprotective attributes of GLP-1 agonists, which include anti-inflammatory, anti-apoptotic, and neurotrophic properties. These mechanisms present a promising avenue for therapeutic intervention aimed at slowing down or even arresting the progression of PD. Numerous clinical studies have explored the efficacy of GLP-1 agonists in PD patients, yielding promising outcomes. Exenatide, a commonly studied GLP-1 agonist, has shown improvements in motor symptoms, as well as potential disease-modifying effects. Other GLP-1 agonists, such as Liraglutide and Dulaglutide, have also exhibited promising results in small-scale trials. However, challenges such as optimal dosing, long-term safety, and patient selection remain to be addressed. Continued research efforts are warranted to

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refine GLP-1 agonist therapy and pave the way for improved outcomes in PD management. This article aims to review all the aspects related to Parkinson's disease and the usage of GLP-1 agonists in the affected patients. It shall reflect upon all the relevant information that is required for a physician to know before diagnosing such conditions and prescribing the appropriate medications for the patients.

Keywords: Parkinson's disease; GLP-1 agonists; treatment therapy; new interventions; successful outcome.

1. INTRODUCTION

Parkinson's disease is a progressive neurodegenerative condition typically diagnosed in older individuals, characterized by symptoms like slowed movements called bradykinesia, tremors, and muscle rigidity. It affects approximately 1% of those aged 60 and above [1].

The primary cause is the loss of dopamine-producing neurons in the substantia nigra region of the brain, often accompanied by the presence of abnormal protein deposits known as Lewy bodies. While most cases have no clear cause and are conveniently termed idiopathic, about 10% are linked to genetic factors, usually in younger patients [2].

Symptoms typically begin subtly, with tremors being a common initial sign, followed by bradykinesia and rigidity. Postural instability, which can severely impact daily activities, usually develops later in the disease course [3]. Additionally, non-motor symptoms like loss of smell, sleep disturbances, mood changes, excessive saliva, constipation, and abnormal movements during sleep, such as REM behavior disorder can occur [4].

Early diagnosis is primarily based on clinical history and examination, although SPECT scans may be used in uncertain cases or to rule out other conditions. Understanding these clinical features is highly important for timely intervention and management strategies in Parkinson's disease [1].

Histologically, Parkinson's disease (PD) is characterized by the presence of abnormal protein aggregates called Lewy bodies and Lewy neurites, primarily composed of alpha-synuclein, within neurons. This accumulation of alpha-synuclein is known as Lewy-related pathology. The hallmark of neurodegenerative diseases like PD is the selective loss of neurons, with the most significant loss occurring in the substantia nigra pars compacta region of the brain [5].

However, research has shown that Lewy bodies are not confined to the substantia nigra but extend throughout the brain. Based on the distribution of alpha-synuclein pathology, a staging scheme proposed by Braak and colleagues outlines the progressive spread of neuronal pathology in PD [6].

This scheme is based on the idea that the initial steps of the illness are characterized by neurodegeneration in the dorsal nuclei of the vagus in the medulla and anterior olfactory nuclei in the olfactory bulb. In the course of the PD, the locus ceruleus in the pons and the substantia nigra pars compacta dopaminergic neurons are affected largely [7].

Pathology of the connections between the brains defeat more and more areas of the brain, including the basal forebrain, amygdala, and medial temporal lobe structures. Finally, cortical areas on the surface of the brain getting affected by the disease [5].

This staging scheme provides insights into the spread of pathology in PD, aiding in understanding its progression and potentially informing therapeutic interventions.

2. CURRENT TREATMENT APPROACHES FOR PARKINSON'S DISEASE

Pharmacologically, the mainstay of Parkinson's disease treatment is levodopa, often combined with Carbidopa to reduce side effects and enhance its effectiveness in the central nervous system [8]. In younger patients, dopamine agonists like Pramipexole or Ropinirole may be prescribed as initial therapy, although they may not be as potent as levodopa but are associated with fewer side effects. Anticholinergics or Amantadine may be utilized, especially if tremors

are the predominant symptom needing control [9].

Selegiline is commonly used in early-stage disease to provide mild relief of symptoms. However, most medications for Parkinson's offer satisfactory symptom management for around 3 to 6 years, after which disease progression often renders them less effective. Generally, younger patients are treated more aggressively than older individuals [10].

A comprehensive approach to Parkinson's management is crucial, involving a multidisciplinary team. Structured physical therapy tailored to Parkinson's patients can significantly improve balance, gait, and overall mobility [11].

Unique aspects of the condition, like rhythm and movement responsiveness, have been effectively utilized in therapies such as music therapy, cycling, and boxing. Addressing associated issues like depression, caregiver fatigue, constipation, REM sleep disorder, and psychosis is essential, as they can either be medication side effects or part of the disease itself [12].

However, some patients may develop medication resistance, experience abrupt motor fluctuations, or suffer from debilitating dyskinesias. Adjusting the pharmacokinetics of levodopa, through newer formulations like delayed-release versions or continuous infusion via a gastrointestinal pump, can be beneficial [13].

Additionally, deep brain stimulation (DBS) techniques targeting specific brain regions like the subthalamic nucleus or globus pallidus have shown promise in managing treatment-resistant symptoms, although the exact mechanism of their effectiveness is still being explored. Overall, DBS offers new hope for advanced Parkinson's patients and represents an area of active research and progress [14].

3. EXPLORING THE USAGE OF GLP-1 AGONISTS IN THE TREATMENT OF PARKINSON'S DISEASE

Currently, the focus of Parkinson's disease (PD) treatment aims at developing drugs that not only replenish dopamine levels but also potentially slow down disease progression. GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide) receptor agonists have emerged as potential neuroprotective agents by mitigating neuronal insulin resistance in various preclinical models [15].

Like agonists of Glucagon-like Peptide-1 (GLP-1) receptor, especially in the treatment of diabetes type 2, by binding to GLP-1 receptors, they will cause insulin secretion in pancreas. Although GLP-1 receptors are also seen in the brain, it is hypothesized that they can be known to be potential aids in the treatment of Parkinson's disease (PD) [16,17].

Additionally, insulin signaling inhibits apoptotic cell signaling. Research indicates desensitized insulin signaling in the brains of PD patients, possibly explaining the association between type 2 diabetes and PD risk. GLP-1 receptor agonists are typically administered via subcutaneous injection [18].

The utilization of animal models has been instrumental in unraveling the underlying pathophysiology of PD and the formulation of therapeutic approaches. However, it is important to note that each animal model has its unique characteristics, and there is not a single model that fully recapitulates all aspects of human PD [17].

Despite disparities in clinical manifestations between animals and humans, locomotor tests in animals assess parameters like bradykinesia, diminished motor activity, tremors, muscle rigidity, and motor coordination. Additionally, neurobehavioral assessments in animals encompass aspects such as anxiety, depression, and memory loss [19].

Efforts will be made in this study to align outcomes from animal models with clinical observations in humans wherever feasible. Morphological findings in animals will also contribute to investigating mechanisms of action applicable to both animals and humans. Naturally, the subsequent discussion will address the utility and constraints of existing PD animal models [20].

Clinical trials for neurodegenerative diseases like Parkinson's disease (PD) face the challenge of distinguishing between the symptomatic effects and disease-modifying effects of potential therapeutic agents [21].

Conventional clinical assessment scales used in PD trials, such as those measuring motor

impairment or quality of life, cannot discern between these two types of effects. Therefore, to demonstrate disease modification, a novel treatment must show evidence of halting or slowing disease progression over time, typically evidenced by the absence of deterioration in clinical outcomes compared to a control or placebo group [22,23].

However, various confounding factors may influence therapeutic effects. For instance, GLP-1 has been associated with weight loss, while levodopa, a common PD medication, shows reduced effectiveness with higher body weight. Therefore, understanding the potential impact of GLP-1-induced weight loss on PD treatment outcomes is crucial in studying GLP-1 receptor agonists in PD therapeutics [24].

4. THE IMPACT OF INTORDUCING GLP-1 AGONISTS FOR THE TREATMENT OF PARKINSON'S DISEASE IN THE LONG TERM

Recent advancements in understanding the neuroprotective effects of incretin-based therapies, particularly GLP-1 receptor agonists, have sparked significant interest in their potential repurposing as treatments for various neurodegenerative disorders, including Parkinson's disease (PD). Encouraging findings from clinical trials have fueled this interest further [25].

For instance, individuals with PD who participated in an open-label clinical trial of Exenatide demonstrated clinical improvement, with subsequent evidence revealing sustained motor improvement even 12 months after discontinuing the medication [26].

Similarly, a recent double-blind clinical trial showed that PD patients treated with Exenatide exhibited improved motor function 60 weeks post-medication cessation, while those on placebo experienced worsened motor symptoms [27].

Given these promising outcomes, there is a pressing need for a comprehensive review of GLP-1 receptor agonists in the context of PD. Such a review will not only summarize the current evidence but also provide a foundational platform for updating the evidence base as results from additional studies become available.

This aims to consolidate the existing knowledge and inform future research directions in exploring the therapeutic potential of GLP-1 receptor agonists in PD management.

Moreover, there is also a favoring fact that the current strategies to reduce alpha-synuclein levels for Parkinson's disease (PD) treatment has yielded disappointing results in clinical trials [28].

This suggests that the "misfolding protein" hypothesis may not be the most fruitful avenue for therapeutic development. Instead, there is growing excitement around the potential of growth factors like GLP-1, which can penetrate the blood-brain barrier (BBB), to offer substantial benefits to PD patients [29].

Indeed, emerging evidence indicates that growth factors such as GLP-1 have demonstrated remarkable effects in PD patients, pointing to their potential as the future of drug discovery in PD treatment.

By focusing on agents like GLP-1 that can effectively traverse the BBB and exert neuroprotective effects, researchers may uncover novel and more effective therapeutic approaches for managing PD. This shift in focus reflects a paradigmatic change in the understanding and treatment of PD, signaling a promising new direction in the field of neurodegenerative disease research [30].

5. CONCLUSION

Parkinson's disease (PD) poses significant challenges due to its complex and progressive nature. While traditional treatments aim to manage symptoms, recent advances have shifted focus towards disease-modifying therapies. GLP-1 receptor agonists, originally developed for diabetes treatment, have emerged as promising candidates for PD therapy due to their neuroprotective effects and ability to traverse the blood-brain barrier. Clinical trials investigating GLP-1 agonists such as Exenatide have shown encouraging results, with evidence of sustained motor improvement even after discontinuation of treatment. These findings underscore the potential of GLP-1 agonists to not only alleviate symptoms but also modify the course of PD.

However, challenges remain, including the need to differentiate between symptomatic and

disease-modifying effects in clinical trials and to address confounding factors such as weight loss. Moving forward, continued research efforts are essential to refine GLP-1 agonist therapy, elucidate underlying mechanisms of action, and explore novel treatment strategies. By leveraging the neuroprotective properties of GLP-1 agonists and advancing our understanding of PD pathophysiology, we can strive towards improved outcomes and better quality of life for individuals living with PD.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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