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THE TREATMENT OF PARKINSON'S DISEASE IN RELATION TO MULTIPLE
THERAPIES AND THE FUTURE

by

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Abstract

Parkinson's disease has become a growing issue worldwide and has yet to be presented with a cure. Various treatment methods have been introduced that include physical exercise, genetic therapy, pharmacological treatment, and/or alternative methods. An extended literature review was conducted evaluating numerous articles and focus was given to an ongoing research project in an effort to present current information. As a result, various routes of effective treatment have been evaluated for treating Parkinson's diseases by observing if symptoms or the progression/prevention of the disease is hindered/reduced. Thus, a summary is given concerning what methods are effective in treating the disease. Regarding the future, suggestions are given considering what can be done to improve current methods and what other opportunities may be available. In all, this thesis presents a discussion of Parkinson's disease in terms of its history, current methods of treatment, and future studies.

KEY WORDS: Parkinson's disease, Rock Steady, levodopa, physical exercise, DOPAL

Table of Contents

Introduction

From an international perspective, health and quality of life are a common goal that all countries share, as demonstrated by the progress made within the past century towards increasing life expectancy (Senior Living, 2017). However, there are various health issues that still exist that have yet to be cured. One primary example that needs to be addressed is Parkinson's disease, which is the second most common neurodegenerative disease in the United States (Earhart & Williams, 2012). Based on the U.S. 2010 census, approximately 680,000 people at the age of 45 and older suffer from this disease (Marras et al., 2018). Overall, it is estimated by 2020, this number will rise to 930,000, and by 2030, to 1,238,000 (Marras et al., 2018). Therefore, society needs to begin to understand this disease, as it is becoming an increasing threat to the well-being of the population. Explicitly, the older population holds the most considerable risk, with the average age of diagnosis being 60 years old (Michael J. Fox Foundation, 2019). In all, in order to treat this threatening issue, its history and biology must be understood to determine an effective method by which this disease can be treated.

In 1817, a man by the name of James Parkinson became the first person to define Parkinson's disease (Mhyre et al., 2012). Initially, it was referred to as "shaking palsy" due to the tremors experienced (Jankovic, 2008; Mhyre et al., 2012). Altogether, Parkinson wrote *An Essay on Parkinson's Disease* in 1817, which sought to describe the disease (Obeso et al., 2017). Throughout the rest of history, more information became known about the disease as discoveries were continually made through various studies. For example, a discovery in the brain that has allowed scientists to begin to understand the pathology of Parkinson's disease is the presence of Lewy bodies, which are intracellular protein aggregates that have been identified as a causative

factor (Mhyre et al., 2012). Thus, as progress has been made over time, the overall perception of why Parkinson's disease occurs has developed.

Currently, research has attributed the cause of Parkinson's disease to a metabolite called 3,4-dihydroxyphenylacetaldehyde, which is referred to as DOPAL (Burke et al., 2008). Altogether, when analyzing the biology of Parkinson's disease, DOPAL has been shown to have a toxic effect on the brain (Burke et al., 2008). Specifically, the substantia nigra, which helps control movement by processing feedback, is affected by DOPAL (Brown et al., 2014; Burke et al., 2008). Thus, Lewy bodies accumulate in the substantia nigra, which causes feedback to malfunction (Burke et al., 2008). As a result, this has led to four cardinal motor symptoms forming as a result. The first symptom that characterizes Parkinson's disease is a tremor, which is often demonstrated by a shaking of the hands (Jankovic, 2008). The second symptom is rigidity, which is the inability to complete movements without some resistance from the contraction of the muscles within the body (Jankovic, 2008). Third, bradykinesia is a physical trademark of Parkinson's disease. It is typically described as slow movement, and it can be observed by how those with Parkinson's disease shuffle their feet when they walk (Jankovic, 2008). Last, postural deformity occurs, which is typically exemplified by the back and/or neck being extremely flexed (Jankovic, 2008). Additionally, this can also occur in the legs, leading to instability (Jankovic, 2008). As a result, falling can be common. Aside from motor symptoms, non-motor symptoms also occur. These include cognitive disorders, depression, constipation, rapid eye movement disorder, and olfactory dysfunction (Zhang et al., 2016). Altogether, the complexity of Parkinson's disease and its wide range of symptoms has made it difficult for scientists to find a cure that is able to address each aspect of the disease

Presently, no cure has been found for Parkinson's disease. Therefore, therapeutic methods have been introduced in order to alleviate symptoms and improve quality of life (Zhang et al., 2016). Thus, this issue at hand provides a list of questions that need to be answered:

- What therapies or methods are currently available that can treat the symptoms of Parkinson's disease?

- In light of there being many proposals for treatment, how many are effective and what factors of the disease does it treat?

- For the future, what therapies may be increasingly used or introduced?

- If possible, are there any hypotheses that are being tested in order to hopefully find a cure?

Throughout this thesis, various types of therapies will be discussed in terms of their effectiveness and what areas of the disease they impact. Thus, the overall quality of life for the patient, and the severity of the disease will be discussed. Then, the future of treatment will be considered in order to propose what specific methods will either be introduced or used more on a routine basis. Altogether, the hopes for a cure will be discussed as well in terms of what is being done to achieve this goal.

Review of Literature

After conducting research throughout various databases and reading a plethora of articles, three general categories were found that serve as a method of treatment. First, physical exercise has been shown to be the most diverse method as it contains a multitude of routes by which one can exercise to treat their symptoms. Second, genetics has been shown to be a route of treatment. However, very little work has been done within this field. Third, pharmacological methods have been utilized to reduce the symptoms of Parkinson's disease, but side effects have been shown to create a complicated situation. Fourth, various alternative therapies have been introduced in order to provide treatment. Finally, as research continues, the future of treatment will progress by either emphasizing certain treatments or introducing ideas that could lead to a cure. In all, when addressing current treatment, each category is a different route by which various scientists have attempted to alleviate the symptoms of Parkinson's disease. Therefore, it is critical to understand the impact of each category and its methods.

Physical Exercise as a Method for Treatment

Initially, when attempting to evaluate the efficacy of physical exercise, two articles were predominantly used to determine if this route was productive and significant. First, a study by Fabian David and Julie Robichaud (2015) was analyzed in which the cognitive factor of the disease was assessed in relation to resistance and strengthening exercises. Overall, this article was chosen due to its specific focus on the topic of cognitive benefits and its usage among the scientific community with 59 total citations. Within the article, 38 patients were split into two groups, and one participated in resistance exercises while the other took part in strengthening exercises (David et al., 2015). Altogether, each group experienced cognitive benefits that improved working memory and conflict resolution (David et al., 2015). However, the resistance

group experienced improvements in selective attention as well (David et al., 2015). In all, this article displayed that physical exercise benefits the non-motor symptoms of Parkinson's disease. In the second article by Franciele Cascaes da Silva and Rodrigo da Rosa Iop (2018), motor symptoms were assessed by addressing various methods such as tango dancing and Wii-Fit. Within the study, nine different articles were evaluated that discussed these physical exercises and, it was found that motor symptoms did improve, as shown in specific methods such as Wii-Fit and treadmill training (da Silva et al., 2018). Overall, this article reinforced the concept of utilizing physical exercise as a method of treatment as well.

Aside from the advantages of physical exercise, the disadvantages also need to be addressed. In a study done by Terry Ellis and Jennifer Boudreau (2013), 96 patients with idiopathic Parkinson's disease were evaluated for why they did not consistently exercise each week to improve their health. These participants stated that low outcome expectations, lack of time, and fear of falling were the three primary reasons why they did not partake in physical exercise programs (Ellis et al., 2013). Therefore, the patients explained that they did not expect to reap any significant benefits while also believing that they did not have enough time to exercise. Additionally, the fear of falling, which was most likely due to postural instability, was described as limiting their motivation (Jankovic, 2008). Through this study, it can be shown that limitations do exist within this methodology, as the symptoms of this disease decrease motivation and belief that improvements can occur. Aside from these three limitations, an additional barrier was also found to exist. Due to those with Parkinson's disease typically being older, physical degeneration must also be taken into account as a potentially limiting factor (Michael J. Fox Foundation, 2019). Therefore, orthopedic surgery may be necessary as the hip, knee, or spine can be damaged from prolonged constant pressure. In addition, orthopedic surgery

has been found to be a limitation for those who want to undergo physical treatment based on a study by Catherine C. Price and Shellie Anne T. Levy (2015). Within the study, eight patients with Parkinson's disease were admitted into the test (Price et al., 2015). Altogether, three of the participants had not undergone orthopedic surgery, while the other five had undergone a procedure (Price et al., 2015). Overall, it was found that orthopedic surgery was associated with cognitive decline, thus labelling it as a potential factor that would inhibit treatment (Price et al., 2015). In the end, these were the only two articles found that addressed limitations as no other studies specifically addressed any other limitations such as lack of motivation and procedures that may inhibit treatment.

After conducting this initial research on physical exercise as a method for treatment, specific routes were then researched in order to examine what was offered and how effective the procedures were. Thus, an article by Jie Dong and Yanhua Cui (2016) was selected, as it involved a review of a multitude of physical treatment methods. Altogether, Tai Chi, dance, and yoga were some of the main mechanisms discussed, and they were found to produce motor benefits such as improved balance, strength, and flexibility (Dong et al., 2016). When conducting research specifically on these methods, an article by Xiaojia Ni and Shaonan Liu (2014) was found that addressed Tai Chi. Within the procedure, these authors analyzed Tai Chi by collecting various articles about the subject and evaluating them to determine which ones were the most reliable and impactful (Ni et al., 2014). Overall, it was found through the article that Tai Chi was shown to improve mobility along with the quality of life (Ni et al., 2014). Concerning dance, an article by Kristi Michels and Ornella M. Dubaz (2018) was found that addressed dance as a method of treatment. In the procedure, 13 patients with Parkinson's disease were split into groups where only one participated in dancing for 10 weeks (Michels et al., 2018). After the

study, the two groups were then compared in order to analyze the benefits of dancing. The patients within the exercise group were found to improve emotionally, mentally, and physically (Michels et al., 2018). Therefore, it was supported that dance is a potential physical method of treatment. Finally, when addressing yoga, a study by Marieke Van Puymbroeck and Alysha A. Walter (2018) was chosen as it specifically addressed the disease by having 30 patients with Parkinson's disease partake in the experiment. Within the procedure, the 30 participants were split into a control group and yoga group. Then, an eight-week program began for the yoga group, and at the end of the trial, the groups were compared. Altogether, it was discovered that motor symptoms for the yoga group improved significantly in factors such as balance and posture (Van Puymbroeck et al., 2018). In another article, the authors, Corjena Cheung and Rozina Bhimani (2018), also tested yoga in relation to Parkinson's disease. Within the study, 20 patients with Parkinson's disease were chosen to undergo a 12-week program. Every week, the patients would participate in two hour-long sessions of yoga (Cheung et al., 2018). In order to provide results, the participants were evaluated at baseline, 12 weeks, and six months post-intervention (Cheung et al., 2018). In all, motor symptoms were shown to improve in the participants when they were examined post-intervention (Cheung et al., 2018).

When looking for other methods not mentioned by Dong and Cui, several other programs were found. For instance, treadmill training was addressed in an article by Gammon M. Earheart and April J. Williams (2012). Within the procedure, 203 patients were chosen that had Parkinson's disease with severity ranging from stages one to three based on the Hoehn & Yahr scale (Earhart & Williams, 2012). Each participant underwent evaluations that assessed gait, walking speed, freezing of gait, the severity of symptoms, and quality of life (Earhart & Williams, 2012). Then, sessions on the treadmill were conducted and, evaluations were taken

post-intervention (Earhart & Williams, 2012). Overall, each field was shown to improve, along with no adverse events occurring (Earhart & Williams, 2012). In another study by Lisa M. Shulman and Leslie I. Katzel (2013), treadmill training at different intensities was compared to strength and resistance exercises. A total of 60 patients with Parkinson's disease were tested, and it was shown in every type of exercise that improvements in fields such as VO2 peak and distance walking were observed (Shulman et al., 2013). In comparison to strength and resistance exercises; however, treadmill training showed better results for VO2 peak while only strength benefits came from the strength and resistance exercises (Shulman et al., 2013). In all, treadmill training was verified by each study as a method of treatment for Parkinson's disease that specifically affected motor symptoms (Earhart & Williams, 2012; Shulman et al., 2013). Aside from these sources, no articles were found in order to provide further data relative to treadmill training.

Concerning another method of treatment, it was found that in an article by Alessandro Picelli and Stefano Tamburin (2014), robot-assisted arm training was tested to evaluate if motor improvements would occur. In total, 10 patients with idiopathic Parkinson's disease underwent five training sessions a week, for two weeks where a robot-assisted them in passive and active movements of the right arm (Picelli et al., 2014). By the end of the experiment, the functionality of the arm and hand was shown to have improved, but the quality of life showed no changes (Picelli et al., 2014). This lack of change could have possibly been attributed to the procedure having no long-term follow-ups (Picelli et al., 2014). In the end, if another trial were to occur, long-term follow-ups would need to be utilized. Altogether, when looking for additional data on robot-assisted training in relation to Parkinson's disease, no other articles were found.

Another trial that has been proposed is boxing training. In an article by Stephanie A. Combs and Dyer Diehl (2011), seven male patients with Parkinson's disease joined the program, Rock Steady Boxing, for a total of 12 weeks. Within the program, the participants engaged in exercises that activated the upper and lower body through activities such as punching and shuffling of the feet (Combs et al., 2011). At the end of the experiment, improvements in mobility, balance, and quality of life were observed (Combs et al., 2011). Overall, boxing was shown to be a potential method of treatment, but further studies would need to be conducted that involved females, as only males participated in the trial. When looking for further information, no other articles were found that reinforced or debated the results of the study.

Finally, one last physical exercise that has been presented is a balance program. In a study by David W. Sparrow and Tamara R. DeAngelis, 23 patients with idiopathic Parkinson's disease were separated into two groups that would each undergo a three-month balance program and a three-month period of inactivity (Sparrow et al., 2016). Overall, balance and fear of falling were assessed utilizing various tests such as the Falls Efficacy Scale-International and the Mini-BESTest (Sparrow et al., 2016) Altogether, it was observed that improvements occurred for each group (Sparrow et al., 2016).

Genetics as a Method for Treatment

Within the past decade, research within genetics has become a topic for addressing Parkinson's disease (Lin & Farrer, 2014). This is due to various experiments, such as a genome-wide association study that was able to identify 11 different loci in Parkinson's disease patients (Lin & Farrer, 2014). Altogether, the linkage between genetic mutations and Parkinson's disease has been supported and led to research ventures in order to develop genetic methods of treatment (Lin & Farrer, 2014).

In the article by Dong and Cui (2016), gene therapy was introduced as a potential method of treatment in order to reverse the effect of the defective genes. Methods, such as using a vector to import a carried gene, have been tested and shown to improve the severity of symptoms (Dong et al., 2016). In a study conducted by Raymond T. Bartus, Marc S. Weinberg, and Richard Jude S. Samulski (2014), five different gene therapies were utilized in order to evaluate if benefits would be reaped. First, adeno-associated viral vectors and glutamic acid decarboxylase were used to see if motor control would improve (Bartus et al., 2014). Within the trial, 45 subjects with Parkinson's disease were selected with 50% undergoing treatment, while the other half was a sham group (Bartus et al., 2014). After conducting the trial, a difference of 3.4 points was observed in the Unified Parkinson's Disease Rating Scale based on a clinician-scored motor evaluation (Bartus et al., 2014). Despite these positive results, the clinical effects were observed to be minimal overall. For example, five subjects were eliminated from the study after the trials as the magnetic resonance imaging showed that the injections were off-target (Bartus et al., 2014). Additionally, when the PDQ-39 was used to evaluate the health status of the subjects, 21 efficacy points out of 39 were observed to show no difference before and after treatment (Bartus et al., 2014). Overall, it was concluded that the results were shown to be minimal and insignificant (Bartus et al., 2014).

In the second trial, adeno-associated viral vectors and aromatic L-amino acid decarboxylase were used to enhance dopamine levels (Bartus et al., 2014). Before human trials, 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine was used on monkeys to replicate the symptoms of Parkinson's disease, as this compound has been found to target the same neurons that degenerate the brains of those with the disease (Bartus et al., 2014; Sian et al., 1999). After conducting the trial on the primates, the process was shown to be safe and moved forward to

human clinical trials. In the selection process, 15 humans with moderately advanced Parkinson's disease were chosen (Bartus et al., 2014). Due to clinical difficulties, treatment did not begin for another year, as the program shifted companies and locations (Bartus et al., 2014). However, after the period of waiting, two separate trials were conducted 10 years apart that both targeted the putamen, which is a structure in the brain concerned with movement and learning (Bartus et al., 2014; Mehrnoosh Ghandili & Sunil Munakomi, 2019). In both trials, the dosage was a topic of debate. Concerning the putamen, one trial was shown to cover 30-40% of the structure but only resulted in 5-6% of AADC-expressing neurons being activated (Bartus et al., 2014). Thus, the dosage in relation to volume and density remains uncertain, and further study is still needed. Overall though, modest results were still shown for treating symptoms (Bartus et al., 2014).

For the third trial, Lenti-aromatic L-amino acid decarboxylase along with tyrosine hydroxylase and guanosine 5′-triphosphate cyclohydrolase1 were tested (Bartus et al., 2014). Within the procedure, 15 subjects with Parkinson's disease received injections to test the effectiveness of the infusions in relation to the dosage amount (Bartus et al., 2014). Overall, three-ascending doses were tested that each consisted of a five-fold dose range (Bartus et al., 2014). By the end of the trials, modest improvements were observed (Bartus et al., 2014). For example, the patients' scores for the Unified Parkinson's Disease Rating Scale experienced improvements six and 12-months after the treatment started (Bartus et al., 2014). In terms of adverse events, no severe complications occurred and were deemed unrelated to treatment (Bartus et al., 2014). However, it was found that when L-dopa dosage was lowered, the level of dyskinesia being experienced also lowered (Bartus et al., 2014). In the end, the treatment was still deemed as relevant despite the complications experienced by the patients (Bartus et al., 2014).

Concerning the fourth trial, adeno-associated viral vectors and neurotrophic factors were evaluated. Within the procedure, two phase two trials were conducted that appeared to have disappointing results in terms of improving motor abilities (Bartus et al., 2014). However, it was shown that improvements did occur in aspects, such as quality-of-life (Bartus et al., 2014). In order to improve this process, another protocol was conducted that introduced changes such as increasing the dose and volume of the vector to the putamen (Bartus et al., 2014). Other changes that occurred were that the subthalamic nucleus was targeted to a greater extent, while the blind assessment period was extended for several months (Bartus et al., 2014). Based on trials with animals, the hypothesis was that these changes would improve the biological responses to the injections (Bartus et al., 2014). After conducting this phase of trials, similar results occurred as in the initial phase two trials (Bartus et al., 2014). Thus, the methodology was reevaluated, and it was determined that the treatment might be ineffective due to a poor therapeutic gene transport system to the pathological brain tissue. (Bartus et al., 2014). As a result, the dosage was increased by three- to four-fold while the volume per injection increased by 10-fold in the putamen alone (Bartus et al., 2014). In order to ensure an active repair of neurons in the subthalamic nucleus, a sizeable dosage was also injected into the degenerating cells of this location (Bartus et al., 2014). By the end of this trial, significant results still did not occur (Bartus et al., 2014). Thus, it was concluded that merely improving the blanket gene delivery coverage may not result in improvements of symptoms (Bartus et al., 2014). In terms of other factors, the structure of the brain was then assessed to see if possible axonal damage may have occurred (Bartus et al., 2014). If damage did occur, then it was possible that the injection was not reaching the putamen (Bartus et al., 2014). After conducting an autopsy of a human brain with Parkinson's disease and comparing it to an animal brain also diagnosed with Parkinson's disease,

it was observed that the neuronal pathology was more severe in the human brain (Bartus et al., 2014). Thus, it was acknowledged that in order to produce improvements, animal models needed to greater reflect clinical conditions (Bartus et al., 2014). As a result, this would then allow future experiments to effectively target certain areas of the brain (Bartus et al., 2014).

Finally, adeno-associated viral vectors and glial-derived neurotrophic factors were assessed (Bartus et al., 2014). As in the fourth trial, no significant improvements were observed to have occurred (Bartus et al., 2014). Thus, the issue of axonal damage was also addressed (Bartus et al., 2014). Overall, no further progress was made in the trials, as it was stated that more information was needed in order to determine if axonal damage was a factor or not (Bartus et al., 2014)

Altogether, when searching for further articles on gene therapy, an article by Amaal AlDakheel and Lorraine V. Kalia (2013) discussed kinase inhibitors and α-synuclein-directed therapies. Regarding kinase inhibitors, the target of the inhibitor would be a mutated LRKK2 gene, which is the most common genetic cause of autosomal dominant Parkinson's disease (AIDakheel et al., 2013). Thus, it has been hypothesized that if the toxic kinase activity of an LRKK2 gene can be inhibited, then it can result in a disease-modifying effect (AIDakheel et al., 2013)

Concerning the α-synuclein gene, its mutation is associated with the pathogenesis of Parkinson's disease due to it being responsible for the formation of Lewy bodies, which are hallmarks of Parkinson's disease (AIDakheel et al., 2013). Additionally, the α-synuclein mutation has also been associated with Parkinson's disease due to the event that its oligomers aggregate, which leads to the most toxic forms of α-synuclein being created (AIDakheel et al., 2013). As a result, this toxic formation can result in neuronal dysfunction and death (AIDakheel

et al., 2013). In order to combat Parkinson's disease, it was hypothesized that the correction of this mutated gene would result in neuroprotection, thus inhibiting any further progression (AIDakheel et al., 2013). In terms of addressing the issue, a vaccine route is being pursued where antibodies would destroy the mutated gene (AIDakheel et al., 2013). For methods that have been proposed but not pursued, a variety is available. For example, directly blocking α-synuclein aggregation with monoclonal antibodies, short peptides, or small molecules has been proposed (AIDakheel et al., 2013). Additionally, the promotion of chaperone function could cause α-synuclein clearance (AIDakheel et al., 2013). Finally, RNA interference technology has also been proposed to reduce the levels of harmful proteins present (AIDakheel et al., 2013).

In all, the methods proposed were deemed likely to hold potential for treatment, but were still in the early stages of testing and not fully confirmed as effective (AIDakheel et al., 2013). With regards to the future, gene sequencing will need to continue in order to identify if there are more loci associated with Parkinson's disease (Lin & Farrer, 2014). In terms of research, no other sources were found that directly addressed Parkinson's disease. Therefore, these articles were chosen as they were the only ones found that were reliable.

Pharmacological Therapies as a Method for Treatment

Another aspect of treatment for Parkinson's Disease is the pharmacological field, which consists of a variety of methods that have been tested in order to determine which drugs are useful for treating various symptoms or improving motor skills. Currently, levodopa-carbidopa, a capsule taken orally, is the first choice for symptomatic treatment (Rizek et al., 2016). It has been shown to have a better, more controlled effect on motor symptoms in comparison to other methods such as dopamine agonists (Rizek et al., 2016). Within a study conducted by Lin-Lin Gao, Jia-Rong Zhang, Piu Chan, and Ta Wu, 30 patients with Parkinson's disease were treated

with levodopa-carbidopa to examine its effects on the basal ganglia motor circuit (Gao et al., 2016). Regarding the basal ganglia motor circuit, it is a necessary component in the brain for conducting motor and cognitive skills that can be affected by Parkinson's disease by decreasing its connectivity for neural communication (Caligiore et al., 2017; Gao et al., 2016). As a result, this has been found to lead to bradykinesia (Gao et al., 2016). For comparison, a control group of 30 participants without Parkinson's disease were collected and studied as well (Gao et al., 2016). At the end of the study, levodopa-carbidopa was found to rebuild connectivity for the basal ganglia motor circuit and other various regions of the brain, with the most significant motor benefits being reaped on the side most affected by the disease (Gao et al., 2016). Specifically regarding bradykinesia, its effects were also shown to be reduced (Gao et al., 2016). Altogether, various limitations were addressed in the study that pertained to the lack of observation of other symptoms, such as tremor and rigidity (Gao et al., 2016). No other analyses were conducted for other antiparkinsonian medications to observe their effect on the basal ganglia motor circuit (Gao et al., 2016). Concerning rigidity, another study was conducted by Philippe Rizek, Niraj Kumar, and Mandar S. Jog that found that rigidity was improved with levodopa-carbidopa treatment (Rizek et al., 2016). Within this study, levodopa-carbidopa was found to be beneficial, but various limitations of the drug were addressed. It was observed in patients that after taking levodopa-carbidopa treatment, dyskinesia was shown to have been inducted as a result (Rizek et al., 2016). In another study, dystonia was also shown to be induced by levodopa-carbidopa (Obeso et al., 2017). Due to these side effects, dopamine agonists, despite their lesser potential for effective treatment, have been introduced as a possible initial treatment (Rizek et al., 2016). However, it was shown that after 10 years of taking this medication, the benefits diminished and were then equal to levodopa-carbidopa (Rizek et al., 2016).

A variation of the levodopa-carbidopa capsule that has been introduced as a potential method for treatment is a levodopa-carbidopa intestinal gel (Rizek et al., 2016). By utilizing percutaneous tube insertion, the gel is injected into the jejunum continuously for 16 hours every day (Rizek et al., 2016). In regards to safety, there is no age limit for the treatment, but it has been recognized that those with severe dementia may be unable to retain the jejunal tube (Rizek et al., 2016). Overall though, this method has been shown to lead to faster absorption of the medication compared to oral levodopa-carbidopa (Rizek et al., 2016). In a seven-year-long study of 59 patients with Parkinson's disease, 90% stated that they experienced improvements in quality of life and autonomy (Rizek et al., 2016). Only 19-26% reported discontinuation of the treatment method due to reasons such as adverse drug reactions, poor compliance, lack of efficacy, and adverse procedure/device-related events (Rizek et al., 2016). Altogether, levodopa-carbidopa intestinal gel has been shown to be a viable option when considering a treatment that utilizes levodopa-carbidopa.

Another form of pharmacological treatment that has been introduced for Parkinson's disease is nonsteroidal anti-inflammatory drugs (Ren et al., 2018). Due to Parkinson's disease partially being caused by neuroinflammation, nonsteroidal anti-inflammatory drugs have been proposed as a method of treatment since they have been shown to eliminate inflammation of the limbs (Ren et al., 2018). As a result, nonsteroidal anti-inflammatory drugs have been used widely in clinical settings (Ren et al., 2018). However, there are concerns regarding the link between liver damage and nonsteroidal anti-inflammatory drugs (Ren et al., 2018). This is primarily due to the various chemicals present that can be toxic for the liver when processed (Bessone, 2010). For example, salicylic acid, which is used in aspirin, can trigger mitochondrial dysfunction (Bessone, 2010). This leads to a decrease in intracellular adenosine triphosphate, which can then

result in lethal hepatocellular injury (Bessone, 2010). Overall, it has been reported that 10% of the total drug-induced hepatotoxicity incidents are related to nonsteroidal inflammatory drugs (Bessone, 2010). Altogether though, the rate of occurrence concerning these drugs and liver damage is low, as an estimated 0.29 to 3.1 people per 100,000 exposed have been found to have issues (Bessone, 2010). Thus, this route of treatment has been deemed safe, as it holds minimal risk for the user (Bessone, 2010).

Regarding specific goals in relation to pharmacological treatment, a study done by Amaal AlDakheel and Lorraine V. Kalia (2013) utilized drugs and multiple substances to focus on the subjects of neuroprotection and disease modification. In the study, antioxidants and mitochondrial enhancers were addressed along with dopamine agonists and L-dopa (AIDakheel et al., 2013). Additionally, trophic factors and other methods, such as apoptosis drugs, were also utilized (AIDakheel et al., 2013). Altogether, the results of the study were not conclusive, and it was suggested that further studies needed to be conducted. In another study, neuroprotection and disease modification were also addressed by using metabotropic glutamate receptors as potential targets for neuroprotection (Masilamoni & Smith, 2018). This was due to their role in neuronal excitability, transmitter release, and long-term synaptic plasticity (Masilamoni & Smith, 2018). Overall, improved neuroprotective properties were obtained as a result (Masilamoni & Smith, 2018). In all, this study revealed that this methodology holds potential and requires further study for human applications (Masilamoni & Smith, 2018).

Despite the various benefits of pharmacological treatments, a variety of side effects have been reported for numerous drugs. First, the usage of pergoline and cabergoline, which are ergoline dopamine agonists, have been linked to fibrotic cardiac valve damage, as demonstrated in a study of 11,417 participants (Csoti et al., 2016). Second, pramipexole, which is another

dopamine agonist, has been shown to lead to cardiac insufficiency (Csoti et al., 2016). Third, dopamine agonists, along with amantadine, have been shown to cause peripheral edemas in the ankles and legs (Csoti et al., 2016). Overall, the study of numerous patients showed a prevalence ranging from five to 40 percent (Csoti et al., 2016). Next, it has been demonstrated that some Parkinson's disease medications prolong the QT interval for the beating heart (Csoti et al., 2016). As a result, drugs, such as budipine, have been shown to cause arrhythmia (Csoti et al., 2016). A fifth side effect that has been reported is that the frequent usage of catechol-O-methyltransferase inhibitors have been linked to diarrhea (Csoti et al., 2016). Additionally, dopa decarboxylase inhibitor benserazide has been observed to cause diarrhea on rare occasions (Csoti et al., 2016). Altogether, it has also been reported that these drugs have also been shown to cause liver failure (Csoti et al., 2016). Sixth, levodopa has been shown to influence insulin secretion, which can possibly result in pathological glucose tolerance and insulin resistance (Csoti et al., 2016).

Pertaining to the severity of complications, various drugs have been banned as a result of their associated complications (Rizek et al., 2016). Primarily, drugs that block dopamine receptors have been shown to result in parkinsonism, weakened motor skills, and neuroleptic malignant syndrome (Rizek et al., 2016). Thus, neuroleptics, antiemetics, tetrabenazine, and antihypertensives have been removed as medications for Parkinson's disease (Rizek et al., 2016). Specifically concerning those receiving monoamine oxidase B inhibitors, it has been recommended that meperidine not be taken as well, as this can lead to serotonin syndrome, which can include fever, confusion, death, and other various symptoms (International Anesthesia Research Society, n.d.; Rizek et al., 2016).

Finally, the usage of antiparkinsonian medications can have negative implications, as the abrupt withdrawal of this treatment can cause akinesia and neuroleptic malignant syndrome

(Rizek et al., 2016). Additionally, the abrupt discontinuation of dopamine agonists can cause withdrawal symptoms (Rizek et al., 2016). Overall, various other side effects can occur, such as levodopa-induced dyskinesia and dystonia (Obeso et al., 2017). Thus, when considering drugs for treatment, the side effects should be taken into consideration before usage, as the benefits can be equaled by the disadvantages.

In regards to a potential cure instead of a therapy, one particular hypothesis has been proposed. Within this idea, it has been suggested that a drug can be created that can break down DOPAL. Therefore, the progression of the disease will stop as a result. Currently, this hypothesis is being tested at Southeastern University, where a research team has been conducting experiments in order to yield DOPAL through various routes (Darby Huber et al., 2019). Overall, the goal of the team is to send off this product to another lab in hopes that it can then be studied to create an inhibitory drug (Darby Huber et al., 2019). Over time though, this task has been shown to be difficult, however, as it has been observed that DOPAL quickly oxidizes (Darby Huber et al., 2019). Thus, when DOPAL comes into contact with the atmosphere, it automatically breaks down due to the oxygen present (Darby Huber et al., 2019). As a result, modifications have been made by the research team to address this issue (Darby Huber et al., 2019). Within the past year, these modifications have allowed the research team to produce a pure yield of 20% (Darby Huber et al., 2019). In light of this success, the research team is currently focusing its efforts to now increase this yield by improving the routes used (Darby Huber et al., 2019). Additionally, the team is also introducing other possible routes, in hopes that a better method may be discovered (Darby Huber et al., 2019). In all, work is still being conducted by the research team at Southeastern University to produce higher yields so that more

products can be sent to other labs for research to create a DOPAL-inhibiting drug (Darby Huber

et al., 2019).

Alternatives Therapies as a Method for Treatment

When searching for various therapies for treatment, a multitude of procedures were found

that did not meet the criteria of the other three categories. Therefore, they were labelled as

alternative therapies. Concerning a study by Taehun Kim and Kiho Cho (2012), herbal medicines

were addressed in relation to treating Parkinson's disease. Within the study, 59 articles were

chosen that tested four different trials (Kim et al., 2012). First, herbal medicines, such as

Banisteriopsis caapi extract, were compared to placebo treatment. Second, herbal medicines were

compared to conventional medicines. Third, herbal medicines were combined with an active

drug and compared to the active drug being used solely. Finally, herbal medicines were

combined again with an active drug and compared to placebo treatment plus an active drug. In

all, once all the studies were completed, it was concluded that herbal medicines do not hold

potential solely as a method of treatment because of their minimal benefits for symptoms.

However, it was proposed that they may serve well as an adjunctive treatment to conventional

drugs (Kim et al., 2012). Overall, when analyzing other articles, Dong and Cui (2016) also

addressed herbal medicines within their article. Multiple benefits, such as improving

neuropsychiatric symptoms, were discussed, but no conclusive statements were given regarding

the overall effectiveness of herbal medicines (Dong et al., 2016). Concerning other articles,

multiple studies were conducted as well, but the results were not reliable. Therefore, the articles

discussed in this paragraph were deemed to be the only reliable results for discussion.

Next, an alternative method that has been proposed is deep brain stimulation. In the

article written by Dong and Cui (2016), this procedure is described as electrodes being implanted

in the brain in order to stimulate the subthalamic nucleus and globus pallidus internus. Overall, the goal is to dissociate both input and output information and block unusual signals through the cortico-basal ganglia loop (Dong et al., 2016). Within the study, it was reported that through this procedure, improvements occurred for dopaminergic neuron survival along with increased brain-derived neurotrophic factor levels in the substantia nigra and primary motor cortex (Dong et al., 2016). Altogether, it was stated that these improvements would help alleviate symptoms and provide neuroprotection (Dong et al., 2016). In another study conducted by Esra Doğru Hüzmeli and Atilla Yılmaz (2018), deep brain stimulation was tested in 24 patients with idiopathic Parkinson's disease. In all, after evaluations were conducted before and after the experiment, it was found that motor disabilities were reduced, and quality of life improved as a result (Hüzmeli & Yılmaz, 2018). Thus, deep brain stimulation was verified as useful for treating Parkinson's disease. Overall, these articles were chosen to analyze deep brain stimulation as they both discussed the process and the multiple benefits that could be reaped through the procedure.

Finally, one last alternative method that has been proposed is stem cell therapy (AIDakheel et al., 2013). Due to Parkinson's disease resulting in the loss of neurons, there is hope that cell transplantation therapy could possibly be able to restore these losses (AIDakheel et al., 2013). For example, animal trials in the past have yielded promising results (AIDakheel et al., 2013). Concerning human and stem cell therapy, transplants for various issues have occurred since 1980 (AIDakheel et al., 2013). However, controlled clinical trials have yielded insignificant results with no major improvements occurring (AIDakheel et al., 2013). Additionally, it has also been recognized that the complexity of Parkinson's disease may also be an issue (AIDakheel et al., 2013). For example, it has been observed that Parkinson's disease is caused by a widespread multisystem nature (AIDakheel et al., 2013). Thus, if the restoration of

dopaminergic cells was successful, the treatment may be ineffective. This is due to the most

disabling and treatment-resistant features of the disease occurring at the later stages, which

typically are less dependent on dopaminergic cells (AIDakheel et al., 2013). In the end, stem cell

therapy appears to be riddled with complexities and limitations, as human trials for various

issues have been relatively unsuccessful while Parkinson's disease is also complex and not easily

addressable (AIDakheel et al., 2013).

Methodology

For the methodology of the thesis, a quantitative extended literature review was chosen.

Primarily, this process was selected in order that a variety of therapies could be discussed from

an objective viewpoint. Thus, this would allow no bias towards a specific treatment. Data and a

variety of sources were initially verified before being used for the thesis through methods such as

investigating the author's credentials and the number of citations the article has. Concerning the

origin of the sources chosen, a vast majority of the articles were retrieved from Pubmed.gov,

which is a database sponsored by the U.S. National Library of Medicine and the National

Institutes of Health. The site only contains peer-reviewed articles and is utilized by scientists

around the globe for research projects and/or literature reviews. Therefore, the articles coming

from this database have been shown to be valid and containing information that is relevant and

accurate. Regarding the research at Southeastern University, the experiments being conducted

are supervised by the research professor in order that sound methodology and results are

obtained. Thus, the data collected is applicable. For the outline of the thesis, a logical order is

utilized, as the background information of the disease is presented first so that the reader can

understand the subject. Then, the various therapies are introduced in order to address the disease

and what can be done to cure or regulate it. Finally, future therapies and a conclusion are

presented in order to hypothesize the progression of treatment and what currently needs to be done.

Next, the topic of the thesis is finally discussed with the various therapies to treat Parkinson's Disease being presented. Concerning the order of the therapies evaluated, physical exercise was chosen to be the first subject, as it is the most prevalent form of therapy currently. Next, genetics was then discussed in order to provide a non-physical route of treatment. Then, pharmacological therapies were addressed. Finally, alternative therapies were then discussed last, as they are the outlier in terms of the therapeutic techniques used.

Last, the future of treating Parkinson's Disease is discussed in light of the methods presented along with the efforts being made to find a cure. Overall, this methodology functions to introduce the reader to a complex topic by providing general information concerning the disease. This is done in a logical manner that builds upon the data presented in previous sections. Thus, the reader should be able to understand the issue and what is being done to combat it in terms of the present and future.

Analysis of Data

Therapeutic Analysis

Presently, Parkinson's disease has developed into a nationwide issue, as millions of people have been found to be affected by the disease (Marras et al., 2018). Overall, the causative agent for this disease has been attributed to Lewy bodies, which aggregate in the brain and lead to neurodegeneration (Mhyre et al., 2012). Additionally, DOPAL works in conjunction with Lewy bodies, specifically in the substantia nigra, to cause motor feedback malfunctioning (Burke et al., 2008). As a result, various symptoms form, with the main four being tremors, rigidity, bradykinesia, and postural deformity (Jankovic, 2008). Altogether, other symptoms can develop

due to complications from the disease and therapies (Csoti et al., 2016; Price et al., 2015).

However, explicitly concerning therapies, the majority of therapies are primarily beneficial

rather than harmful.

Pertaining to physical exercises as a therapeutic method, various methods were tested and

found to improve quality of life. First, Tai Chi was utilized in an experiment and found to

improve mobility and quality of life (Dong et al., 2016). Second, dance was also tested and found

to improve the participants' emotional, mental, and physical levels (Michels et al., 2018). Third,

30 patients with Parkinson's disease underwent a yoga program and were able to improve their

motor abilities (Van Puymbroeck et al., 2018). Fourth, treadmill training involved two studies for

Parkinson's disease and resulted in improvements for gait, walking, freezing of gait, the severity

of symptoms, quality of life, distance walking, and VO2 peak (Earhart & Williams, 2012;

Shulman et al., 2013). Fifth, robot-assisted arm training was tested and led to improvements in

functionality for the arm and hand (Picelli et al., 2014). Sixth, boxing was a therapeutic method

that was shown to refine mobility, balance, and quality of life (Combs et al., 2011). Finally, a

balance program was utilized and improved balance and fear of falling (Sparrow et al., 2016).

Concerning genetics, five primary therapies were tested in order to observe if the severity

of symptoms for Parkinson's disease could be improved (Bartus et al., 2014). The first trial

involved adeno-associated viral vectors and glutamic acid decarboxylase, with 45 subjects split

between a treatment group and a sham group (Bartus et al., 2014). Overall, the treatment had

minimal results, as there was only a 3.4 point difference in the Unified Parkinson's Disease

Rating Scale between the groups (Bartus et al., 2014). The second trial involved adeno-

associated viral vectors and aromatic L-amino acid decarboxylase in enhancing dopamine levels

(Bartus et al., 2014). Altogether, two trials were conducted with modest results occurring for

alleviating symptoms (Bartus et al., 2014). For the third trial, Lenti-aromatic L-amino acid decarboxylase along with tyrosine hydroxylase and guanosine 5′-triphosphate cyclohydrolase1 were tested among 15 subjects with Parkinson's disease (Bartus et al., 2014). In the end, modest results also occurred with some minor complications (Bartus et al., 2014). Fourth, adeno-associated viral vectors and neurotrophic factors were tested in three different trials (Bartus et al., 2014). Improvements in quality of life and motor abilities were observed, but the methodology was reevaluated due to unsatisfactory therapeutic gene transport system to the pathological brain tissue (Bartus et al., 2014). Thus, future studies were advised for improving mechanisms to target the brain (Bartus et al., 2014). Finally, the fifth trial involved adeno-associated viral vectors and glial-derived neurotrophic factors with no significant improvements occurring (Bartus et al., 2014). Altogether, other possible therapeutic methods were discussed in other articles pertaining to kinase inhibitors and α-synuclein-directed therapies (AIDakheel et al., 2013). In all, other viable methods were discussed for treating Parkinson's disease in light of its pathology (AIDakheel et al., 2013).

Regarding pharmacological therapies, levodopa-carbidopa capsules have been shown to have positive effects on improving the effects of Parkinson's disease (Rizek et al., 2016). However, dyskinesia dystonia can be induced as a result (Obeso et al., 2017; Rizek et al., 2016). Thus, dopamine agonists have been used as a replacement (Rizek et al., 2016). Another method of treatment that has been proposed is a levodopa-carbidopa intestinal gel, which is a variation of the capsule (Rizek et al., 2016). Altogether, it is a relatively safe method and can result in faster absorption with improvements in life and autonomy (Rizek et al., 2016). A third method that has been proposed is nonsteroidal anti-inflammatory drugs, which have been shown to reduce inflammation (Ren et al., 2018). Overall, issues have arisen concerning the possibility that these

drugs cause Parkinson's disease (Ren et al., 2018). However, studies have shown not to be inaccurate (Ren et al., 2018). As a result, nonsteroidal anti-inflammatory drugs hold potential as a method of treatment (Ren et al., 2018). Finally, neuroprotection and disease modification were addressed by utilizing various types of drugs (AIDakheel et al., 2013; Masilamoni & Smith, 2018). Overall, varied results were obtained depending on the method of treatment, but routes, such as using metabotropic glutamate receptors as potential targets, resulted in improved neuroprotection (AIDakheel et al., 2013; Masilamoni & Smith, 2018). In all, the side effects of numerous treatments have become a concern, as various symptoms or issues can arise (Csoti et al., 2016; International Anesthesia Research Society, n.d.; Obeso et al., 2017; Rizek et al., 2016). Thus, care must be taken when utilizing drugs, as the benefits must outweigh the disadvantages. In all, a cure rather than a therapy is currently being researched at Southeastern University and could hold great promise for treating the disease in the future (Darby Huber et al., 2019).

Finally, alternative therapies were tested for treating symptoms. First, neuroprotection and disease modification were addressed by evaluating various methods such as antioxidants and mitochondrial enhancers (AIDakheel et al., 2013). Overall, the results were inconclusive and in need of further studies (AIDakheel et al., 2013). Herbal medicines were then evaluated by analyzing three different methods, but all three were found to have no potential when used solely as a method of treatment (Kim et al., 2012). However, it was stated that herbal medicines might hold value when used in conjunction with conventional drugs (Kim et al., 2012). Deep brain stimulation was evaluated by examining two different studies and was found to be useful as a method for treatment (Dong et al., 2016; Hüzmeli & Yılmaz, 2018). Last, stem cell therapy was tested and yielded insignificant results with various complexities and limitations occurring (AIDakheel et al., 2013).

In all, physical, genetic, pharmacological, and alternative methods for treatment have been shown to yield benefits to various degrees. Exercise was found to contain the best chances of success, as the multitude of therapies yielded positive benefits. For genetic therapy, benefits were observed but were not as significant in comparison to physical therapeutic methods. Regarding pharmacological therapies, various benefits were also observed depending on the method used, but the numerous side effects presented complications concerning what medications should be used. Overall though, a pharmacological cure may be found through research hopefully. Finally, the various alternative methods addressed had a variety of results. For example, stem cell therapy was found to be insignificant, while deep brain stimulation was deemed effective (AIDakheel et al., 2013; Dong et al., 2016; Hüzmeli & Yılmaz, 2018). In all, the diversity of the alternative methods section requires looking at each therapy individually, as each proposed treatment addresses Parkinson's disease in its own unique manner.

Future Methods

Altogether, as a treatment for Parkinson's disease begins to progress, new methods will be introduced, and others will become more prominent. Therefore, when examining the sources discussed above, it can be acknowledged that some of these methods hold great potential. For example, gene therapy provides a great opportunity as the genome is currently being studied to discover Parkinson's-associated mutations that can be treated to reverse the effects or stop the pathological progression (AIDakheel et al., 2013; Lin & Farrer, 2014). Thus, if an effective method were to be found, then gene therapy may be widely used for treatment. Concerning pharmacological therapy, future research may yield different drugs that prevent Parkinson's disease or reduce the symptoms without causing severe side effects. Thus, therapies, such as nonsteroidal anti-inflammatory drugs, may hold potential for the future (Ren et al., 2018).

Another therapy that may increase in usage is robot assistance, as it has been demonstrated to improve the functionality of the hand and arm (Picelli et al., 2014). In all, when addressing the research being conducted at Southeastern University, additional routes are being examined to determine if other options may hold potential for yielding higher amounts of DOPAL (Darby Huber et al., 2019). As a result, the timeline for finding a cure has been extended, as various options are now being evaluated (Darby Huber et al., 2019). However, this possibly provides a higher chance of finding a cure, as more options will be available for synthesizing DOPAL (Darby Huber et al., 2019).

Conclusion

In all, a thorough review of literature has been conducted in order to assess the variety of treatments that are available for treating Parkinson's disease. Physical exercise, gene therapy, pharmacological therapy, and alternative methods were the primary treatments evaluated and each type was found to have numerous benefits. In the end, these assessments promoted a discussion of the future, as certain procedures may increase in usage. A hypothesis was also formulated in terms of addressing a possible new method that could provide a cure. Therefore, when evaluating this thesis, numerous approaches can be utilized to provide an understanding of what Parkinson's disease is and what can be done to treat it.

When addressing the future for this current study, the next step that needs to be taken is to conduct further research on the methods addressed above. For example, further investigation needs to occur for gene therapy, as no other potential sources have been found so far. Thus, the primary goal for the future should be directed towards reinforcing the methods that have already been introduced. In terms of finding new methods, further research will also need to be conducted to discover if more opportunities are available for treatment. In all, as this process continues, more of the details for each study will be expounded upon, as the steps for each experiment will be discussed along with the specific results. As a result, the study will continue to be up-to-date and able to provide current information on the progress being made towards the treatment of Parkinson's disease.

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