2024

Lifestyle Changes and Medication vs. Medication Alone: Symptom Control of Parkinson Disease

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By

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Master of Physician Assistant Studies, University of North Dakota 2024

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A Scholarly Project

Submitted to the Graduate Faculty of the University of North Dakota

in partial fulfillment of the requirements for the degree of

Master of Physician Assistant Studies

Grand Forks, North Dakota

May 2024

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Acknowledgements

It is with great pleasure I present this project. I would like to extend a special thank you and deepest appreciation to my advisor Julie Solberg PA-C, and Professor Russell Kauffman, PA-C for their guidance and critique of this project. I want to thank my classmate Brianna Droessler-Aschliman for taking the time to review this paper and provide feedback on formatting and grammar. I am grateful for my husband, Carter, who has not only supported me, but has also helped with review of this paper. Finally, I would also like to express my gratitude to my extended family for supporting me on my journey to becoming a physician assistant. Perhaps most importantly, I extend a very special acknowledgment to my grandfather who suffered from Parkinson disease and passed away in March of 2023. He inspired me to further research this topic.

Abstract

Parkinson disease is multifactorial, and predominantly affects the geriatric population. The mainstay of treatment for patients diagnosed with Parkinson disease is currently symptomatic treatment with dopamine replacement. The goal of this literature review is to identify possible lifestyle modifications that can delay progression of the disease or help prolong OFF time of symptoms. Lifestyle modification predominantly considered during this review included diet and physical activity. Included in the study were MIND, Mediterranean, and DASH diets. Considering the role of medication in this disease levodopa, dopamine agonists, monoamine oxidase B inhibitors and the addition of ropinirole to levodopa and their efficacy in treating parkinsonian symptoms was investigated. A literature review was conducted using electronic search databases including, PubMed, Clinical Key and DynaMed. After thorough review of 12 articles regarding management of Parkinson disease with various modifications along with medications, it was found lifestyle modifications are not significant in the management of Parkinson disease alone. However, there is evidence to support the benefits lifestyle modifications can have, including diet and physical activity, for those diagnosed with Parkinson disease. The addition of these changes have shown the possibility of reducing the OFF time in the disease as well as reducing the daily medication regimen needed.

Key terms: Parkinson disease, MIND diet, Mediterranean diet, DASH diet, Levodopa, dopamine agonists, monoamine oxidase B inhibitors, ropinirole.

Introduction

Parkinson disease was first described as a neurological condition in 1817 by James Parkinson. Parkinson disease is a movement disorder that occurs predominantly due to loss of dopaminergic neurons in the pars comapcta region of the substantia nigra. The disease is characterized by presence of tremor, rigidity, bradykinesia, impaired posture and balance, impaired sleep, depression, loss of automatic movements, speech changes, writing changes as well as GI changes. GI changes can include drooling, cramping, abdominal pain, vomiting, bloating, dyspepsia, constipation, and fecal incontinence. Among those 65-69 years old the prevalence of Parkinson disease is 0.5-1%, with an increased prevalence of 1-3% in those 80 years and older, with incidence being higher in men compared to women. The prevalence and incidence of this disease is expected to rise by more than 30% by 2030 (Chen, 2001). Currently, the treatment focuses on symptomatic relief with medications to restore dopamine levels or to act on the postsynaptic dopamine receptors. The purpose of this literature review is to identify if lifestyle modifications in the form of diet changes and physical activity can be beneficial in reducing symptoms and progression of the disease.

Statement of the problem

Management of Parkinson disease is complex and multifactorial. The pathophysiology of the disease is not well understood, aside from recognizing the need for dopamine replacement. The standard of care treatment for Parkinson disease is management of symptoms with medication as each component presents. This can be difficult as it leads to polypharmacy and taking medications multiple times a day. This is especially troublesome as the prevalence of this disease affects the geriatric population. Having indications for lifestyle changes may be

beneficial to lessen the burden of early and frequent medication use in Parkinson disease. This will be beneficial as early prescribing of levodopa-carbidopa can lead to tolerance and the need for higher/more frequent dosing of the medication as well as potential for additional medications sooner. Lastly, as this disease primarily affects the geriatric populations, multiple medications dosed multiple times a day can lead to non-compliance simply due to forgetting to take or the difficulty of tracking medications throughout the day.

Research Question

How does lifestyle modification with medication alter the progression and symptoms of Parkinson disease compared to the standard of care of medication treatment alone?

Methods

A literature review was completed using electronic search databases, PubMed, Clinical Key and DynaMed. Keywords and mesh terms were used to assess and analyze literature regarding the progression of Parkinson disease with diet interventions, including the Mediterranean, DASH and MIND diets as well as physical activity. Further review was completed to address the use of medications such as Levodopa, dopamine agonists, monoamine oxidase B inhibitors and the addition of ropinirole to levodopa and their efficacy in treating parkinsonian symptoms. Additional research articles were found via similar articles in PubMed. Reference list of articles were examined, and picked based on applicability. All searches were narrowed to the past 25 years. The searches revealed 826 studies regarding Parkinson disease and diet and 23,676 studies for pharmaceutical treatment for Parkinson disease. Many studies were excluded as many were meta-analysis compiling data from multiple studies. All studies not in English were excluded. Ultimately, twelve studies were included; seven regarding diet and exercise (lifestyle), five regarding medication use in Parkinson disease.

Literature Review

Diet and Lifestyle Modifications Along with Medications in the Treatment of Parkinson Disease

In 2018 Agarwal et al. published a cross sectional study to identify the association of the MIND diet to the incidence and progression of Parkinson disease in older adults. The MIND diet is defined as Mediterranean-Dash Diet Intervention for Neurodegenerative Delay, that targets the health of the aging brain. The study was conducted with participants who were enrolled in the Memory and Aging Project, who were followed to observe motor impairments including parkinsonian signs, including bradykinesia, parkinsonian gait, rigidity, and tremors (Agarwal et al., 2018). A total of 706 (529 females and 177 males) Memory and Aging Project participants between the ages of 59-97, with an average age of 80.3 years, and without parkinsonism symptoms at baseline were assessed annually for the presence of four parkinsonian signs. Exclusion criteria included baseline cases of parkinsonism (n=286) and Parkinson disease (n=10) (Agarwal et al., 2018). Assessment included a 26-item modified version of the United Parkinson's Disease Rating Scale. Parkinsonism was defined as the first occurrence over 4.6 years of follow-up of two or more parkinsonian signs. To assess the progression of symptoms, researchers used the change in their global parkinsonian score. Adherence to the MIND, Mediterranean and DASH was determined and validated by the food frequency questionnaire. Researchers established diet groups based off the food frequency questionnaire completed by each participant. After 4.6 years of following the cohort, higher MIND diet scores were associated with a decreased risk of parkinsonism and a slower rate of parkinsonism progression ($p = 0.04$). The Mediterranean diet was marginally associated with a reduced progression of parkinsonism ($p = 0.06$) (Agarwal et al., 2018). The DASH diet was not associated with a

progression or reduced progression of parkinsonism. After completion of this study, it was concluded that the MIND diet may be associated with decreased risk and slower progression of parkinsonism in older adults (Agarwal et al., 2018). This was a strong study with a large population size. This study also had the benefit of being conducted over 4.6 years. Although the researchers used a variety of diets to measure effects on those with Parkinson disease, they could have included the FODMOP diet as patients with Parkinson disease often have constipation, and the FODMOP has been found to improve this. One downfall of this study is that it was a cross sectional study which used many different participants at different stages of the disease rather than following individual participants for an extended period.

The Hellenic Longitudinal Investigation of Aging and Diet (HELIAD), a large-scale population-based, multidisciplinary study, was designed to assess the prevalence and incidence of several neuropsychiatric conditions of aging and possible associations with diet, in Greece. It investigated the reduced probability of prodromal Parkinson disease while adhering to a Mediterranean diet (Maraki et al., 2019). Patients underwent thorough health histories prior to participating in the study. Most of the participants were poorly educated and had common morbidities such as hypertension (66.1%), dyslipidemia (40.8%) and diabetes mellitus (17.7%) (Maraki et al., 2019). Many also were overweight (10%) and were smokers. Participants in this study included 705 males and 1026 females ranging in age from 65 and older, with the average age of participants being 73 years old. Exclusion criteria included prior diagnosis of Parkinson disease, as the goal of the study was to evaluate the decrease in prodromal symptoms of Parkinson disease. Daily dietary intake and physical activity were assessed with a food frequency questionnaire (FFQ), and the Athens Physical Activity Questionnaire (APAQ). Participants were to evaluate themselves using the FFQ and APAQ from the previous month and the previous

week (Maraki et al., 2019). The FFQ was specific regarding the frequency of foods consumed that fell into the Mediterranean diet guidelines and adherence was evaluated through the MeDi score. A MeDi score is calculated on a 55-point scale and is directly related to the consumption of foods within the Mediterranean diet. Consumption of unrefined cereals, fruits, vegetables, legumes, potatoes, fish, and olive oil is presumed to closely adhere to the MeDi pattern and scored positively, whereas consumption of meat and meat products, poultry, and full-fat dairy products is presumed to diverge from this dietary pattern and scored negatively (Maraki et al., 2019). The total score ranges from 0 to 55, with higher values indicating greater adherence to the MeDi. After conclusion of the analysis, it was found that the median probability of prodromal Parkinson disease was 1.9% in 1731 Parkinson disease-free individuals aged 65 or greater. There was a statistically significant lower probability ($p < 0.001$) for prodromal Parkinson disease in the higher Mediterranean diet adherence groups (Maraki et al., 2019). This data was driven mostly by nonmotor markers for prodromal Parkinson disease including, depression, constipation, urinary dysfunctions, and daytime somnolence. For each increase in adherence to the Mediterranean diet, there was a 2% decreased probability of prodromal Parkinson disease ($p < 0.001$) when compared to participants that did not have good adherence to the diet (Maraki et al., 2019). This study also had a large population size. Being that the population was of the older generation it is likely that there will be comorbidities to consider but if a study could be conducted of individuals with no comorbidities, or divided into comorbidity groups may decrease interference of aspects that could play into the role of developing prodrome Parkinson disease. Additionally, having participants with these comorbidities helps make the conclusion applicable to this patient population as a great number of elderly individuals have these conditions. A downside to this study is that all data was patient reported via questionnaires. In

addition to having to self report, the study also depended on patients remembering what they ate a month prior to filling out the forms.

Metcalfe-Roach et al. conducted a cross sectional study in 2020 to determine whether "adherence to the MIND diet is associated with the age of Parkinson disease onset in a manner superior to that of the Mediterranean diet". The cross-sectional study included a total of 286 participants. Of the participants, 225 were previously diagnosed with Parkinson disease within the past 12 years, and 156 were controls. Participants were excluded if they had incomplete dietary surveys (n=93) as well as those who did not have an age of onset of Parkinson disease (n=2). This made for a research group of 167 participants with Parkinson disease and 119 control (Metcalfe-Roach et al., 2020). Food frequency questionnaires were used to score MIND and Mediterranean diet adherence, the data gathered by the food questionnaires were used to place participants into specific diet groups. Questionnaires were scored and compared between genders, as well as between Parkinson disease and control groups. The Parkinson disease diet adherence was correlated with age of onset using univariate and multivariate linear models (Metcalfe-Roach et al., 2020). With thorough review it was found that females adhered more closely to the MIND diet than males, and diet scores were not modified by disease status. Those whose onset was later in life correlated most strongly with MIND diet adherence in the female subgroup with a difference of up to 17.4 years ($p < 0.001$). Mediterranean adherence was also significantly associated with later Parkinson disease onset across all groups ($p = 0.05$-0.03). Conversely, adherence to the Mediterranean diet correlated with later onset across males in both Parkinson disease and control groups with a difference of 8.4 years ($p = 0.002$) (Metcalfe-Roach et al., 2020). This study identified a strong correlation of age of onset of Parkinson disease with dietary habits. Metcalfe-Roach et al. (2020) study suggests that the MIND and Mediterranean

diet may be an effective tool to delay onset and progression of Parkinson disease. This is a strong study with a large population size in both the control and those with Parkinson disease. This study could have been improved by explicitly dividing further into male/female subgroups and by age specifically instead of looking at them as a whole. In addition, an assessment by a neurologist would be beneficial in directly linking Parkinson disease symptom changes and dietary habits.

Mischley et al. (2017) conducted a cross-sectional study of 1053 individuals 45 years and older who were previously diagnosed with Parkinson disease. The primary outcome of this study was to compare specific foods and food groups with the progression of symptoms with Parkinson disease. Participants of the study had an average age of 63, with an average of 5.2 years since diagnosis. Gender and income were evenly distributed throughout the population with little diversity in those involved. Researchers put together two surveys for patients involved to record and report. One survey was a patient reported outcome (PRO-PD) of 33 common symptoms of Parkinson's. They were asked to rate each symptom on a scale of 0-100 (Mischley et al. 2017). Participants completed a "pre–PRO-PD" evaluating their symptoms at onset of diagnosis and a "post PRO-PD" evaluating their symptoms after a minimum of one year since diagnosis. The second survey was a food frequency questionnaire to assess dietary intake. The patients rated their consumption from never to five to six times daily. The results were then compared with an individual's rate of Parkinson disease progression based on their post PRO-PD (Mischley et al. 2017). After analysis of the self-reported food frequency questionnaire, Mischley (2017) found that fresh fruits and vegetables, nuts, and seeds, non-fried fish, olive oil, wine, coconut oil, fresh herbs and spices reduced the rate of Parkinson disease progression ($p < 0.05$). They also found that supplements coenzyme Q10 ($p = 0.026$) and fish oil ($p = 0.019$) were associated with

reduced Parkinson disease progression (Mischley et al. 2017). There were also foods reported that showed a more rapid progression of Parkinson disease. Foods associated with the rapid progression included canned fruits and vegetables, diet and non-diet soda, fried foods, beef, ice cream, yogurt, and cheese ($p < 0.05$) (Mischley et al. 2017). This was a strong study with a large population of participants. Though this was a cross sectional study, the patient reported outcomes allowed for patients to analyze their diets over many years. Participants in this study were similar in age but with different lifestyles. This is helpful in generalizing the findings to a diverse population of patients. A limitation to this study includes self-reported outcomes. In addition to the self-reporting, participants also needed to recall their symptoms from onset as well as after a year of onset. This study relies heavily on participants' memory, which can be inconclusive as to how accurate the data may be.

In 2020 Molsberry et al. completed an analysis to assess the relationship between diet pattern and prodromal Parkinson's features. The study included 47,679 participants from the Nurses' Health Study and Health Professionals Follow-up Study. Every 4 years, both cohorts collected dietary information and calculated scores for adherence to the alternate Mediterranean diet (aMED) and Alternative Health Eating Index (AHEI). In 2012, participants responded to questions that pertained to prodromal Parkinson disease symptoms which included constipation and probable REM sleep behavior disorder (Molsberry et al., 2020). Of the studies' participants, 17,400 people responded, and were then asked to answer five additional questions regarding prodromal features of Parkinson disease between 2014 to 2015. Multinomial logistic regression was used to approximate the association between the baseline diet pattern scores in 1986 and number of prodromal features in 2012-2015. Additional analysis was done to further investigate the association between long-term adherence to these dietary patterns over 20 years and

prodromal features suggestive of Parkinson disease (Molsberry et al., 2020). After detailed analysis, Molsberry et al. (2020) found that long term high adherence to aMED and AHEI was inversely associated with individual prodromal features, including constipation, excessive daytime sleepiness, and depression *(*$p < 0.001$). The study found that adherence to a healthy diet may reduce the occurrence of nonmotor symptoms that often precede Parkinson disease diagnosis. Although this study had a large population group with a mix of genders, it did not break down gender percentages, which may be helpful in clarifying risk in males vs. females. In addition, the data collected were all patient reported outcomes that were analyzed by a third party whom did not have direct interaction with each individual, increasing the margin of error in reporting. This study is beneficial as it follows a wide range of individuals over a prolonged period.

In addition to the gross motor function symptoms that are frequently associated with Parkinson disease, constipation and impaired GI motility are significant issues in patients with the disease. Rusch et al. (2021) completed a single arm seven-week study of individuals with Parkinson disease to determine whether a Mediterranean diet intervention is feasible and its effects on GI function, intestinal permeability, and fecal microbial communities. Eight patients with Parkinson disease were recruited to participate from the University of Florida Norman Fixel Institute for Neurological Diseases in Gainesville, Florida. Partners of each participant agreed to provide urine and stool samples as a control group for this study (Rusch et al. 2021). Daily and weekly questionnaires were completed to determine changes in participants GI symptoms. Patients completed a two-week baseline period that followed their usual diet and level of physical activity. After the initial two weeks patients met with a dietician to be educated on the Mediterranean diet followed by a five-week period with this diet intervention. Participants were

to use MEDAS as a food diary to improve their diet adherence. Dietitians that partnered with the study followed up with the participants weekly via phone to help ensure adherence to the Mediterranean diet, which includes a variety of fruits, vegetables, legumes, unrefined cereals, healthy dietary fats from olive oil, avocadoes, nuts, and seeds. It also includes a moderate amount of fish, poultry, eggs, and dairy with limited intake of red meats or sweets (Rusch et al., 2021). Following this diet allows for an increase in dietary fiber, as fiber is widely under-consumed in the typical western diet. Fiber helps to reduce constipation by maintaining stool frequency. Urine and stool samples were collected at baseline and again after the five-week diet interventions were completed (Rusch et al. 2021). Samples were used to assess intestinal permeability and fecal microbial communities. Daily questionnaires assessed stool frequency, stool form using the Bristol Stool Scale and adverse events. Weekly questionnaires were completed to assess GI symptoms using the Gastrointestinal Symptom Rating Scale (GSRS). A neurologist trained in movement disorders determined baseline motor and non-motor symptoms using the Movement Disorder Society-unified Parkinson's Diseases Rating Scale (MDS-UPDRS) and cognitive function using the Montreal Cognitive Assessment (MoCA) (Rusch et. al., 2021). Throughout the study period, participants were to continue their daily regimen of medications. It was found that participants were able to increase their intake of Mediterranean diet-based adherence scores from baseline to week five ($p < 0.01$). Constipation syndrome scores decreased ($p = 0.04$), Bilophila was higher at baseline in Parkinson disease ($p = 0.02$) and slightly decreased after the diet intervention ($p = 0.01$) (Rusch et al. 2021). It was found that the proportion of Roseburia was significantly lower in participants with Parkinson disease compared to the controls *(*$p = 0.02$) and increased at week five ($p = 0.01$). The number of bowel movements per week and average weekly stool form using the Bristol Stool Scale were not

significantly different after the diet intervention ($p = 0.31$) compared to baseline ($p = 0.37$) (Rusch et al. 2021). In conclusion it was found that adherence to the Mediterranean diet in the short term is feasible in patients with Parkinson disease (Rusch et al., 2021). Based on these findings, following the special diet has shown to potentially improve constipation as well as modify gut microbiota. This study is relevant and up to date and shows promising data that the Mediterranean diet can improve GI symptoms in patients with Parkinson disease. This study is also beneficial as the control group were the partners of the participants with Parkinson's. This helps with the regulation of comparing diets as it is likely that each couple had similar meals each day. Having almost exact diets for each couple helps solidify data in the effects on those with Parkinson's versus those without the disease. A larger group of participants over a longer period would make for a better study in the future. This study also did not follow up with the motor functions of the participants though they gathered a baseline motor function for each participant.

In addition to diet, another lifestyle modification that has shown to be beneficial for management of Parkinson disease is physical activity. In 2021 Yoon et al. completed a longitudinal cohort study looking at physical activity (PA) levels and mortality rate of patients diagnosed with Parkinson disease. Participants were identified between January 2010 and December 2013 and were followed until December of 2017, with data analysis occurring between September 2020 and March 2021. To be selected for this study a patient had to have had a medical exam at least two years prior to diagnosis of Parkinson disease and at least once, two years after diagnosis (Yoon et al., 2021). This study included a total of 10,699 participants with Parkinson disease. Of the participants, 46% were males and 54% were females, with the mean age of participants being 69.2 years with a standard deviation of 8.8 years. When defining

physical activity (PA), Yoon (2021) analyzed a self-reported questionnaire that was based on a seven-day recall by each individual at their medical follow ups. The PA questionnaire included how many days per week the patient spent performing each activity and at which intensity level. High-intensity PA was defined by Yoon (2021) as, "running, aerobics, fast biking, and climbing for more than 20 minutes" and was considered vigorous activity. Moderate-intensity PA, such as fast walking, riding a bicycle at a normal speed, and doubles tennis, for more than 30 minutes was defined as moderate activity. Light-intensity PA, such as walking to and from work or for leisure, for more than 30 minutes was regarded as light activity" (Yoon et al, 2021). Participants were considered physically active or physically inactive based on guidelines released by American College of Sports Medicine. If a patient reported vigorous PA three or more times or moderate/light PA for five or more times a week, they were considered physically active. All others were labeled as physically inactive. After eight years of observation, of the 10,699 participants with Parkinson disease, there were 1823 deaths (17% mortality rate). There was a significant difference in age and gender of those who died and those that did not. The average age of those who did not die was 68.3 years versus those who died were 73.2 years ($p < 0.001$) (Yoon et al., 2021). Yoon et al. (2021) concluded that those who were physically active prior to diagnosis as well as after diagnosis showed the greatest reduction in mortality ($p < 0.001$). PA after Parkinson disease diagnosis also showed reduced mortality ($p < 0.001$). Inversely, those that were inactive showed an increase in mortality rate ($p < 0.001$) (Yoon et al., 2021). This study's strengths were in gathering data and following up with the participants. The eight year follow up provided for a significant amount of data. Participant self-reporting and the seven-day recall is a weakness of the study. The self-reporting, in addition to the recall factor, could have skewed results both in favor of PA as well as for inactivity of a particular individual. By only

looking at seven days you could catch a participant in a week of activity or in a week of inactivity which would give mixed results. To improve this study in the future, it would be best for participants to keep a journal of their activity daily and then review the journals. This would eliminate the amount of recall, potentially improving the accuracy of the data.

Treatment of Parkinson Disease with Medications

ADVANCED-PD investigators conducted a randomized, double blind controlled clinical trial looking at the efficacy of carbidopa levodopa immediate release (CD-LD IR) against carbidopa levodopa extended release (CD-LD ER). To measure the effects of each of the drugs, Hauser (2013) had participants record in-home diaries of their, "ON time", defined as time without dyskinesia and their "OFF time", defined as time with dyskinesias caused by their Parkinson disease (Hauser et al., 2013). To be included in this study participants had to be at least 40 years at time of diagnosis. Additionally, participants needed to be taking a total daily levodopa dose of 400 to 2400mg for a minimum of four weeks, with a dosing frequency of four to nine times a day. Lastly, to be included, participants needed to have a three-day average of 2.5 hours or more of OFF time per day (Hauser et al, 2013). Exclusion criteria included, "atypical or secondary parkinsonism, previous neurosurgical treatment for Parkinson disease, lack of response to levodopa, controlled release CD-LD apart from a single bedtime dose, extended-release CG-LD, additional CD or benserazide, catechol O-methyl transferase inhibitors or a history of psychosis within the past ten years (Hauser et al, 2013). Of the 770 patients screened, the study enrolled 471 patients with Parkinson disease who experienced motor fluctuations with OFF time of a minimum of 2.5 hours per day. Participants began with a three-week course of CD-LD IR to get to an optimal dose to control their symptoms followed by a six-week CD-LD ER optimization period. After each patient had found their optimal dose for each medication, participants started a

13-week randomized, double blind maintenance period where they would receive either their optimized dose of CD-LD IR, CD-LD ER or a placebo. Based on self-report through patient diaries, OFF time and ON time without troublesome dyskinesia improved significantly more with CD-LD ER ($p = 0.0001$) compared to CD-LD IR ($p = 0.0002$). On average, the treatment difference was a decrease of 1.17 hours of OFF time ($p < 0.0001$) and an increase of .93 hours of ON time ($p = 0.0002$) without dyskinesia (Hauser et al, 2013). Benefits of the extended release were managed in an average of 3.6 doses per day while the immediate release formula averaged five doses per day ($p < 0.0001$), though the mean dose of ER was approximately twice that of the IR group (Hauser et al., 2013). This study had a significant number of participants to allow for adequate data in each medication group. It also allowed researchers to find the beneficial dose for each participant to determine the most adequate coverage for each participant. Doing this allowed for the management of the disease to be tailored and for the result to be generalized across the population. The downside is that the outcomes were patient reported. This study could have been improved by involving a neurologist to assess the patients and their conditions.

Lieberman et al. (1998) conducted a six-month randomized, placebo controlled double blind trial of the addition of ropinirole to levodopa in patients with Parkinson disease. The study included 149 patients with Parkinson disease with predictable motor fluctuations that were randomized and given either ropinirole (95 patients) with a dosage of 3 mg/day to a maximum dose of 24 mg/day divided into 3 doses, or a placebo pill (54 patients) (Liberman et al., 1998). Participant evaluations were performed at baseline and at each study visit. Patients were evaluated according to the Clinical Global Impression and home diary reflecting hours ON and OFF during two consecutive days before each of their visits. Each evaluation was performed by the same blind evaluator (Liberman et al., 1998). As participants increased their dose of

ropinirole, their levodopa dosage was reduced, which contributed to some dopaminergic adverse effects. Patients who were assigned to the ropinirole group experienced at least a 20% reduction in daily OFF time and a 20% reduction in levodopa dose compared to 13% of participants taking placebo ($p = 0.002$) (Liberman et al., 1998). The average dosage of levodopa was significantly decreased with the ropinirole treatment group ($p < 0.001$) along with the awake time spent OFF ($p = 0.039$). This concluded that ropinirole permits a reduction in levodopa dosage with an increased benefit for Parkinson disease patients with motor functions (Liberman et al., 1998). This study did not have an even distribution between the placebo group and the treatment group, giving less of a control to the study. In addition, patient reported outcomes can be less reliable. This study did include objective evaluations by researchers who were blinded to the medication that the participant was taking, which does give an objective approach to results. This study also was conducted over an extended time period allowing for adequate amounts of data to evaluate and reach a conclusion.

EASE-PD Adjunct Study Investigators conducted a double blind, placebo-controlled 24-week study to evaluate the efficacy of ropinirole 24-hour prolonged release as an adjunct to levodopa in patients with Parkinson disease with motor function. Pahwa et al. (2007) enrolled 393 participants with Parkinson disease and motor fluctuations with at least three hours of OFF time per day to the study. Of the participants, 202 patients were randomly assigned to the ropinirole group and 191 to a placebo group. The primary outcome measure was reduction in OFF time hours. Secondary outcome measures included change in hours and percent of daily "OFF" time and "ON" time without troublesome dyskinesia (Pahwa et al., 2007). The Unified Parkinson Disease Rating Scale of motor and activities of daily living subscales, Beck Depression Inventory-II, PDQ-39 subscales of mobility, activities of daily living, emotional

well-being, stigma and communication, and Parkinson disease Sleep Scale were significantly improved at week 24 for those in the ropinirole group (Pahwa et al., 2007). The prolonged release ropinirole was dosed between 2 and 24 mg/day and was guided by therapeutic response and adverse effects. The mean dose of ropinirole among the participants was 18.8mg/day with a mean reduction of levodopa by 278mg (Pahwa eta., 2007). Participants in the ropinirole group showed significant improvement in daily OFF time. The OFF time had an average reduction of 2.1 hours ($p < 0.0001$). The ON time that participants experienced without troublesome dyskinesia averaged an increase of 1.5 hours ($p < 0.0001$) (Pahwa et al., 2007). They found that the addition of prolonged release ropinirole was effective and well tolerated in patients with Parkinson disease who were not optimally controlled with levodopa alone. The ropinirole group showed an improvement in both motor and non-motor Parkinsonian symptoms, while also allowing a reduction in previous levodopa dose (Pahwa et al., 2007). This study had a large number of participants that were equally distributed between control and treatment group. The researchers also did a good job identifying outcome measures to be sure they had adequate data to come to a conclusion. This study could have had less patient reported outcomes, but these surveys are standard measures for those with Parkinson disease. Additionally, if this study could have been conducted for a longer period of time that may provide beneficial data to see effects of the lower levodopa levels on progression of dyskinesias.

Gray et al. (2014) conducted an open-label randomized trial between November 2000 and December 2009. Their goal was to investigate the long-term effectiveness of dopamine agonists, or monoamine oxidase B inhibitors (MAOI-B) compared to levodopa as first line treatment in Parkinson disease. They observed 1620 patients who were newly diagnosed with Parkinson disease and randomly assigned each participant (1:1:1) between levodopa sparing (632 dopamine

agonists, 460 to MOAI-B) and levodopa alone (528). Primary outcome measures were analyzed through mobility dimension on the 39-item patient-rated Parkinson's disease questionnaire (PDQ-39), quality-of-life scale (range 0–100 with six points defined as the minimally important difference), and cost-effectiveness (Gray et al., 2014). Participants in the study had a median follow up of three years with some following up over the entire nine-year period of observation. The results showed a PDQ-39 mobility score with a mean of 1.8 points higher with the patients that were randomly assigned to levodopa ($p = 0.005$) than patients assigned to levodopa-sparing therapy. There was also a statistically significant difference between MAOI-B and dopamine agonists. On average, those taking MAOI-B reported 1.4 points better on the PDQ-38 than those taking dopamine agonists ($p = 0.05$) (Gray et al., 2014). Gray et al. also measured rates of dementia ($p = 0.14$), admissions to institutions ($p = 0.4$), and death ($p = 0.17$) which were not significantly different. This study also considered that 28% of patients taking dopamine agonists and 23% taking MAOI-B discontinued their treatments due to side effects, while only 2% of participants taking levodopa discontinued medication due to side effects ($p<0.0001$) (Gray et al., 2014). Participants were also asked to evaluate their function of activities of daily living, stigma, cognition, communication, and bodily discomfort. These subscales were also significantly better with levodopa than with levodopa-sparing therapy ($p < 0.05$) (Gray et al, 2014).

When discussing which medication to initiate in a patient newly diagnosed with Parkinson disease, the hesitancy of starting levodopa right away, especially in the population under 70 years, is the development of dyskinesias. This study found that patients in the levodopa group were more likely to develop dyskinesias than the levodopa-sparing group (p-0.003) but there was no difference in motor fluctuations ($p = 0.3$) (Gray et al, 2014).

This study had an adequate number of participants to effectively evaluate each medication that researchers investigated. Although they were able to conclude that levodopa does have a significantly improved efficacy, it does have a greater probability of an increase in dyskinesias. Overall, levodopa has less side effects than the dopamine-sparing agents. This study could be improved by longer follow up. The other possible error in this study could be patient bias as they know which medication they are taking as well as self-reported effects of the medication.

Frequin et al. (2023) conducted a double-blind, placebo controlled, randomized, delayed start trial to analyze the effects of levodopa in patients with early Parkinson disease. A total of 445 participants with early Parkinson disease were included in this trial with an age range of 64-73 years. Patients with early Parkinson's were randomized to receive levodopa/carbidopa 300/75 mg daily for 80 weeks (early-start group) or to receive a placebo for 40 weeks followed by levodopa/carbidopa 300/75 mg daily for 40 weeks (delayed-start group) (Frequin et al., 2023). The effect of the medication was then analyzed using the Unified Parkinson's Disease Rating Scale on bradykinesia, rigidity, and tremor. After completion of the 80 weeks each participant answered three questions regarding motor response and fluctuations. The early start group included 222 patients and the delayed start group included 223 patients. The difference between the early and delayed start groups in average change from baseline to week four, expressed as "Hedges *g* effect size", was -0.33 for bradykinesia, -0.29 for rigidity, and -0.25 for tremor favoring the early start group (Frequin et al., 2023). From baseline to week 22, respectively, -0.49, -0.36, and -0.4; and from baseline to week 40, respectively, -0.32, -0.19, and -0.27. At 80 weeks, fewer patients in the early start group (46 of 205 patients, 23%) experienced motor response fluctuations than patients in the delayed-start group (81 of 211, 38%; $p < 0.01$). In patients with early Parkinson disease, levodopa/carbidopa improved bradykinesia, rigidity, and

tremor. For all three symptoms, effects were greater at 22 weeks compared with four weeks. At 80 weeks, there were fewer patients with motor response fluctuations in the group that had started medication earlier (Frequin et al., 2023). This is a good study as it followed a large population for over a year's time. This could be an improved study if they continued to follow patients to see if there is a correlation in motor response fluctuations after a certain time using levodopa/carbidopa. Additionally, an improvement to this study would be to find the therapeutic dose for each participant over three months, and then assign each to treatment and placebo groups using individual optimal dosage for each participant.

Discussion

In this comprehensive review of literature, comparing standard of care of medication treatment to the initiation of lifestyle changes on the effects of Parkinson Disease it was found that lifestyle changes can have a clinically significant benefit. Specifically, after analysis of the data, initiation of the MIND and Mediterranean diet can help to reduce prodrome symptoms of Parkinson disease as well as symptoms of Parkinson disease for those already diagnosed.

All studies were conducted with the use of patient reporting of diet and physical activity. This can make drawing a definite conclusion difficult as patient recall and honesty of participants plays a major role. Studies that researched specific dietary changes, including the MIND and Mediterranean diets, as well as the addition of physical activity, showed that there may be a strong correlation with decreased risk and slower progression of parkinsonism in older adults. The DASH diet was investigated in one study which did not show a statistically significant benefit in reducing symptoms. These lifestyles change considerations showed improvement in both prodrome symptoms, as well as in those who were previously diagnosed with Parkinson

disease. In addition, the changes showed improvement not only in dyskinesias but also with constipation, depression, urinary dysfunctions, and daytime somnolence.

When analyzing the studies considering medication treatment, we know that levodopa carbidopa plays a significant role in controlling symptoms of Parkinson's. The main question for each patient is, which dose and at what frequency does the medication need to be taken. The concern with the early use of levodopa carbidopa is the earlier onset of dyskinesias followed by the increased dosage needed of the medication to get the same amount of relief from dyskinesias. Due to this adverse effect, ropinirole has been added to treatment plans. In the studies that were reviewed, those who used ropinirole showed an improvement in both motor and non-motor Parkinson's symptoms, while also allowing a reduction in previous levodopa dose. This could be a beneficial adjunct to those with Parkinson disease to reduce their levodopa dosage and the adverse effects that accompany it.

Although it is widely accepted that a prescription of levodopa carbidopa is the mainstay of treatment for those with Parkinson disease, the above investigation shows that there is a strong correlation between diet and activity that can help reduce risk and slow progression of Parkinson's in older adults. Further investigation should be completed following a younger population over multiple decades to verify the risk reduction as well as onset age of the disease. To eliminate sole dependance on patient reported outcomes, a study should be conducted with a Mediterranean meal plan for participants to follow. This could be done with a food service that can deliver the food to the home to ensure the meal plan is easily adhered to.

Overall, this literature review does not suggest sole reliance on lifestyle changes for the management of Parkinson disease. However, there is evidence to support the benefits of lifestyle

modifications, including diet and physical activity, can have for those diagnosed with Parkinson disease.

Conclusion

Management of Parkinson Disease is complex and multifactorial. After thorough research it can be determined that primary management of Parkinson disease is with pharmaceutical treatment. There is minimal evidence to show that lifestyle changes alone can effectively manage the disease. Research did show that lifestyle modifications such as diet and physical activity, can be beneficial, however, it is not significant enough to discontinue medication use. Further research should be completed to include long term effect of lifestyle changes in the middle age population and the effect it has in potential later onset of parkinsonian symptoms.

Applicability to Clinical Practice

This literature review study can be helpful in clinical practice. Overall, this study can be generalized to the elderly population of those 65 years of age and older. This research provides valuable insight into the benefits of lifestyle modifications for those with prodrome Parkinson's or those previously diagnosed with Parkinson disease. Further research does need to be conducted to make definitive recommendations, however, there is some evidence to show that physical activity and diet modifications can lead to a reduction in symptoms as well as an increase in medication efficacy.

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