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Thesis

THE EFFECTS OF SLEEP DISTURBANCE, RACE, SEX, AND AGE ON HOEHN YAHR SCORES IN PARKINSON'S PATIENTS: A CROSS-SECTIONAL STUDY

by

CHRISTOPHER SEAN BAYERS

B.S., Fordham University, 2013

Submitted in partial fulfillment of the

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Master of Science

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Approved by

First Reader

Fernando Garcia-Diaz, Ph.D.
Associate Professor of Physiology and Biophysics
Boston University, School of Medicine

Second Reader

Anna Hohler, MD.
Associate Professor of Neurology
Boston University, School of Medicine

Third Reader

Stacey Hess Pino, MS, MS.
Assistant Director, MS in Clinical Investigation Program
Boston University, School of Medicine

DEDICATION

I would like to dedicate this work to my grandfather Silvio Drinkwater. Silvio struggled with Parkinson's disease for ten years, which sparked my interest in Parkinson's research. Hopefully though the intense study of Parkinson's disease better treatments will become available to help patients in the future.

ACKNOWLEDGMENTS

I would like to thank my committee members for their support and guidance through the thesis process, as well as for their assistance with editing. I would also like to thank Emily Bowman for her support and editing assistance.

THE EFFECTS OF SLEEP DISTURBANCE, RACE, SEX AND AGE ON HOEHN YAHR SCORES IN PARKINSON'S PATIENTS: A CROSS-SECTIONAL STUDY

CHRISTOPHER SEAN BAYERS

ABSTRACT

The objective of this study was to determine the effects race, sex and sleep disturbance have on the severity of Parkinson's disease as assessed by the Hoehn Yahr (HY) score in both the medicated (ON) and non-medicated (OFF) states. The potentially confounding variables of age, time in years from the onset of symptoms to database entry, and education were taken into account. Secondary analysis was also conducted to determine how the non-motor symptoms of dementia, hallucinations and autonomic dysfunction impacted Hoehn Yahr ON and OFF scores.

This study used the statistical techniques of the Student's t-test, ANOVA, Tukey-Kramer test, univariate linear regression, and multivariate regression. The t-tests and ANOVA test revealed that there was no significant differences in mean HY ON and OFF scores between the sexes, patients with and without sleep disturbance, and between the different races analyzed in this study. Patients with and without sleep disturbance did show significantly higher HY ON scores as compared to HY OFF scores, which is peculiar as this finding suggests that these patients are not responding to their medication.

The univariate linear regression models did show, however, that time in years from the onset of symptoms to database entry did significantly impact both HY ON and OFF scores, whereas age is only shown to have a significant impact on HY OFF scores. Additionally, the univariate linear regression model analyzing the association between

education and HY OFF scores showed that having some high school education, but not receiving a degree, was associated with an increase in HY OFF scores.

Several multivariate linear regression models where built to assess the impact different predictor variables had on HY ON and HY OFF scores. The first two multivariate models used the predictor variables of age, race, and time in years from the onset of symptoms until database entry. These models showed that only time in years from the onset of symptoms until database entry impacted HY ON scores, whereas all three of these predictor variables impacted HY OFF scores. Two additional multivariate linear regression models were built to assess how age, race, time in years from the onset of symptoms until database entry, dementia, autonomic dysfunction and hallucinations all impacted HY ON and OFF scores. These models revealed that all of these predictors, when taken together, significantly impacted HY OFF scores, but not HY ON scores.

Finally a scatter plot was made comparing HY ON and HY OFF scores. A LOWESS scatter plot smooth line was also superimposed on top of this plot to show the overall trend these scores had on one another. This scatter plot was interesting because it suggested that there were two spate groups of patients contained in this database, those that responded well to medication and those that did not.

Overall, this study showed that age, time in years from the onset of symptoms until database entry, education and race impacted HY OFF scores. Furthermore, the analysis indicated that patients who were asked about sleep disturbance did not appear to be responding to medication. There are several limitations to this study, however, with the most important being missing data and the cross-sectional design. Missing data

prevented sleep disturbance from being thoroughly analyzed and the cross-sectional design does not allow for any causal relationships to be determined.

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LIST OF ABBREVIATIONS

AAAD ..... Aromatic Amino Acid Decarboxylase

AH ..... Auditory Hallucinations

ANOVA ..... Analysis of Variance

BUMC ..... Boston University Medical Centre

COMT ..... Catechol-O-methyltransferase

DMN ..... Dorsal Motor Nucleus

EDS ..... Excessive Daytime Sleepiness

GABA ..... γ-aminobutyric acid

GPe ..... External Globus Pallidus

GPi ..... Internal Globus Pallidus

HRQoL ..... Health Related Quality of Life

HY ..... Hoehn and Yahr Scale

IRB ..... Institutional Review Board

LB ..... Lewy Body

LC ..... Locus Ceruleus

L-dopa (Levodopa) ..... L-Dihydroxyphenylalanine

LN ..... Lewy Neurite

MCI ..... Mild Cognitive Impairment

MDC ..... Movement Disorders Clinic

MSA ..... Multiple Systems Atrophy

nbM ..... Basal Nucleus of Meynert

NMS ..... Non-Motor Symptoms

NMSQuest ..... Non-Motor Symptoms Questionnaire

NMSS ..... Non-Motor Symptoms Scale

OH ..... Orthostatic Hypotension

OSA ..... Obstructive Sleep Apnea

PD ..... Parkinson's disease

PSP ..... Progressive Supranuclear Palsy

RBD ..... Rapid Eye Movement Sleep Behavioral Disorder

REM ..... Rapid Eye Movement

RLS ..... Restless Legs-Syndrome

SN ..... Substantia Nigra

SNpc ..... Substantia Nigra Pars Compacta

SNpr ..... Substantia Nigra Pars Reticulata

STN ..... Subthalamic Nucleus

UPDRS ..... Unified Pakinson's Disease Rating Scale

VH ..... Visual Hallucinations

YOE ..... Time in Years from Disease Onset to Database Entry

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder that primarily affects the dopaminergic system in the brain.[1,2] Parkinson's disease was first described in 1817 by James Parkinson in his paper titled *An Essay on Shaking Palsy*.[2,3] French neurologist Jean-Martin Charcot was the first to advocate for the use of the term Parkinson's disease over shaking palsy because Charcot observed that PD patients did not always present with the symptom of a resting tremor and did not have muscle weakness.[3]

PD is the second most common neurodegenerative disease[1], the most common movement disorder[4], and was ranked as the 14th most common cause of death in the United States in 2010.[5] PD is estimated to effect more than 500,000 people currently, with 50,000 new cases reported annually.[1] PD usually effects patients who are 60-years of age or older[1], but PD has been seen in younger patients as 10% of PD cases develop before the age of 50.[2]

The costs associated with PD are significant in the United States. In 2010 the estimated cost incurred by each PD patient on Medicare was 10,387 dollars.[6] The annual cost of PD is estimated to be around 25 billion dollars annually[7], which will only increase as the current population ages.

Pathophysiology/Staging

The main macroscopic change seen in the brain of PD patients is the loss of neuromelanin-containing neurons in the substantia nigra pars compacta (SNpc).[2,8] Neuromelanin is a dark pigment that causes the SN to have a black appearance, which is where its name substantia nigra, Latin for 'black substance', originates.[8] In addition to the SN, neuronal degeneration also occurs in the locus ceruleus (LC), the dorsal motor nucleus of the vagus (DMN), and the basal nucleus of Meynert (nbM).[2,8] The loss of pigment, which accumulates with age in the SN and LC, is indicative of neuronal loss.[8] Lewy bodies (see below) are also a pathological hallmark of PD.[2,8] Furthermore, the brains of PD patients might also exhibit enlarged ventricles, particularly in the frontal horns, as well as mild atrophy of the frontal lobe. Otherwise the brains of PD patients appear to be normal, which can help to distinguish progressive supranuclear palsy (PSP) and multiple systems atrophy (MSA) from PD. PSP exhibits atrophy of the midbrain and MSA exhibits atrophy of the pontine nucleus of the basal ganglia.[8]

Microscopically, PD patients have Lewy bodies (LBs) as well as neuritic processes throughout the SN, LC, DMN and nbM.[8] LBs are eosinophilic intracytoplamsmic globular granular inclusions that are composed of α-synuclein and ubiquitin.[8] α-synuclein is normally found at the presynaptic terminals of neurons and it is still unknown how α-synuclein becomes deformed and accumulates in the cytoplasm of neurons to form LBs.[8] There are two different types of neuritic process that occur within the brains of PD patients: those that stain with hematoxylin and eosin, referred to as

intraneuritic LBs, and those that remain invisible on routine histological examination, referred to as Lewy neurites (LNs).[8] LNs are frequently seen in the amygdala, hippocampus and neocortex.[8]

Many of the motor symptoms experienced by PD patients are accounted for by degeneration of the basal ganglia. The basal ganglia is composed of the following: the dorsal striatum, that contains the caudate nucleus and the putamen; the external globus pallidus (GPe); the internal globus pallidus (GPi); the substantia nigra (SN), that is made up of the pars compacta (SNpc) with dopaminergic neurons and the pars reticulata (SNpr) with GABAergic neurons; and the subthalamic nucleus (STN).[8]

There are two major pathways within the basal ganglia that control motor movements by modulating the activity of the thalamus; the direct and indirect pathways.[9,10] These two pathways work in a reciprocal fashion with the direct pathway stimulating the thalamus resulting in increased movement, and the indirect pathway decreasing activity within the thalamus, thereby reducing movement.[9]

The direct pathway functions in the following way: Excitatory glutiminergic neurons project from the cortex to the striatium and to the STN, stimulating their excitation.[9] The striatum sends inhibitory γ-aminobutyric acid (GABA) –ergic neurons to the GPi[2], which also sends GABAergic neurons to the thalamus resulting in its inhibition.[9] The thalamus sends glutiminergic projections to the motor cortex resulting in its excitation.[9] This

pathway ultimately leads to a decreased inhibition of the thalamus allowing it to send more excitatory signals to the motor cortex, thereby stimulating more movement.[10] The STN helps to modulate the amount of movement produced in the direct pathway by exciting the SNpc, which sends excitatory dopaminergic neurons to the striatum.[9,10] Dopamine then binds to D1 receptors[9] on the inhibitory neurons of the striatum leading to further inhibition of the GPi. Consequently, the thalamus is less inhibited, producing more movement.[2,8,9] When the SN becomes over-stimulated the SNpr sends GABA to the STN via GABAminergic neurons, thereby inhibiting the STN. The inhibition of the STN results in less excitation of the SNpc, ultimately leading to more inhibition of the thalamus and deceased movement.[8–10]

The indirect pathway is composed of GABAergic striatal neurons that project to the GPe.[9] The GPe has GABAergic neurons that project to the STN, which has glutamatergic neurons that project to the GPi resulting in its excitation.[2,9] Stimulation of the GPi results in increased inhibition of the thalamus causing decreased movement.[8,9] The SNpc sends dopaminergic projections to the striatum, which binds to D2 receptors[9] in the striatum causing the GABAergic projections of the striatum to be inhibited, leading to decreased inhibition of the thalamus and ultimately more movement.[8,9]

Both the direct and indirect pathways reveal the key role that SN plays in modulating movement through the two distinct neuronal populations. The degradation of SN that occurs in PD patients ultimately results in the decreased activity of the direct pathway

and an increased activity of the indirect pathway.[2,8–10] It is postulated that the increased inhibition of the thalamus from the indirect pathway is one of the primary means by which bradykinesia results in PD patients.[2,9] This model does have some short comings as it cannot explain the observed reduction of bradykinesia and dyskinesia from a pallidotomy.[2] Additionally, this model doesn't explain the non-motor symptoms (NMS) that are also observed in PD.

There is a model proposed by Braak that does account for some of the NMS that occur in PD. Braak and his team assumed that the pathology of PD develops in a predetermined manner through the brain before the clinical motor symptoms become apparent.[11] From this assumption Braak and his team believed that cases of PD could be staged from those with no symptoms to those with severe symptoms, and from this order it would be possible to deduce the progression of PD from one region within the brain to the next.[11] Braak obtained 41 brains from patients who had a confirmed diagnosis of PD as well as 69 brains from patients who had none of the characteristic motor symptoms of PD, but had the presence of LBs and LNs at various locations within the brain.[11] Braak also had a control group composed of 58 brains derived from people who had no PD motor symptoms or psychological symptoms.[11] From the study of these brains Braak derived a six-stage classification for PD.[11]

The first stage is characterized by the degeneration of the olfactory bulb and the anterior olfactory nucleus, which is thought to account for the olfactory dysfunction that occurs in

many PD patients before the onset of motor symptoms.[12] The pathological process spreading to the lower brain stem defines Braak's second stage. The degeneration of the lower brain stem is thought to explain the disruption of sleep and other autonomic symptoms of PD such as sexual dysfunction. The first two stages in Braak's system are referred to as the pre-clinical stages as the iconic motor symptoms of PD are not seen until the third stage. Stage three is when the SNpc begins to develop LNs as well as some LBs,[11] which results in the motor symptoms that are classically associated with PD.[12] Stage four has the same pathology as stage three, but with additional pathological changes occurring within temporal mesocortex.[11] Stages three and four are when PD shifts from a pre-motor to a motor disorder, and it is at this point when PD is diagnosed.[12] Braak's stages five and six are classified by the presence of LBs within the limbic system and mature neocortex. During these stages patients may develop the symptoms of depression, cognitive impairment and visual hallucinations.[12] While this staging system is helpful, Braak's system does have a few shortcomings.

This staging system is based solely on the presence on LNs and LBs within the brain as opposed to the development of neuronal degradation.[12] Additionally, Braak's system does not account for PD patients who present with cognitive symptoms at an early stage, such as hallucinations or dementia.[12] Braak's staging also does not account for the development of restless leg syndrome (RLS) or constipation as pre-clinical symptoms of PD.[12]

The final PD staging scale that will be considered is the Hoehn and Yahr (HY) scale. The HY scale has also been incorporated into the Unified Parkinson's Disease Rating Scale (UPDRS), which will be considered in more detail later on. Dr. Hoehn and Dr. Yahr proposed the Hoehn Yahr five-stage scale in 1967, as a way to rate the severity of PD in a consistent and convenient fashion.[13] This scale filled a void because it enabled physicians to rank the severity of PD in different patients, and track the progression of the disease, while simultaneously assessing the effectiveness of treatment.[13]

Currently, the HY scale is widely implemented in a modified form that includes two additional stages: Stage 1.5 and Stage 2.5. This modified form of the scale will be utilized in this study. The modified HY stages are defined as follows: Stage 0, no signs of the disease; Stage 1, when PD only effects one side of the body; Stage 1.5, when PD is unilateral with axial involvement; Stage 2, when PD occurs bilaterally, but the patient has no balance impairment; Stage 2.5, when the patient has mild bilateral disease and when the patient is able to recover from the pull test; Stage 3, involves mild to moderate bilateral disease with some postural instability, but with physical independence; Stage 4, when the disease is severe, but the patient is still able to stand and walk without assistance; and, Stage 5, the most severe form of PD, when the patient is unable to get out of bed or out of a wheelchair without assistance.[8]

Motor Symptoms

The symptoms of PD are commonly split into motor and non-motor. Motor symptoms are frequently the most common first complaint of PD patients and are fundamental to the diagnosis of PD.[14] There are four cardinal symptoms of PD, which are assembled under the acronym TRAP: Tremor, Rigidity, Akinesia (bradykinesia), and Postural instability, and these symptoms oftentimes present asymmetrically.[15,16,17]

Tremor is very useful in the diagnosis of PD, but is not always present in patients.[3,14] Tremors can be observed when the patient is at rest, when the patient is moving or when the patient assumes a position.[14] In some cases PD patients will report a tremor when none is apparent during a physical exam.[14] These tremors are called subjective tremors and can precede the observable tremors by months or even years.[14] The classic tremor is the resting tremor, and is most associated with PD.[18] Postural tremors are different from resting tremors because they usually have a higher rate of oscillation and can be present in the absence of resting tremors.[18]

The severity of a resting tremor is not associated with the severity of dopamine deficiency in the substantia nigra.[18] The severity of a resting tremor is, however, correlated with dopamine depletion in the pallidum.[19] Even when a PD patient is treated with dopamine replacement therapy, the severity of the tremor might not respond or may even worsen depending upon the source of the dopamine depletion.[18] Alternatively,

treatment with anticholinergic agents has proven to be somewhat effective in treating resting tremors in PD patients.[18]

Currently, the pathophysiology of the resting tremor is an area of research. Some researchers have suggested that there are two different mechanisms at work, resulting in both resting and postural tremor.[18] When the motor cortex is stimulated with a transcranial magnetic field, the resting tremor and the postural tremor in PD patients who had both types (of tremors) were reset.[18] However, when the cerebellum was stimulated with a transcranial magnetic field only the postural tremor was reset.[18] This difference led the researchers to conclude that these types of tremors had different underlying pathophysiological mechanisms.[18]

Rigidity is rarely noticed by patients and is mainly detected by physicians, as patients usually report a feeling of general stiffness or pain.[2,14] Rigidity can be localized to a particular limb, be diffuse throughout the patient's body or can be localized to the patient's trunk.[2] Additionally, rigidity in PD patients can be observed when a patient moves a limb opposite to the limb affected by rigidity.[2] There are two major types of rigidity: 'lead-pipe' rigidity, characterized by a constant resistance to passive movement when tremor is not present, and 'cogwheel' rigidity, characterized by a clicking resistance due to the presense of a tremor.[2]

Bradykinesia is the most clinical significant motor symptom of PD as it is not possible to diagnose a patient with PD unless bradykinesia is present.[14] Bradykinesia is used to describe slowness or difficulty in making voluntary movements, and is identified as either axial, distal or proximal.[14,20] Symptoms of axial bradykinesia include having difficulty getting out of a chair, turning over in bed, and difficulty changing the direction of movements, while symptoms of distal bradykinesia include having trouble buttoning clothes, or tasks such as beating an egg.[14]

Bradykinesia is also seen in the face of PD patients, where it usually manifests as a reduction in spontaneous as well as emotional facial expressions.[20] Bradykinesia is unique in this regard as tremor and rigidity do not typically affect the facial muscles, perhaps due to the difference in physiology between the facial and limb muscles.[20] The reduction in spontaneous facial movements and emotional facial expression, referred to a hypomimia, usually occurs in a bilateral and symmetrical fashion.[20] Interestingly, hypomimia improves during rapid eye movement (REM) sleep and during rapid eye movement sleep behavioral disorder (RBD), which might result from the activation of the primary motor cortex and lower motor neurons.[20]

PD usually progresses faster in patients who are primarily afflicted with bradykinesia and rigidity compared to PD patients primarily afflicted with tremor.[4,14] There are two major subtypes to PD: Akinetic-rigid and Tremor-dominant.[4] There is a faster progression of disease in PD patients who suffer from the akinetic-rigid subtype, than patients who

present with the Tremor-dominant subtype.[4] Neuroimaging has shown that tremor-dominant patients have better preservation of the nigro-striatal pathway, while severe cell loss in the substantia nigra pars compacta is associated with the akinetic-rigid subtype.[4] These pieces of evidence are thought to help explain the observed differences in disease progression for these two subtypes of PD.[4]

Postural instability results from the loss of postural reflexes and is usually observed during late stage PD.[15] PD patients often complain about feeling unstable or having a lack of confidence when walking.[14] Postural instability is assessed using the pull test where the patient is quickly pulled backwards or forwards by the shoulders.[15] If the patient takes more than two steps backwards or has no postural response as seen by the manifestation of an abnormal postural response, then the patient is said to have postural instability.[15] Postural instability is a serious symptom as it can lead to an increase risk of falls.[15] Several PD risk factors are thought to increase postural instability including orthostatic hypotension, age, and a decrease in kinaesthetic ability.[15]

In addition to the four characteristics motor symptoms of PD, many patients also experience other motor difficulties, including problems with gait and bulbar symptoms.[14] Common gait problems of PD include slow shuffling strides, accelerating gait, and variable stride times.[21] There are basically two categories of gait dysfunction: continuous and episodic.[22] Continuous gait dysfunction is observed as changes in the walking pattern of PD patients that are consistent and apparent most of the time.[22] Conversely, episodic

gait dysfunction occurs intermittently and randomly.[22] Two common episodic gait disturbances are start hesitation and the freezing of gait.[22] Freezing of gait is most commonly experienced by patients in the late stage of PD.[22]

Gait debilitation is a chief complaint of patients, and is a major cause of morbidity and mortality in PD because it leads to a loss of independence and is a major cause of falls.[22] The risk of falls are very serious for PD patients as they can cause serious physical injuries, such as hip fractures. Falls can also cause a fear of falling that can in turn contibute to the institutionalization of these patients.[22] One study found that the relative risk for falling over a six month period for PD patients compared to healthly controls was 9.0.[22]

Bulbar symptoms (otherwise known as speech deficits) include dysarthria (difficulty in articulation of speech), hypophonia (abnormally weak voice), dysphagia (difficulty in swallowing) and sialorrhea (excessive salivation).[14,15] The majority of these symptoms present during the later stages of PD. Sialorrhea is the exception as some PD patients may initially present with this symptom.[14] These symptoms are thought to be related to orofacial-laryngeal bradykinesia and rigidity.[15] Dysarthria and hypophonia are also commonly observed within the elderly population making it unclear if they have a pathological relation to PD.[23] Dysphagia is often caused by PD patients being unable to start the swallowing reflex or by prolonged movements of the larynx or oesophagus.[15] PD related drooling may also be due to decreased swallowing.[15] Furthermore, dysphagia

greatly impacts the quality of life of PD patients as it can lead to complications with taking medication and can result in aspiration pneumonia, which is a major cause of death in PD.[24] Sialorrhea can often have many negative sideffects in PD patients such as embarrassment, poor oral hygiene and aspiration pneumonia, making it a serious problem in PD.[25]

The Rating of Motor Symptoms

The current scale used to rate the motor symptoms as well as many other symptoms seen is PD is the Unified Parkinson's Disease Rating Scale (UPDRS). This scale was developed in the 1980s and is divided into four parts: Part I, mentation, behavior and mood; Part II, activites of daily living (ADLs); Part III, motor exam; and Part IV complications.[26] Part III of this scale is very widely used in both research and clinical practice.[26] Overall, however, parts II and III are the most widely used parts of this scale in both the clinic and in research.[26] Studies have found that the UPDRS scale is most useful in the assessment of moderate to severe PD and is not optimally configured to address the signs and symptoms of mild PD.[26] This scale has been validated, has been shown to correlate with the Hoehn Yahr sclae for PD severity, and has both scientific as well as clinical credability.[26] One of the main drawbacks of this scale is that it does not have a comprehensive assessment of the non-motor symptoms of PD.[26] This limitation has been addressed in a modified form of the UPDRS, which will be discused in the rating of non-motor symptoms section.

Non-Motor Symptoms

The non-motor symptoms (NMS) of PD, which include neuropsychiatric symptoms, sleep disorders, autonomic symptoms, gastrointestinal symptoms, sensory symptoms, and other symptoms such as weight loss, have gone unrecognized for much of the history of PD, however, are now known to play an important role in PD.[4,27–32] Currently, PD is thought of as a multisystem disease associated with the degredation of the dopaminergic, serotonergic, noradrenergic and cholinergic systems, all of which play a role in the development of NMS in PD. However, more work needs to be done to elucidate the exact physiopathology behind NMS in PD because NMS significantly impacts the quality of life of PD patients, and are thought to greatly contritube to institutionalization.[4,12, 25,30-33]

Research has shown that many NMS, such as cognitive impairment, occur during the later stages of PD.[12,28,34] Other NMS, such as depression, tend to present in the earlier stages of PD or may even precede the development of the motor symptoms of PD like REM-sleep behvioral disorder (RBD) and olfactory dysfunction.[12,28,34] Studies have reported that NMS occur with a prevalance of 21% before the initial diagnosis of PD, and increase to 88% seven years from the onset of PD.[33] Furthermore, it is very common for PD patients to exhibit more than one NMS, with many studies reporting patients struggling with an average of 9-12 NMS.[32,35–37] Possible reasons why NMS frequently occur together is that several NMS may share common pathological mechanisms and similar secondary triggers.[36] For example, depression might result from persistent sleep

disturbances or possibly from the constant day to day disability associated with PD.[36]

Neuropsychiatric Non-Motor Symptoms

The neuropsychiatric NMS of PD include depression, anxiety, apathy, hallucinations, psychosis, dementia and confusion.[12,28,34] Depression in PD is thought to result from the combined damage of the serotoninergic system, the limbic noradrenergic, and the dopaminergic system. [12,38] PD associated depression affects 10-45% of patients and tends to precede the classic motor symtopms of PD, making it the most common of the neuropsychiatric NMS symptoms.[12,28] Interestingly, the occurrence and intesity of depression in PD patients is not correlated with the severity of motor symptoms.[38]

Over the past ten years, apathy, a state of decreased motivation characterized by a decrease in goal-directed behaviors, has been established as a distinctive symptom of PD, separate from depresssion and fatigue.[12,37] Apathy can also be observed as a loss of interest which cannot be attributed to a decreased level of cognition, a state of emotional distress, or a decreased level of consciousness.[39] Apathy is very similar to depression in many ways, except it includes the characteristic symtpoms of blunted affect, decreased intellectual curiousity, and decreased executive function.[39] Twenty-to-thirty-six percent of PD patients have been diagnosed with apathy in both the early and late stages of PD.[39] This is an important statistic because apathy is characteristic of the worsening of PD because it is predictive of a decrease in functioning of daily activities, in quality of life, in

response to therapy, and is indicitive of a poor outcome.[39] Hallucinations, like apathy, are also indicative of a decrease in daily functioning.

As many as 40% of patients, during the follow-up stages of PD experience hallucinations.[28] Visual hallucinations (VH) are the most common hallucinations experienced by PD.[12,40] Rarely, auditory hallucinations (AH) have been reported independently of or along with visual hallucinations.[12,40] Hallucinations were traditionally thought of as resulting from treatment with levodopa, but are now recognized as an intrinsic symptom to PD.[41] The presence of VH in PD patients has been associated with the presense of lewy bodies as well as lewy neurites in the limbic system, frontal cortex, temporal lobe, and parietal lobe.[41] Hallucinations in PD have also been greatly associated with sleep dysfunction, which will be futher discussed in the sleep dysfunction part of this paper.[41,42] VH are also predictive of cognitive decline and the future development of dementia, which will be discussed further.[41]

Dementia is another characteristic symptom of PD, occurring in up to 40% of patients (6 times the rate of observed in apparently healthly individuals).[12,28] Dementia in PD is characterized by a loss of visio-spatial abilities and memory, and a decrease in attention span and verbal fluency.[28,34] Dementia is progressive in PD and is thought to result from the degeneration of dopamenergic nigral cells as well as cholinergic cell loss in the nucleus basalis of Meynert.[12]. However, studies have shown that the most significant predictors of dementia were age, decreased semantic fluency, and difficulty in pentagon

copying.[34] Additionally, PD patients who initially presented with mild cognitive impairment (MCI) were also shown to be at greater risk of developing dementia than patients who did not present with MCI.[34]

Sleep Disturbance

Sleep disorders, another common NMS of PD, are estimated to affect between 40-90% of patients and tend to increase with the severity of PD.[43] This wide distribution can be attributed to differences in study populations and methodologies used throughout different studies.[43] While the impact of sleep disorders are quite expansive, sleep disorders are a significant problem in PD as they can occur during any and all stages of PD and tend to increase with the severity of PD; there are limited treatments available; and, they have a significant impact on the health related quality of life (HRQoL) and social functioning of PD patients.[43,44] Interestingly, patients often do not report sleep disturbance when asked.[43] REM sleep behavioral disorder (RBD) is one of the most heavily researched sleep disorders that is commonly observed in PD, and will be more thoroughly considered here.

RBD is characterized by patients acting out their dreams during sleep resulting from the pathologic loss of muscle atonia which acompanies REM sleep.[44,45] Movements associated with RBD, including punching, kicking, leaping out of bed, talking, shouting, crying, laughing, and singing, appear to be purposeful and tend to be violent in nature, potentially placing both the patient and their sleeping partner at risk of injury.[42,43,45,47-51]

REM sleep atonia provides a protective function as it allows humans to have physically engaging dreams without actually resulting in any of the physical movements during sleep, preventing them from harm.[48] The dreams that occur often have a negative context to them, and often involve violence where the patient is rarely the one initiating the violence within the dream.[45,48,49] In fact, a study conducted by Olson et al showed that 98% of patients with RBD report defending against an attacker during their violent dreams.[49]

RBD has received a lot of attention from the research community as this symptom is highly associated with PD and has even been reported to occur years before the clinical manifestation of PD symptoms. RBD has been estimated to have a 30-60% prevalance in PD patients, which is signficantly higher than estimates (of RBD) in the general population (0.5%).[42,47,50]

There is some evidence to suggest that PD patients who initally present with RBD are at a greater risk for developing dementia as well as VH compared to PD patients who do not initally present with RBD.[41,45,47,51] In an 8 year follow-up study conducted by Onofrj et al, RBD was found to be an independent predictor of VH in PD.[51] Additonally, studies have found PD patients with RBD to have three times the risk of developing VH as compared to PD patients without RBD, and up to 50% of PD patients with RBD have hallucinations in general.[45] Gagnon et al also demonstrated that 73% of PD patients with RBD exhibited mild congitive impairment, whereas only 11% of PD patients without

RBD showed only mild conginitive impairment.[52] Similarly, Postuma et al. found that, over a 4 year follow-up period, 48% of PD patients with RBD developed dementia compared to 0% of PD patients without RBD.[53] Interestingly, all of the patients in this study who developed dementia exhibited mild congitive impairment during the beginning stages of the study, suggesting that mild cognitive impairment, RBD and dementia might be interrelated in PD.[53] Finally, there also appears to be a male predomince of RBD in PD patients.[43]

Insomina is a nonspecific symptom commonly reported amongst PD patients, as studies have shown that 60-76% of PD patients have insomnia.[50,54] Insomia is classified by a variety of symptoms including sleep initiation problems, sleep fragmentation or early awakenings, poor sleep quality, as well as non-restorative sleep, and has been shown to have a great impact on the HQRoL of PD patients.[50,55] Insomnia is one of the most subjective complaints in PD as each individual experiences the severity of insomnia differently, there are many different causes of insomnia, there is a large variability in how long the insomia lasts, and it is difficult to stage the intensity of insomnia through questionnaries.[55] All of these different factors are believed to play a role in the large difference in which PD patients report insomia.[55] Further, several other common PD symptoms have also been linked to insomnia, such as depression and motor symptoms.

Depression, motor symptoms, and nocturia are also thought to play a role in the development of insomnia. It is not clear if insomnia causes depression or if depression is

a cause of insomnia, but the two have been correlated in many different studies.[56] Furthermore, the medication perscribed to PD patients to mitigate the motor symptoms of PD, such as levodopa, have the potential to disrupt sleep as well.[55] Insomnia has been reported to occur during the early stages of PD.[56] The presence of insomnia during the early stages of PD is consistent with Braak's hypothesis of PD progression as Braak found that the brain regions reponsible for sleep/wake regulation develop lesions relatively early on in the development of PD.[11] Lastly, the frequency of insomia in PD patients has been found to correlate with increased disease severity in PD patients.[50] Another common sleep disorder thought to contrbute to insomia is restless leg syndrome.

Restless leg syndrome (RLS) was first described in 1945 by Dr. Karl-Axel Ekbom.[57] RLS and PD are commonly associated, but the pathophysiology behind RLS in PD is curently a topic of debate as it remains unknown if RLS and PD share common pathophysiologic mechanisms.[58] RLS does, however, respond to dopaminergic drugs indicating that there could be some similar pathological process to PD.[59] RLS, unlike RBD, is not recognized as a pre-clinical symptom of PD, and RLS is not associated with the risk of devleoping PD.[43,57] No clear risk factors for the occurance of RLS in PD patients have been identified, however, RLS appears to be less severe in PD patients than in the general population.[58] RLS symptoms occur relativly late in PD patients as RLS symptoms have mainly been shown to occur after the onset of the PD motor symptoms.[43,58] Most of the PD patients who go on to develop RLS do not have a family history of RLS, suggesting that there is no prominent genetic factor playing a role.[43,58,60] Females have also been

found to have a more frequent occurrence of RLS within the general population, but this gender distribution of RLS has not been seen in PD patients.[58,60]

Many of the symptoms associated with RLS occur in PD patients who do not have RLS.[58] Akathisia, when a patient has an inner restlessness with an urge to move, is a major overlapping symptom between PD and RLS as akathisia is usually reported in late stages of PD in patients who both receive and do not receive dopamine replacement therapy.[58,61] Akathisia is still a current topic of research as it is not clear if akathisia and RLS are two separate conditions or if they are part of the same spectrum of motor restlessness in PD.[58] In addition, RLS symptoms are closely mimicked by sensory and fluctuating symptoms in relation to dopaimergic treatment within PD patients, making the distinction even more difficult.[58] RLS has been known to occur secondarily to other medical conditions like iron deficency anemia, end stage renal disease, diabetes mellitus, and rheumatoid arthritis.[62,63] Furthermore, more studies need to be done to address the proper way to teat PD patients who have RLS and RLS like symptoms, as no studies have been done on this topic and the current methodology used to treat these patients comes from treatments that are used in idopathic RLS.[57,58]

Currently, sleep disordered breathing has not been extensivly studied in PD. Obstructive sleep apnea (OSA) is the most common form of sleep disordered breathing. Past studies have indicated that OSA is more prevalent in PD patients as compared to healthy controls, but more recent studies have shown that the prevalence of OSA is not

significantly different between PD patients and healthy controls.[43,45] Additionally, no relationship has been established between OSA, disease severity, the duration of disease, daytime sleepiness, nocturia, depression, and congnitive impairment in PD patients.[43,45] This lack of association seems to indicate that PD and OSA may not be related to one another.

Excessive daytime sleepiness (EDS) is commonly observed as a persistent sleepiness that can occur from both inadequate and adequate quality and duration of sleep.[44] EDS occurs in up to 50% of PD patients.[43,45,50] The etiology behind EDS is thought to be multifactoral as it is thought that EDS results from the degeneration of the cholinergic, serotoninergic, noradrenergic, and orexin systems.[43–45] This makes sense because EDS is common to neurodegenerative diseases in general like Alzheimers Disease and PD.[44]. Sleep disorders like RLS and insomnia are also thought to play a role in the development of EDS within PD patients, although an association has not been found between nocturnal sleep disturbances and EDS.[45]

Additional Non-Motor Symptoms

There are many other NMS that occur in PD and they will be briefly mentioned here. These other NMS include: orthostatic hypotension, sexual dysfunction, bladder distrubances, sweating, and xerostomia (dry eyes), nausea, vomiting, constipation, defecatory dysfunction, pain, paresthesia and olfactory dysfunction. [12,64–66]

This section will specificlly focus on orthostatic hypotension, sexual dysfunction, constipation, pain, and olfactory dysfunction.

Orhtostatic hypotension (OH) results, in patients seeing black spots within the visual field, dizziness, faintess, and the loss of conciousness.[67] OH is a major problem in PD because it has an impact on the mortality[67] of the PD population and can cause physical injuries by inducing falls.[68] Sexual dysfunction is not highly prevelent in PD[8] and both a decreased and abnormally high sex dirve have been reported by patients.[12,28] Sexual dysfunction has also been reported more in males than females, although both sexs have reported changes in sexual activey after the onset of PD.[69] Constipation is generally defined as less than three bowel movements per week.[64] Additionally, conspitation is now recognized as a symptom that can occur before the onset of the cardinal motor symtpoms in PD,[8,70] with some studies reporting that constipation can occur 18 years before the onset of the diagnostic motor symtpoms.[8] Pain is very prevelent in PD as it effects about 54% of patients, but is often undertreated. [71,72] Pain has also been found to be the leading factor on the physical HRQoL of early stage PD patients, making it an important issue from the patients prospective.[71,72] Olfactory dysfunction is hugely prevelent in PD as it occurs in about 90% of PD cases.[28,73] Olfactroy dysfunction is also particularly interesting as it is a pre-clinical symptom of PD.[12,73–75] Furthermore, people who have olfactrory dysfuncation have been shown to be at an increased risk of developing PD in the future.[73,75]

Rating of Non-Motor Symptoms

Now that some of the various NMS of PD have been discussed, this paper will now briefly go through some of the major tools that are used to research and detect the NMS of PD both in the research and clinical setting. NMS have been becoming more researched in the PD literature over time, which eventually led to the creation of the NMS questionnaire in 2006 by a panel of experts.[29] The NMSQuest is a screening questionnaire that is not intended for the assessment of the severity of NMS in PD.[29] This questionnaire is composed of 30 items that are to be completed by the patient with the patient indicating yes or no box next to the described symptom.[29] The questionnaire groups the NMS of PD into 10 different catagories: gartrointestinal tract, urinary tract, sexual function, cardiovascular, apathy/attention/memory, hallucinations/delusions, depression/anxiety/anhedonia, sleep/fatigue, pain, and miscelaneous (ex wieght loss).[29]

A limitation of the NMSQuest is the fact that it cannot rate the severity of NMS in PD patients, resulting in the development of the Non-Motor Symptoms Scale (NMSS) in 2007. One of the major differences between the NMSQuest and the NMSS, is that a physician is the one who records the NMS experienced by the patient instead of the pateint themselves.[76] The NMSS is a 30 item survey which records both the frequency, from 1-4, and the severity, from 0-3, for NMS.[76] The frequency and severity are then multiplied together in order to give a numerical score for each of the 30 items.[76] Accordingly, the NMSS is able to capture symptoms that are severe and infrequent as well as those that are frequent and not severe.[76]

The NMSS was initally studied in 242 PD patients in the UK, Italy, Germany, Japan, and the US by Chaudhuri and his team in 2007.[76] In this study the NMSS score of PD patients was found to increase as the severity of the disease increased as meaured by Hoehn and Yahr stages (HY).[76] The NMSS is intended to be used to obtain a holistic assessment of the severity and frequency of NMS in PD, not as a diagnostic pannel for NMS is PD.[76]

In addidition to both the NMSQuest and the NMSS, there are many other scales that can be used to look for the presence as well as the severity of NMS in PD. The most inclusive NMS scale after the NMSQuest and the NMSS is the modified version of the unified Parkinson's disease rating scale (UPDRS), developed by the Movement Disorder Society in 2008. The modified scale is called the movement disorder society-unified Parkinson's disease rating scale (MDS-UPDRS). This scale is very similar to the UPDRS except that it has an additional section that covers NMS in PD.

The MDS-UPDRS covers several NMS such as sleep problems that occur both in the day and during the night, pain, urinary problems, constipation, and salivation.[77] Furthermore, the MDS-UPDRS differs from that UPDRS in that symptoms are reported as slight/mild/moderate/severe from mild/moderate/severe/marked, making it easier to detect early symptoms of PD.[26] Therefore the MDS-UPDRS will most likely be utilized more in the future as clinical trials begin focusing on the early symptoms of PD.[26]

Finally, the MDS-UPDRS has been shown to perform very well in comparison to the UPDRS and has been validated.[26]

Sex

The role that sex plays in the development and manifestation of different PD symptoms has not been well studied in the past, but is an active subject of current research. There has been an increase in interest in the impact biological sex has on the development of PD because PD appears to affect men and women differently.

There is a difference in the prevalence and incidence of PD amongst men and women, as PD is seen more commonly in men across all ages and ethnic groups.[78,79] The incident rates of PD in men compared to women range from 1.37 to 3.70, respectively.[78] Additionally, men are two times as likely to be diagnosed with PD than women.[79] Studies have also suggested that women have a greater average age of PD onset than men, however different studies have reported different ages of onset in each gender.[78,79] The difference in the observed ages of onset between studies is most likely due to differences in the sampled populations studied.[79]

There also appears to be some differences in the presentation of motor and neuropsychiatric symptoms associated with PD in both sexes. Women tend to have a delayed onset of certain motor symptoms and are more likely to present with the tremor-dominant subtype of PD.[78,79] This observation is interesting as the tremor-dominant

phenotype of PD has been associated with a slower progression of PD as measured by the UPDRS.[79] Some experts suggest that the observed delay of onset of motor symptoms in females could be due to higher levels of dopaminergic activity in women, however, this notion is not supported in the research.[79] Women are more likely than men to report greater disability and a lower quality of life, however this finding is not unique to PD as women, compared to their male peers, are more likely to report a functional disadvantage.[79] One study found that women have greater difficulty with postural instability as compared to men.[79].This is of clinical importance because women are more prone to falls than men and have a lower bone mineral density than men, which also increases their risk of sustaining a fracture.[79]

Women are at a higher risk of developing cognitive decline, dementia, depression, constipation and dyskinesia, a common side-effect of levodopa treatment, as compared to men.[78–80] On average women take higher doses of levodopa per kilogram of body weight, which is thought to play a role in the observed difference of dyskinesia reporting between the sexes.[80] Men are more likely to have EDS, dribbling and sexual symptoms.[78] There have also been observed differences in sleep disorders between the two sexes with a higher prevalence of RBD in men than women.[78–80] Researchers have called into question the role estrogen might have in PD patients. Many studies focusing on estradiol have shown that estradiol has a neuroprotective effect, however, most of the evidence comes from animal models.[78] Finally, sex genes are also being investigated as the SRY gene

(responsible for determining the male sex on the Y-chromosome) is expressed in a subset of dopaminergic neurons in the SNpc in males.[78]

Race

The impact of race on the outcome of patients with PD has only recently begun to be studied. Currently, epidemiology studies have not focused on the distribution of PD in non-whites within the US.[81] Past studies have shown conflicting evidence regarding the distribution of PD within different races with studies showing that different races have the highest prevalence of PD.[81,82] They also found a much higher prevalence of PD in Whites as compared to Black and Asians, which seems to suggest that there is a genetic component driving this observed difference.[81]

Even though previous studies appear to shows that Blacks suffer more severely from PD, it is unclear if the increased morbidity is due to biological reasons or due to a difference in timing of PD diagnosis. Studies have found that Blacks were more likely to be diagnosed at a later stage of PD than their White peers.[83,84] Additionally, it has been observed that Blacks report less motor disability than Whites when both had the same level of motor impairment.[83] The under-reporting of motor disability in Blacks accounts for a significant difference of the stage at which Blacks where diagnosed as compared to Whites.[83] These studies suggest that the observed increase in mortality of PD patients who are Blacks is caused by the later stage at which Blacks receive their PD diagnosis. Overall, it is important to consider both biological, socioeconomic, and access to health

care resources when trying to deduce the cause behind the increased mortality associated with Blacks who have PD.[82]

Treatment Methodologies

There are many different types of treatments used for PD. Currently, all the treatments that are used to treat PD simply reduce the symptoms associated with the disease, having no effect on the rate of neurodegeneration characteristic of neuropathology in PD. A majority of the current research on PD treatment is focusing on new therapies that will have a neuroprotective effect and thus will slow the progression of PD. The pharmacologic therapies that will be considered in this section are levodopa (L-dopa), monoamine oxidase B (MAO-B) inhibitors, catechol-O-methyltransferase (COMT) inhibitors, and dopamine agonists (DA).

The use of levodopa in PD began in the early 1960s and was approved by the FDA in 1967. Levodopa (L-dopa) is still considered the "gold standard" treatment in PD today, and the development of L-dopa is viewed as one of the most important advances in the treatment of neurodegenerative disorders. L-dopa is a precursor of dopamine and is readily converted to dopamine in the peripheral tissues as well as within the brain.[8] Once L-dopa reaches the brain it is taken up by striatal neurons that subsequently convert L-dopa into dopamine, resulting in an increased amount of dopamine within the brain, reducing the motor symptoms of PD patients.[8] L-dopa treatment is limited in that it has a short half-life of approximately 90 minuets that is mainly due to the actions of aromatic

amino acid decarboxylase (AAAD) and COMT.[8] Many physicians will often prescribe an AAAD inhibitor, carbidopa or benserazide, as well as a COMT inhibitor with L-dopa resulting in an increased bioavailability of L-dopa within the blood stream.[8] COMT inhibitors are also thought to help to smooth out the levels of L-dopa within the plasma over time, allowing for a more continuous delivery of L-dopa, which is thought to help reduce motor fluctuations as well as dyskinesia.[8]

MAO-B inhibitors are also frequently used to treat PD. MAO-B is an enzyme that plays an integral role in the metabolism of dopamine within the CNS. MAO-B inhibitors are thought to be beneficial to PD patients by preventing the degradation of dopamine by MAO-B in the CNS, inhibiting dopamine reuptake, and indirectly promoting the increased release of dopamine.[8] Interestingly, MAO-B inhibitors have been shown to have neuroprotective effects in both cellular and animal models through multiple mechanisms such as down regulating proapoptotic proteins, up regulating antiapoptotic proteins, and increasing the amount of antioxidant enzymes.[8]

Dopamine agonists (DA) are synthesized molecules that bind to dopamine receptors. DAs are thought to have several advantages over levodopa in terms of their pharmacokinetic and pharmacodynamic properties. DAs do not have to be converted or stored in nigrostriatal neurons as they act directly on the dopamine receptors.[8] Additionally, DAs are not metabolized by the liver as readily as L-dopa is, allowing for more of the DA to be available in the systemic circulation after the first pass.[8]

Furthermore, DAs have a longer half-life than L-dopa allowing for higher levels of active chemical within the systemic circulation over time[8]. DAs are limited in that they are not tolerated as well as L-dopa is by patients as they are associated with a higher rate of occurrence of orthostatic hypotension, nausea and vomiting.[8] Sleep disturbances are also commonly reported with both DA and L-dopa therapy, with the sudden onset of sleep being the most troubling.[8]

Conclusion

The primary objective of this study is to determine how race, sex and sleep disturbance impact the severity of PD as recorded by the modified HY scale in the ON and OFF medication states, while controlling for the confounders of age and time in years from onset of PD symptoms to database entry. The current literature on how PD impacts different races is inconclusive as some studies suggest that there is a biological difference causing the observed differences in PD severity between the races while others suggest that socioeconomic factors explain these differences. Sex has also just recently been studied in PD and it is still unclear how sex impacts PD symptoms and severity. Additionally, sleep disturbance has been shown to greatly impact PD patients and therefore it will be interesting to see how disease severity is impacted in PD patients with sleep disturbances at Boston University Medical Centre (BUMC).

METHODS

Patient Recruitment and Data Collection

This cross-sectional study sought to assess how race, sex, and sleep disturbance impacted the severity of PD in both the ON and OFF medication states as measured by the HY scale. All of the data used for the analysis in this thesis was obtained from the Movement Disorders Database kept by the Boston University Medical Center's (BUMC) Movement Disorder Clinic (MDC). Patients were included in this study if a movement disorder specialist from the MDC diagnosed them with a movement disorder, such as PD or PSP. The movement disorder specialists collected the relevant information for the database by completing a survey and referring to medical records to verify the accuracy of the information obtained. The data collected on the HY scores both in the ON and OFF medication states were obtained from the medical records. This study included data from patients seen at the MDC from 2007-2012. A total of 673 subjects were included in the Movement Disorders Database, of whom 452 patients were diagnosed with PD. Only the PD patients were included for the analysis for this study.

The data from the Movement Disorders Database were saved on a password protected flash drive with the database itself being password protected as well. All patient information was de-identified and the BUMC IRB approved this project.

The primary objective of this study was to determine how sleep disturbance, sex, and race impacted the severity of PD in both the ON and OFF medication states as measured by the HY scale. The confounding factors of age, education, and time in years from the onset of PD symptoms to database entry, where all controlled for to better assess the impact the primary predictive variables had on HY scores both in the ON and OFF states. The secondary objectives of this paper sought to analyze the correlations between hallucinations, dementia and autonomic symptoms and HY ON and HY OFF scores. This secondary analysis was done to get a better idea of how other NMS impacted HY scores. Additionally, this secondary analysis was completed because the large amount of missing sleep disturbance data made it difficult to determine what correlation sleep disturbance had with HY ON and OFF scores. Therefore, it seemed appropriate to look at what relationships dementia and hallucinations had with HY ON and OFF scores as both of these symptoms are thought to be impacted by sleep disturbance.

Information Collected in the Survey

The survey collected information on patient demographics, movement disorder disease diagnosis, family history, current or past medications used, and surgical treatment undergone by the patient. The types of medications included in the survey were not limited to common PD medications like levodopa, but also included any sort of general medications that patients were taking such as anti-inflammatory agents. Additionally, the patients full name, date of birth, current address, primary language, and insurance type were also collected. In the de-identified database used for the analysis of this study, the

patient's full name, address, day and month of birth, were all omitted from the data set to ensure the confidentiality of patient information. Data collected on the patient's racial background, and highest level of education achieved were recorded with regards to predetermined categories. Furthermore, the occupational background of the patient was also collected. The date of onset of the movement disorder, the date of diagnosis of the movement disorder, and any disease diagnosis in the patient's grandparents, parents, siblings or children were also collected. The types of diagnoses that were collected on the patient's next of kin pertained to neurological disorders, such as dementia, depression and dystonias. This survey also collected information on common complications associated with medication such as dyskinesia and motor fluctuations. Additionally, this survey also included categories pertaining to the common NMS associated with PD such as sleep disturbance, depression, dementia, hallucinations, psychosis, compulsive behaviors, freezing of gait, orthostatic hypotension, and other autonomic symptoms.

Statistical Analyses

All statistical analysis was conducted using R version 3.2.3. All missing data was handled such that it was eliminated from statistical analysis. Race was modified by combining many subcategories in order to obtain a large enough sample to include in statistical modeling and testing. The survey consisted of the following African racial categories: African-Black (Sub-Sahara), African North (originating from Sahara or Northern Regions: Algeria, Egypt, Morocco, Tunisia, Ect.), and African- Black (those of African decent originating from Canada, Caribbean, Brazil, US,). These categories were all

combined into the African category. All other racial categories, including: Asian-East (originating from China or Japan or Korea), Asian-West (originating from Bangladesh, India, Iran, Iraq or Pakistan), American Indian/Alaskan native, Native Hawaiian/Pacific Islander, Mixed Race, and other, were combined into the 'Other' racial category. The Spanish and Caucasian racial categories were maintained. Otherwise no other data was combined and the data was left in the original form.

The objective of this study was to examine the differences between HY scores ON and OFF medication as they related to sleep disturbance, race, and gender. Secondary analyses were conducted to assess the effects of dementia, depression, hallucinations and autonomic dysfunction on HY scores ON and OFF medications. Lastly, the potential confounding effects of age, the time from disease onset to entry into the Movement Disorders Database, and education were assessed. Several different statistical tests were used to analyze the association between the primary predictors, secondary predictors and confounders.

The differences between the means in HY scores ON and HY OFF medication between patients who reported sleep disturbances, who did not report sleep disturbances, and patients who were not asked about sleep disturbances were compared utilizing a student t-test. A t-test was used instead of a one-way ANOVA because the main comparison of interest was between patients who reported sleep disturbances versus patients who did not report sleep disturbances. A student t-test was also used to determine if the differences in

mean HY scores ON and HY OFF medication was statistically different between sexes. The comparisons of means in HY scores ON and OFF medication for race were analyzed using a one-way ANOVA test. If statistical significance was found between the various means in HY scores ON and OFF medication for the different racial categories, a Tukey-Kramer test was run to determine the statistical difference between individual racial subgroups.

The confounding variables were analyzed in a similar fashion as the primary outcome variables. A one-way ANOVA test was also used to determine if a statistically significant difference was present in the mean HY scores ON and HY OFF medication for the various educational subgroups. A Tukey-Kramer test was used in conjunction with the one-way ANOVA if a statistical difference was found. The confounders of age and time difference in years from the onset of disease symptoms to entry into the database were analyzed using univariate linear regression. A linear regression model was chosen because the modified HY score used in the database consisted of nine separate categories, allowing the outcome variable of HY scores to be treated as continuous. Additionally, the HY scores also have a rough normal distribution and thus a linear regression model seemed most appropriate for the data.

After the initial analysis, several univariate and multivariate linear regression models were built with the HY scores ON and OFF medication serving as the outcome variable. A total of six univariate linear regression models, for each of the predictor and

confounding variables, were run for both HY scores ON and HY OFF medication. A total of four multivariate linear regression models were built, but only the two excluding sleep disturbance as a predictor are included. The two models including sleep disturbance models provided some useful information, but were limited in that most of the data on sleep disturbance was missing, causing these models to have a very small sample size. Therefore sleep disturbance was eliminated in the additional models reported in this thesis.

Finally the association between HY scores ON and OFF medication and the NMS of depression, dementia, hallucinations and autonomic dysfunction were assessed. These variables were chosen because past literature has shown that they have a great impact on the HRQoL of PD patients, however, research on how these variables affect HY scores both ON and OFF medication states is limited. A multivariate linear regression model was run on these variables and HY scores ON and OFF medication to determine how these NMS impact HY ON and OFF scores. All linear regression models were reported with the calculated regression estimates, 95% confidence intervals around the calculated estimates, p-values obtained for each reported estimate, and the r^2 value. The r^2 value is used to indicate how well the regression line fits to the data. Taking the explained variance and dividing it by the total observed variance calculates the r^2 value. The calculated number ranges between zero and one. Generally, a larger r^2 value is indicative of a superior model fit. However, it is very common to have small r^2 values when working with human data, as there is a lot of variance between people in general. Finally,

a small r^2 value does not mean that the results of a linear regression are not meaningful as the estimates still provide valuable information on how the outcome variable changes with a one-unit change in the predictor variable.

RESULTS

Age, Sex, Sleep Disturbance & Education

Table 1: Age, Sex, Sleep Disturbance, and Education Break Down

Predictors	Number	Percentage
Age:		
0-9	1	0.2
20-29	1	0.2
30-39	2	0.4
40-49	14	3.1
50-59	82	18.1
60-69	131	29
70-79	153	34
80-89	56	12.4
90-99	5	1.1
Sex:		
Male	261	57.7
Female	184	40.7
Sleep Disturbance:		
Yes	54	11.9
No	90	19.9
Race:		
Caucasian	375	83
African	28	6.2
Spanish	17	3.8
Other	19	4.2
Education:		
Less Than High School	17	3.8
Some High School/ No Degree	14	3.1
High School Degree/GED	83	18.4
Associates Degree	10	2.2
Some College/ No Degree	36	8
Bachelor's Degree	110	24.3
Graduate or Professional Degree	109	24.1
Time from Onset to Database Entry		
0-4 Years	106	23.5
5-9 Years	108	23.9
10-14 Years	20	15.5
15-19 Years	45	10.0
20-24 Years	19	4.2

25-29 Years	9	2.0
30-34 Years	4	0.9
35-39 Years	2	0.4

Table 2: Original Racial Categories

Racial Groups	**Number**	**Percent**
African - Black (Sub-Sahara)	1	0.2
African - North (Sahara or Northern Regions: Algeria/ Egypt/ Morocco/ Tunisia/ Etc.)	4	0.9
Black-(African descent/ Originating in: Canada/ Caribbean/ Brazil/ US/ etc.)	23	5.1
American Indian/Alaska Native	6	1.3
Asian - East (China/ Japan/ Korea/ etc.)	9	2.0
Asian - West (Bangladesh/ India/ Iran/ Iraq/ Pakistan/ etc.)	2	0.4
Caucasian	375	83
Mixed Race	1	0.2
Native Hawaiian or Other Pacific Islander	1	0.2
Spanish (Cuban/Iberian Peninsula/ Mexican/South or Central American/ or Other Spanish Origin)	17	3.8
Missing Information:	13	2.9

Sixty-three percent of the study population ranged in age between 60 -79 years, and the study population had a mean age of 68.4 years (+/- 10.5 year SD) (**Table 1**). The age distribution of the population appears to be approximately normally distributed. The study population was mostly composed of males, 57.7%, and was primarily Caucasian, 83%. The second largest racial category, 6.2% of the overall population, was African (**Tables 1 & 2**). The educational background of the study population was fairly evenly distributed with 48.4% of the study population having earned a college degree or higher. Lastly, the time in years from onset of PD symptoms to database inclusion ranged from 0-40 years, with 47.4% of subjects added (to the database) between 0-9 years of symptom

onset. Overall, the average amount of time from the onset of PD symptoms to inclusion in the movement disorders database was 9.4 years (+/- 7 yrs. SD).

Missing Data

Table 3: Missing Data for Predictors, Confounders, and Outcome Variables

Predictors	**Number**	**Percentage**
Age	7	1.5
Sex	7	1.5
Sleep Disturbance	308	68.1
Race	13	2.9
Education	73	16.2
Time from Onset to Database Entry	89	19.7
Outcome	**Number**	**Percentage**
Hoehn Yahr ON	60	13.2
Hoehn Yahr OFF	60	13.2

Table 4: Sleep Disturbance Data by Racial Categories

Race	**Yes**	**No**	**Missing Sleep Data**
African	4	6	18 (64%)
Caucasian	40	73	262 (73%)
Spanish	2	6	9 (53%)
Other	4	3	12 (63%)
Race Missing	4	2	7 (54%)

Table 5: Sleep Disturbance by Sex

Sleep Disturbance	**Male**	**Female**	**Missing Gender**
Yes	37	17	2
No	57	33	0
Missing Sleep Data	167 (64%)	134 (72.3%)	7

Table 6: Hoehn Yahr OFF and ON Medication Scores Break Down:

HY Stage:	**HY OFF**	**HY OFF Percent**	**HY ON**	**HY ON Percent**
0	23	5.1	285	60.3
1	25	5.5	8	2.0
1.5	14	3.1	2	0.4
2	144	32.0	21	4.6
2.5	49	11.0	23	5.1
3	64	14.2	22	4.9
3.5	2	0.4	1	0.2
4	45	10.0	13	2.9
4.5	2	0.4	0	0
5	24	5.3	17	3.8
Total	392	-	392	-
Mean	2.5	-	0.8	-
SD	1.2	-	1.5	-

Missing data for every data category is represented in **Table 3**. The most significant amount of missing data came from the sleep disturbance variable. The 308 patients missing sleep disturbance data, 68.1% of the study population, resulted from these patients not being asked about sleep disturbance by the movement disorder specialist. The missing sleep disturbance data seems to be distributed evenly amongst the various racial categories in terms of percentages (**Table 4**). Additionally, sleep disturbance data had a higher percentage of missing data amongst females, 72.3% versus 64%, for females and males, respectively (**Table 5**). Age, sex and race had little missing data. A little more than 10% of data was missing from both the HY ON and OFF scores (**Table 3**) and the distribution of both the HY ON and HY OFF scores are given by **Table 6**.

Difference in Mean HY ON and OFF Score

Table 7: Difference in Means of HY ON and HY OFF Score

Predictors	**HY ON Score Mean (SD)**	**HY OFF Score Mean (SD)**
Sex:		
Male	0.81 (1.4)	2.40 (1.2)
Female	0.81 (1.5)	2.60 (1.1)
P-value t-test	0.95	0.05*
Race:		
Caucasian	0.80 (1.5)	2.5 (1.2)
African	1.04 (1.7)	2.4 (1.4)
Spanish	0.56 (1.4)	2.2 (0.8)
Other	0.46 (0.9)	2.2 (0.9)
P-Value ANOVA	0.60	0.70
Sleep Disturbance:		
Yes	2.7 (1.2)	1.1 (1.8)
No	2.6 (1.3)	0.8 (1.6)
Missing Data	0.7 (1.3)	2.4 (1.1)
P-value t-test => Yes vs. No	0.71	0.30
Education:		
Less Than High School	0.7 (1.7)	2.8 (1.4)
Some High School/ No Degree	1.3 (2.1)	3.0 (1.4)
High School Degree/GED	0.8 (1.5)	2.3 (1.0)
Associates Degree	0.3 (1.0)	2.7 (1.1)
Some College/ No Degree	1.0 (1.4)	2.5 (1.2)
Bachelor's Degree	0.8 (1.4)	2.4 (1.1)
Graduate or Professional Degree	0.8 (1.5)	2.3 (1.2)
P-Value ANOVA	0.80	0.23
Time from Onset to Database Entry (years)		
Estimate (CI)	0.03 (0.007-0.05)	0.08 (0.07-0.1)
P-value Regression	0.01*	$< 2.2x10^{-16}$ *
Age		
Estimate (CI)	0.007 (-0.006-0.02)	0.03 (0.02-0.04)
P-value Regression	0.29	$1.2x10^{-10}$ *

*** Indicates a P-values less than or equal to 0.05**

The differences in means between the HY scores ON and OFF medication for the predictor and confounding variables are presented in **Table 7**. The time in years from the onset of PD symptoms to entry into the movement disorders database was positively associated with both HY scores ON and OFF medication. The linear regression models for age and HY scores ON and OFF medication demonstrated that age was associated with only the on HY scores OFF medication. There was a significant difference between the mean HY ON and HY OFF scores between males and females, which suggests that sex may have an impact on disease severity in PD. Lastly, race, education and sleep disturbance did not show any significant difference between their mean HY ON and HY OFF scores. The initial analysis presented in **Table 7** suggests that sleep disturbance, race, and education do not appear to have an impact on HY ON and HY OFF scores as their mean HY ON and HY OFF scores are not significantly different from one another.

Differences in Mean Age and Mean Time from Onset to Database Entry

Table 8: Difference in Means between Age and Onset to Database Entry

Confounders	**Age Mean (SD)**	**Years From Onset to Database Entry Mean (SD)**
Sex:		
Male	68.2 (10.4)	9.5 (7.0)
Female	68.6 (11.7)	9.5 (7.0)
P-value t-test	0.71	0.99
Race:		
Caucasian	68.5 (11.1)	9.7* (7.1)
African	70.4 (10.2)	5.7* (4.4)
Spanish	65.4 (6.5)	7.3 (4.5)
Other	63.6 (11.5)	8.8 (6.6)
P-Value ANOVA	0.13	0.03

Sleep Disturbance:		
Yes	66.7 (10.5)	10.0 (7.8)
No	67.7 (9.1)	8.2 (6.2)
Missing Data	68.7 (11.5)	9.7 (7.1)
P-value t-test	0.53	0.20
Education:		
Less Than High School	71.1 (7.6)	6.8 (5.7)
Some High School/ No Degree	68.6 (16.1)	11.6 (7.7)
High School Degree/GED	68.6 (12.8)	9.1 (7.7)
Associates Degree	62.3 (7.0)	9.9 (7.3)
Some College/ No Degree	68.7 (11.4)	12.1 (9.0)
Bachelor's Degree	66.7 (10.8)	8.9 (7.0)
Graduate or Professional Degree	68.2 (10.2)	9.2 (6.0)
P-Value ANOVA	0.47	0.23
Time from Onset to Database Entry (years)		
Estimate (CI)	0.34 (0.18-0.50)	
P-value Regression	$2.3x10^{-5}$ *	
Age		
Estimate (CI)		0.14 (0.08-0.21)
P-value Regression		$2.3x10^{-5}$ *

*** Indicates a P-value less than or equal to 0.05**

Table 8 shows the differences in mean age and mean time in years from the onset of PD symptoms to database entry for the predictor and confounding variables. Sleep disturbance, sex and education were not significantly different in terms of their mean age or in terms of their time in years from symptom onset to database entry. Time in years from symptom onset to database entry did, however, show a significant positive association with age as determined from a univariate linear regression model. Age showed a similar significant positive association with time from PD symptom onset to database entry as determined from a similar univariate linear regression model. Race was

also shown to have significant differences in years from symptom onset to database entry, as determined by a one-way ANOVA test. Further analysis of this significant result with a Tukey-Kramer test, indicated that only Caucasians and Africans had a significant difference in years from Onset to database entry.

Univariate Linear Regression Models

Table 9: Univariate Linear Regression Models Predicting HY ON Score

Predictor	Estimate	CI	P-Value	R^2
Sleep Disturbance:	0.33	-0.28-0.94	0.28	0.0012
Age:	0.007	-0.005-0.02	0.29	0.0003
Sex:				-0.005
Male:	Ref			
Female:	0.009	-0.28-0.03	0.95	
Race:				-0.003
Caucasian:	Ref			
African:	0.24	-0.35-0.83	0.50	
Spanish	-0.24	-0.95-0.46	0.50	
Other:	-0.34	-1.11-0.44	0.40	
Education:				-0.008
Less Than High School	-0.06	-0.83-0.70	0.90	
Some High School/ No Degree	0.56	-0.32-1.50	0.21	
High School Degree/GED	0.05	-0.40-0.51	0.83	
Associates Degree	-0.44	-1.44-0.60	0.40	
Some College/ No Degree	0.22	-0.37-0.80	0.50	
Bachelor's Degree	0.10	-0.32-0.51	0.70	
Graduate or Professional Degree	Ref			
Time Until Database Entry	0.028	0.007-0.05	0.01*	0.02

*** Indicates a P-values less than or equal to 0.05**

Table 10: Univatiate Linear Regression Models Predicting HY OFF Score:

Predictor	Estimate	CI	P-Value	R^2
Sleep Disturbance:				-0.007
No	Ref			
Yes	0.09	-0.38-0.55	0.72	
Age:	0.033	0.023-0.043	$1.2x10^{-10}$ *	0.10
Sex:				0.005
Male:	Ref			
Female:	0.47	-0.68-1.62	0.42	
Race:				
Caucasian:	Ref			-0.004
African:	-0.04	-0.51-0.44	0.90	
Spanish	-0.30	-0.84-0.30	0.35	
Other:	-0.26	-0.88-0.36	0.41	
Education:				0.006
Less Than High School	0.49	-0.1-1.09	0.10	
Some High School/ No Degree	0.74	0.05-1.4	0.03 *	
High School Degree/GED	0.004	-0.34-0.36	0.98	
Associates Degree	0.42	-0.36-1.20	0.29	
Some College/ No Degree	0.24	-0.21-0.69	0.29	
Bachelor's Degree	0.09	-0.22-0.42	0.56	
Graduate or Professional Degree	Ref			
Time Until Database Entry	0.08	0.068-0.10	$<2x10^{-16}$ *	0.25

*** Indicates a P-values less than or equal to 0.05**

Table 9 shows all of the univariate linear regression models that were created to predict HY scores ON medication. The only significant finding from these models was the slight positive association found between time from symptom onset to database entry. **Table 10** shows all of the univariate linear regression models built to describe HY scores OFF medication. Sex, race, and sleep disturbance had no impact on HY scores ON and HY OFF medication. Age, however, was shown to have a significant positive association with HY scores OFF medication, but had no significant association with HY scores ON

medication. Time in years from symptom onset to database entry was also shown to have a significant positive association with HY scores OFF medication. This was the only variable that was shown to have a positive significant association with both HY scores ON and HY OFF medication in the univariate linear models. Finally, having some high school education without obtaining a high school degree was also associated with an increase in HY scores OFF medication. This finding will be discussed further in the discussion section, as the clinical significance of this finding is uncertain.

Multivariate Linear Regression Models

Table 11: Multivariate Linear Regression Model Predicting HY ON Score

Predictor	Estimate	CI	P-Value	R^2
Age:	0.01	-0.003-0.025	0.15	
Race:				
Caucasian	Ref			
Black	0.22	-0.41-0.85	0.49	
Spanish	-0.04	-0.80-0.73	0.93	
Others	-0.07	-1.03-0.88	0.87	
Time Until Database Entry	0.03	0.004-0.052	0.02*	
R^2				0.02

*** Indicates a P-values less than or equal to 0.05**

Table 11 shows the multivariate model run to predict HY scores ON medication using age, race, and time in years from onset until database entry. Gender and education were eliminated from the multivariate analysis as previous analysis indicated that gender and education had no significant effect on HY scores ON or OFF medication. This model yielded no significant results, except for time in years from onset to database entry, and

did not appear to effectively capture what variables were most significant in predicting HY scores ON medication, as indicated by the small R^2 value.

Table 12: Multivariate Linear Regression Predicting HY OFF Score

Predictor	Estimate	CI	P-Value	R^2
Age:	0.02	0.01-0.03	$3.4x10^{-5}$ *	
Race:				
Caucasian	Ref			
Black	0.46	0.02-0.90	0.04*	
Spanish	0.10	-0.41-0.62	0.68	
Others	-0.16	-0.78-0.46	0.61	
Time Until Database Entry	0.08	0.06-0.09	$2x10^{-16}$ *	
R^2				0.30

*** Indicates a P-values less than or equal to 0.05**

Table 12 shows the multivariate model run to predict HY scores OFF medication using age, race, and time in years from onset until database entry. This model showed that age, race and time in years until database entry were all significant in predicting HY scores OFF medication. The significant effect that race has on HY scores OFF medication is very interesting and will be discussed more thoroughly within the discussion section. The positive associations for both age and time in years from disease onset to database entry, are not surprising given the results from the previous analysis.

Secondary Analysis

The secondary analysis sought to investigate the association that NMS might have with HY scores ON and OFF medication. Building multivariate regression models would allow for the associations the NMS had on HY ON and OFF scores to be thoroughly

explored while allowing for previous predictors that were found to have a significant effect on HY scores ON and OFF medication to be effectively accounted for. Previous research indicated that hallucinations, autonomic dysfunction and dementia should have a significant impact on HY scores OFF medication. It is not well known, however, how these symptoms impact HY scores ON medication, making it hard to predict what association these variables might have with HY scores ON medication.

Table 13: Race, Age, YOE, and Non-Motor Symptoms Predicting HY ON

Predictors	**Estimate**	**CI**	**P-value**
Age	0.008	-0.006-0.024	0.24
Race			
Caucasian			
Black	0.22	-0.40-0.85	0.50
Spanish	-0.10	-0.84-0.65	0.79
Others	-0.16	1.06-0.74	0.72
Time Until Database Entry	0.023	-0.001-0.048	0.06
NMS			
Dementia	0.17	-0.25-0.61	0.42
Autonomic Dysfunction	0.19	-0.29-0.67	0.43
Hallucinations	0.12	-0.29-0.54	0.56
R^2 0.016			

*** Indicates a P-values less than or equal to 0.05**

Table 14: Race, Age, YOE, and Non-Motor Symptoms Predicting HY OFF

Predictors	**Estimate**	**CI**	**P-value**
Age	0.018	0.008-0.030	0.0004
Race			
Caucasian	Ref		
Black	0.46	0.048-0.86	0.02
Spanish	0.04	-0.44-0.54	0.84
Others	-0.26	-0.86-0.33	0.38
Time Until Database Entry	0.07	0.05-0.08	$4.1x10^{-13}$
NMS			
Dementia	0.52	0.24-0.80	0.0003
Autonomic Dysfunction	0.47	0.16-0.80	0.003

Hallucinations	0.28	0.007-0.55	0.04
R^2 0.38			

*** Indicates a P-values less than or equal to 0.05**

Tables 13 and **14** show the multivariate regression analysis utilizing age, race, time in years from onset to database entry, dementia, hallucinations, and autonomic dysfunction to predict HY scores ON and HY medication, respectively. None of these variables appeared to have a significant impact on HY scores ON medication, whereas all of these variables appeared to have a significant impact on HY scores OFF medication. The large effect that race has on HY scores OFF medication, while accounting for NMS is very interesting. Additionally, the model depicted in **Table 14** appears to fit the data well, as based upon the R^2 value and residual plots that were reviewed. These results will be examined in more detail in the discussion section.

Figure 1: HY ON Score vs. HY OFF Score Scatter Plot

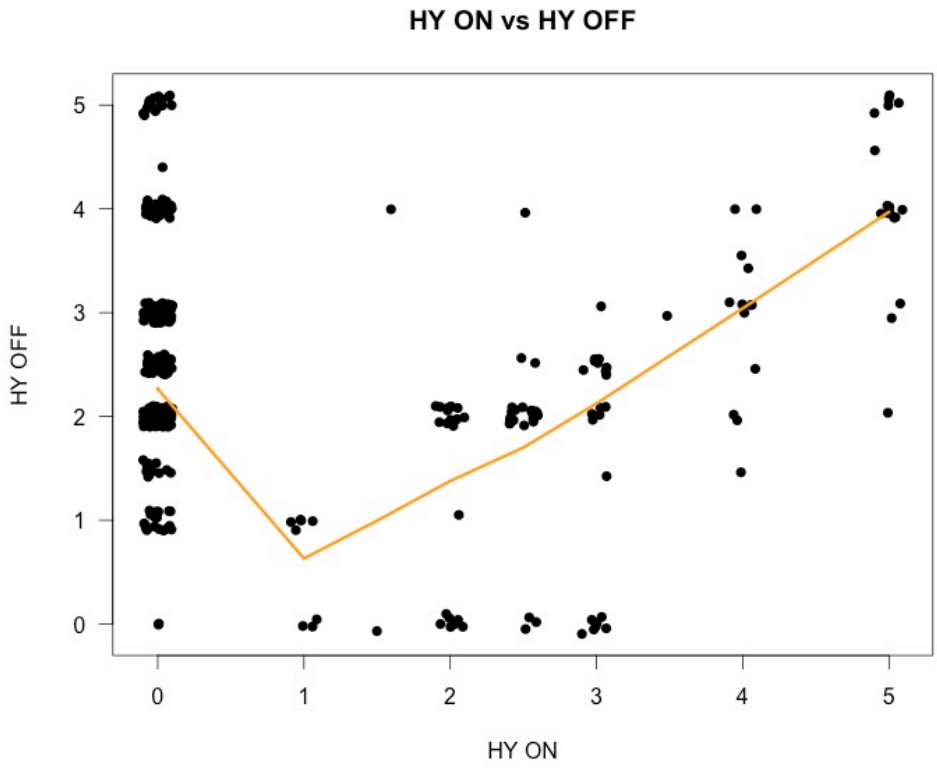

Figure 1 is a scatterplot of HY scores ON vs. HY scores OFF medication. This scatter plot has a locally weighted scatter plot smooth (LOWESS) line that is super imposed on top of it. The LOWESS line is a best-fit line used to show a general trend within a scatter plot. This scatter plot is very interesting, as it appears to show two distinct groups of patients; those who responded to treatment and those who did not. Further analysis is needed to explain why this trend is observed within the data. The implication of this scatter plot will be discussed in more detail in the next section of this thesis.

DISCUSSION

This study had several objectives: First, this study attempted to analyze the impact the primary predictive variables of race, sex, and sleep disturbance had on both HY ON and HY OFF scores. Secondly, this study sought to determine the relationship between the confounding variables of age, time in years from disease onset to database entry, and highest level of education achieved and HY ON and HY OFF scores. Thirdly, as its secondary outcome, this study sought to determine if the common NMS of autonomic dysfunction, dementia and hallucinations had an effect on either HY ON or HY OFF scores. Finally, HY ON and HY OFF scores were compared against each other in order to determine if these scores appeared to influence one another in any sort of meaningful way. The HY scoring system served as the primary outcome for the analysis. Half stage changes in the HY scale were considered clinically significant as both the values of 1.5 and 2.5 were added to the HY scale after its founding in 1967.

Race

The data from the study revealed that the majority of patients were Caucasian and male. This appears to be a little bit odd at first glance as BUMC serves a very diverse patient population. Past literature has reported, however, that the prevalence of PD is higher in Caucasians and Latinos as compared to other racial groups. Therefore, it is not surprising to find that a large percentage of PD patients were Caucasian, however, it is surprising to find a low number of Spanish patients represented in the study. Furthermore, the larger

portion of Caucasian patients, as well as the small number of patients in the other racial categories, may also decrease the power of the study despite thereby resulting in a reduced probability of finding a difference between the HY ON and HY OFF scores in the different races studied when a difference truly exists. The decrease in power therefore limits the conclusions this study can make about the association between race and HY ON and OFF scores.

Additionally, African patients with PD tend to present with more disease severity than their White patient peers. A one-way ANOVA test was used to determine if there was any significant difference between the mean HY ON and HY OFF scores across the various racial groups. The results showed no significant differences in the mean HY ON or HY OFF scores across racial groupings. This result is a bit surprising given the numerous studies that have reported that African patients tend to have greater disease severity as compared to their Caucasian peers. It is very possible, however, that no difference was found in the mean HY ON and HY OFF scores between the various racial groups simply because of the low numbers of subjects represented in the other racial groups, and thus these results should be interpreted with caution. Additionally, the "Other" racial category was composed of many different racial groups, making the results for this category uncertain because the effect of one group may mask the effects of others.

Interestingly, the multivariate linear regression model built to predict HY OFF scores showed that African patients were 0.46 points higher on the HY OFF scale as compared to Whites. This finding was statistically significant as the 95% confidence interval around this point estimate did not cross zero and the calculated p-value was 0.04. This result is not only statistically significant, but is also clinically meaningful as patients who are a half point higher on the HY scale have a significant difference in clinical disability and disease severity as compared to patients who are a half point below.

The models reported in **Tables 11 and 12** do not include sex or sleep disturbance within them. Sleep disturbance was excluded from these multivariate models as the majority of patients were missing sleep disturbance data. If sleep disturbance were included in this model the majority of patient data would not have been used in these models, which could greatly skew the results. Sex was excluded from this model because the student t-test and the univariate linear regression analysis indicated that sex did not have a significant fact on HY ON or HY OFF scores and therefore it seemed unlikely that sex would influence the results within these models. In fact, when gender was included in the multivariate analysis (results not shown) the results of the model were not significantly changed.

Past literature has indicated that the greater disease severity reported in African patient's most likely stems from these patients having been diagnosed at a later stage of disease. Studies have supported this claim by reporting that African patients do not report the

same level of disability as their Caucasian peers, even when both patients have the same level of disease severity. This study, however, seems to suggest that something else may also be causing this observed difference in disease severity between African and Caucasian patients as Caucasian patients were, on average, placed into the movement disorders database after a longer period from initial disease onset (**Table 8**). This finding is a bit limited in that the time in years from disease onset to database entry is only a proxy for estimating the delay between disease onset and diagnosis; however, it is possible that many other factors may have caused this observed difference in disease severity, for example, access to care.

Even though the analysis run on race and HY ON scores yielded no significant differences, the results are still meaningful, as they indicated that patients within the different racial groups has an equal response to treatment. This finding is reassuring, as it appears that the symptoms experienced by PD patients of different races are adequately addressed. The HY scale is a bit biased as it heavily relays on postural instability to indicate disease severity, and therefore it is possible that patients of different races have significant differences in the other PD motor and non-motor symptoms, which are not assessed by the HY scale.

Sex

Past literature has indicated that men are more likely than women to develop PD, and therefore it is not surprising that this study's population was comprised of more men than women PD patients.

The difference between the means of HY OFF in both male and female patients was significantly different, as reported by the results of the student t-test. Interestingly, the results of the multivariate linear regression analysis showed no significant impact of sex on either HY ON or HY OFF scores. Even though the difference in HY OFF scores is significant between males and females, it is a very small difference of only 0.2 points on the HYOFF score. A 0.2 difference is not clinically meaningful because patients who differ by 0.2 points would be impossible to detect clinically and therefore would most likely be grouped into the same HY OFF score category. Furthermore, past literature gives no clear indication of whether males or females exhibit a true clinical difference in PD disease severity.

When the difference between men and women in terms of their HY ON scores were analyzed no significant difference was found both within a multivariate linear regression model and within a student t-test. Again, no difference being found between the HY ON scores indicates that both sexes were adequately treated for the PD symptoms. Even though these data indicated that there was no clinically significant difference between males and females in terms of disease severity as measured by the HY scale, it was very

possible that both sexes experienced PD symptoms differently and that significant differences between the sexes in PD symptoms may exist.

Sleep Disturbance

As previously mentioned in the introduction, sleep disturbance is a highly prevalent problem with PD patients and is a widely recognized preclinical symptom of PD. Sleep disturbances is therefore a very interesting and relevant topic within PD research. This study showed that the vast majority, 68.1%, of PD patients were not asked about sleep disturbance during the survey. This large amount of missing data was a significant obstacle in analyzing the association between sleep disturbance and HY scores both in the ON medication and OFF medication states. Therefore, the only analysis performed on sleep disturbance was a simple t-test to determine whether or not the presence of sleep disturbance was correlated with higher HY ON and OFF scores.

Interestingly, mean HY ON scores were higher, on average, than mean HY OFF scores for patients who both reported and who did not report sleep disturbance. This trend was opposite of all other data included in the study, as mean HY ON scores were typically lower than mean HY OFF scores. This observed trend has not been reported by other studies making it very interesting. The fact that the HY ON scores were higher for patients who both reported and did not report sleep disturbance seems to indicate that something other than sleep disturbance maybe responsible for this observed trend. This line of thinking is also supported by the fact that the student t-test did not find a

significant difference between mean HY ON and HY OFF score for patients who reported and who did not report sleep disturbance. Furthermore, this observation indicates that patients who report and who do not report sleep disturbance were worse on medication than off of it. A follow up-study should be conducted on these patients if at all possible to confirm this result because it seems contrary to what is expected and observed within PD patients.

Additionally, patients who were not asked about sleep disturbance showed an average lower mean HY ON score as compared to mean HY OFF score, which is similar to all other data displayed in **Table 7**. Utilizing a student t-test it was shown that the difference between mean HY ON and OFF scores did not differ significantly for patients who reported sleep disturbance as well as those who did not report sleep disturbance. When analyzing the difference between patients who were not asked about sleep disturbance, as reported by the missing data value in **Table 7**, it was found that the difference between mean HY scores in both the on and off medication states was significantly different between patients missing data and patients who were asked about sleep disturbance. The results from these t-tests are not shown. It is difficult to draw conclusions from this analysis because it is likely that patients who were not asked about sleep disturbance were not a homogeneous group of individuals. The fact that a clinically significant difference does exist between patients who were asked about sleep disturbance and those who were not is interesting and should be explored further in a new study.

Overall, these results indicate that something peculiar is happening within PD patients who were asked about sleep disturbance as compared to those who were not asked about sleep disturbance. It was impossible, however, to explore this relationship further because of the small number of patients who where asked about sleep disturbance. These results do clearly indicate, however, that patients should be asked about sleep disturbance more regularly and possibly in the future another study could seek to analyze the relationship between sleep disturbance and HY ON and HY OFF scores more thoroughly.

Confounding Analysis

Age was shown to have a significant effect in multiple models. The univariate linear models constructed with age predicting HY ON or HY OFF scores showed that age only had a significant impact on HY OFF score. This makes sense as age is a very well know predictor for PD, but is not completely relevant in the ON medication state as time of treatment onset plays a more significant role. Even though age was seen to have a statistically significant effect on the HY OFF score, the effect was not clinically meaningful in any of the models because the largest effect shown for age indicated, that a ten-year increase in age impacted the HY OFF score by only 0.3 points (**Tables 7 and 10**).

The time from disease onset until database entry was shown to be significant in every model constructed to predict HY ON and OFF scores. This finding makes time from disease onset to database entry interesting, as it is the only variable that was observed to

have a significant impact on HY ON scores. Just like age, however, this effect was very small and ultimately not clinically meaningful. The relationship between HY scores and onset of disease deserves further attention in research. A prospective cohort study that follows patients from disease onset would be able to access this relationship more thoroughly, allowing for more conclusive data to be analyzed.

Education was examined as a potential confounder in this study. The relationship between education and the severity of PD is unclear and has not been well studied. Education was largely insignificant in many of the multivariate linear regression models created and analyzed over the course of this project. The univariate linear regression model, **Table 10**, predicting HY OFF score based on education was the only model that showed a statistically significant result. This model showed that some high school education without having graduated was positively correlated with HY OFF scores. This finding also appears to be clinically significant as patients with some high school education without having graduated had a 0.74 point increase in HY OFF score as compared to patients who had a graduate or professional degree. The association behind this relationship is unclear and it is likely that many different factors played a role such as socioeconomic status. Future research would need to be conducted in order to determine what is driving this relationship.

Secondary Analysis

The secondary analysis sought to examine the association between several NMS and how they relate to HY ON and HY OFF scores. These multivariate linear regression models are reported in **Tables 13** and **14**. NMS were looked at in more detail, as sleep disturbance yielded no significant results. The NMS chosen for this analysis included dementia, autonomic dysfunction and hallucinations. Hallucinations were of particular interest because they have been related to RBD. These models also included race, time from onset until database entry, and age. Sex was not included in these models because previous models examining the same variables showed sex to be insignificant.

Table 13 shows the results of the multivariate linear regression model predicting HY ON score. There were no significant results. Time in years until database entry was close to being significant but was not quite significant as indicated by the 95% confidence interval and the p-value or 0.06. Even if this result was statistically significant it would not meet the criteria to be clinically significant, since the impact time from onset to database entry had a very small effect. The effect of time in years from onset to database entry was so small that patients who had a ten year gap between onset of PD and being added to the base would have had their HY ON score increased by 0.2 points. This small increase would not be detectable at the clinical level.

Table 14 shows the same regression model as **Table 13** except this model predicted HY OFF scores. This model had several significant results. Age was shown to have a statistically significant result, and like previous models this result was not clinically significant due to the small value of the estimate. The same was true of time in years from disease onset to database entry. This model also showed that African patients had a 0.46 increase in HY OFF scores as compared to Caucasian patients. This result was very similar to the one depicted in **Table 12**, except the result seen here was more significant as evidenced by the narrower 95% confidence interval and the smaller p-value. Dementia, Autonomic dysfunction and hallucinations all had a statistically significant impact on HY OFF scores. Dementia had the most clinically meaningful impact out of these three NMS as patients who had dementia had an increase in HY OFF score by 0.52 points. This result is both clinically detectable as the HY scale is able to detect half point changes, and clinically meaningful as a half point increase in the HY scale represents a large change in PD disease severity. Autonomic dysfunction had the next most clinically significant result as patients with autonomic dysfunction had an increase of 0.47 points in HY OFF scores as compared to patients without autonomic dysfunction. Hallucinations did not appear to have a clinically significant impact on HY OFF scores. This was because patients who had hallucinations experienced an increase in their HY OFF score of 0.28 points on average, which would be difficult to detect in the clinic. Additionally, the 95% confidence interval around this estimate was fairly large indicating that hallucinations had a more varied effect on HY OFF score as compared

to dementia and autonomic dysfunction. It is interesting how all of these NMS had an independent effect on HY OFF score, as this suggests that patients with multiple NMS could have a drastic increase in disease severity. Patients have been reported to have an average of nine NMS making the individual impact that these NMS have on disease severity an import aspect of PD to consider.

The final analysis that will be considered in this section is depicted in **Figure 1**. **Figure 1** is a scatter plot that shows HY ON scores graphed against HY OFF scores. The orange line that was superimposed on this plot was a logically weighted scatterplot smoothing (LOWESS) line. This line was essentially a best-fit line that was fitted to the data using local polynomials then connected together. This plot was very interesting because it appeared to depict two separate groups of patients, those who responded well to treatment and those who did not. Looking at the far left hand side of the graph, many patients who had high HY OFF scores also exhibited low HY ON scores, implying that these patients responded well to medication. At a HY ON score of one the graph then begins to show a linear trend whereby both HY ON and HY OFF scores increase similarly. Patients who fit along this line appeared to show a gradual and steady increase in both HY ON and OFF scores, indicating that these patients were beginning to experience a decrease in treatment response. It could be possible that patients who were responding well to treatment were still within the "honeymoon" period of PD treatment. This period usually lasts for the first five years of treatment, as this is the period of time where patients have the most

effective response to L-dopa therapy. **Figure 1** shows a very interesting trend between HY ON and HY OFF scores and future researchers should more thoroughly investigate this trend by looking for possible data that may help to explain this observation.

Limitations

The major limitation of this study was missing data. Missing data greatly impacted the conclusions that could be drawn about sleep disturbance. Sleep disturbance was a very interesting topic with PD and has been gaining more attention in the literature over the years. Missing data also impacted the various linear models that were built, as missing data cannot be included into these models. Onset data had a significant amount of missing data, which could have impacted the linear models within which it was included. To accommodate for this problem it would be interesting to re-run all of the regression analysis excluding time in years from onset to database entry in order to determine what effect this missing data might have had on these models.

Another limitation was use of the HY score. The HY score is a fast and useful method for classifying the disease severity observed within PD patients. The HY scale, however, is highly based on postural symptoms and does not account for other symptoms of PD that can contribute to disease severity like NMS. The use of the HY therefore limits the conclusions that can be drawn about the difference in disease severity observed in the study subjects that results from other motor symptoms like tremor, and NMS. The HY

scale is advantageous in that it is a widely used scale, is easily used, and is able to rank the severity of PD in a way that is easy to interpret. The UPDRS, if used, could better account for the different aspects of PD as it is a more holistic scale by accounting for NMS and many of the observed motor symptoms. Using the UPDRS scale is not always practical, however, as it is more time consuming and harder to implement than the HY scale. Additionally, missing data also impacted the HY scale as 60 patients were missing data for HY ON and HY OFF score.

The combining of racial categories was also an issue. Combining racial categories was necessary to increase the sample size of each racial group so that they could be compared statistically. In doing so, however, this may have decreased the accuracy of the results obtained from the analysis. The 'Other' racial category analyzed was most affected by this fact because it was comprised of patients who were from Asian decent, who were Native American and who originated from the pacific islands. It is clear that these racial groups are not at all equivalent and it is not surprising that no significant results were found for this group. The large percentage of Caucasian patients also greatly impacts the results of this study by decreasing the external validity of the study. The external validity, however, may not be as decreased as other studies with a similar number of Caucasian patients, as PD is most prevent within the Caucasian population.

Finally this study shares all the same limitations as other cross sectional studies. The major limitation of cross-sectional study is that it is impossible to figure out whether the

exposure or outcome of interest came first. Therefore it is impossible to determine cause and affect relationships from this study. The fact that the data had been collected and de-identified was necessary for ensuring patient confidentiality and safety, but comes at the price of not being able to consult medical records to collect information that might otherwise be missing.

Overall, the movement disorders database was a valuable tool to analyze various aspects of PD as a wealth of information was stored within it. The movement disorders database therefore enabled many different questions to be asked of it. Even though these limitations restricted the conclusions of this study that can be applied to other populations, this study does accurately reflect PD patients who were receiving treatment at BUMC.

Conclusion

This study aimed to investigate the role sleep disturbance, sex, and race had on severity of PD as measured by the HY scale both in the ON and OFF medication states.

Overall this study found that males and females did have significantly different mean HY OFF scores, but this differences where determined to not be of clinical significance. Furthermore, Africans were observed to have a higher HY OFF score as compared to Caucasians in the multivariable linear regression model. Finally, the limited data collected on sleep disturbance greatly hindered the ability to draw any conclusions about

the correlation between sleep disturbance and HY scores. Therefore, future studies would have to be done at BUMC to figure out what role sleep disturbance plays in the severity of PD.

Additionally, the secondary analysis revealed that dementia, hallucinations, and autonomic dysfunction all had a significant impact on HY OFF scores. Furthermore, the scatter plot of HY ON and HY OFF scores indicated that some patients responded to treatment while others did not, which should be investigated further.

LIST OF JOURNAL ABBREVIATIONS

Ann Neurol.....Annals of Neurology

Ann NY Acad Sci ..... Annals of the New York Academy of Science

Arch Neurol .....Archives of Neurology

Arq Neuropsiquiatr ..... Arquivos de Neuro-Psiquiatria

Adv Neurol ..... Advances in Neurology

Behav Neurol .....Behavioral Neurology

Clin Neurol Neurosurg.....Clinical Neurology and Neurosurgery

Cold Spring Harb Perspect Med ..... Cold Spring Harbor Prospectives in Medicine

Curr Neurol Neurosci Rep ..... Current Neurology and Neuroscience Reports

Curr Opin Cell Biol..... Current Opinion in Cell Biology

Curr Opin Neurol .....Current Opinion in Neurology

Dis Mon .....Disease-a-Month

Exp Neurol ..... Experimental Neuology

Int J Neurosci ..... International Journal of Neuroscience

JAMA..... The Journal of the American Medical Association

JAMA Neurol..... JAMA Neurology

J Clin Sleep Med.....Journal of Clinical Sleep Medicine

J Neurol..... Journal of Neurology

J Neurol Neurosurg Psychiatry ..... Journal of Neurology, Neurosurgery & Psychiatry

J Neurol Sci.....Journal of the Neurological Sciences

J Parkinsons Dis..... Journal of Parkinsons Disease

Lancet Neurol..... Lancet Neurology

Natl Vital Stat Reports..... National Vital Statistics Reports

Nat Neurosci ..... Nature Neuroscience

Neurobiol Aging ..... Neurobiology of Aging Journal

Neurobiol Dis..... Neurobiology of Disease

Neurochem Res..... Neurochemical Research

Neurologist..... The Neurologist

Neurol Sci ..... Neurological Sciences

Neurosci Bull ..... Neuroscience Bulletin

Mov Disord ..... Movement Disorders Journal

Parkinsonism Relat Disord ..... Parkinsonism & Related Disorders

Pharmacol Rep..... Pharmacological Reports

Pract Neurol ..... Practical Neurology

Schizophr Bull ..... Schizophrenia Bulletin

Sleep Med ..... Sleep Medicine

Sleep Med Rev..... Sleep Medicine Reviews

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CURRICULUM VITAE

Christopher Sean Bayers

Address: 28 Lincoln Street; Belmont, MA 02478, (617) 875-4714, cbayers@bu.edu, Year of Birth 1990

EDUCATION:

Fordham University, Bronx, NY
Fordham College at Rose Hill
Bachelor of Science in Biological Sciences 2013
GPA: 3.4

Boston University, Boston, MA
Masters of Sciences in Clinical Sciences 2016
Master of Sciences in Clinical Investigation 2016

WORK EXPERIENCE:

Newton-Wellesley Hospital Newton, MA
Patient Observer Summer and Winter 2011

- Observed patients who were confused or disoriented due to medication or underlying medical complications
- Monitored confused and disoriented patients and prevented them from harming themselves or others by acting as a first responder
- Received and interpreted patient files from Registered Nurses in order to better understand patient needs
- Reported any change in patient behavior or attitude to the patient's Registered Nurse
- Worked extensively with Registered Nurses and Patient Care Assistants as part of a team dedicated to patient care and safety

Tufts University Biomedical Engineering Department Medford, MA
Research Assistant Summer 2012

- Worked under Dean Glettig, a PhD candidate in Biomedical Engineering at Tufts University
- Worked extensively with and differentiated pre-adipocytes and endothelial cells
- Managed the changing of cell media and passaged cells once they reached confluence
- Created silk scaffolds, which served as a three-dimensional cell culture that was used to determine the compatibility between adipocytes and endothelial cells when grown in culture together

Fordham University Undergraduate Research Bronx, NY
Dr. Patricio Meneses Laboratory Fall 2012-Spring 2013

- Study the Human Papillomavirus strain 16 and how it interacted with glypicans
- Use human keratinocyte cells as a model for infection and maintained the cells in culture
- Utilize the techniques of immunofluorescence, western blot and immunoprecipitation to study interactions between the virus and glypicans
- Created independent project studying the interaction between the Human Papillomavirus and Laminin 5 extracellular protein

Fordham University Emergency Medical Services Bronx, NY
Emergency Medical Technician Fall 2011- May 2013

- Attended EMT course at Northeastern University in Summer 2010 and received certification in Massachusetts in April 2011
- Respond to medical emergencies on campus
- Obtain vial signs, treat injured students and transport them to the hospital if necessary
- Write patient reports and submit them to the appropriate hospital staff

Mater Misericordiae University Hospital
Dublin, Ireland
Clinical Research Assistant November 2013-August 2014

- Researching novel bone markers and their relevance to bony disease in multiple myeloma patients
- Analyzing the change in bone marrow samples as patient with multiple myeloma undergo disease progression
- Investigating the role bisphosphonates play in the treatment of multiple myeloma
- Worked extensively with IT to reform PATS database to assist with current and future research endeavors

- Observing Dr. O'Gorman's private ward and public patient clinics, allowing me to interact with the patients whose data I used in my studies

SHADOWING EXPERIENCE:

Newton-Wellesley Hospital Shadowing Experience Newton, MA
Observation of General Surgeons Summer 2010

- Shadowed both Dr. Paul Gryska and Dr. Michael Reinhorn in the operating room
- Observed hernia repair and gall bladder removal via laparoscopic surgery
- Gained knowledge of how the operating technicians, nurses, anesthesiologist and surgeon all worked together as a team to care for the patient and the processes that took place before, during and after surgery

Newton-Wellesley Hospital Radiology Department Newton, MA
Member of the Tufts Medical Student's Radiology Rotation Directed by Joan Rastegar MD Winter 2012

- Toured the entire radiology department at Newton-Wellesley Hospital including both Interventional radiology and Nuclear medicine
- Observed how PET, MRI and ultrasound scans were conducted and how they were interpreted by the radiologist
- Observed the implantation of a power port device in Interventional Radiology
- Attended journal club meetings and other medical conferences with the medical students
- Observed a cardiologist perform stress tests on patients in order to gauge heart functionality

Skills:

- Proficient with Microsoft word, PowerPoint and Excel
- Proficient with cellular culture and microbiological techniques; immunofluorescence, immunoprecipitation and western blot

Interests:

- Accomplished Guitarist
- Played in a Rock band and preformed at the Worcester Palladium and other local venues